CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-896/S-010/S-011

Correspondence

Pelosi, Maureen A

From: Husain, Murad {PDR~Nutley} [MURAD.HUSAIN@ROCHE.COM]
nt: Wednesday, September 05, 2001 8:15 PM
'Pelosi, Maureen'
ubject: Xeloda Revised PI


ATT578266.rtf


Xeloda_Taxotere


Xeloda_Taxotere


wssinfo.txt

Dear Maureen,

In response to your e-mails dated 9/1/01 (FDA's comments on proposed Xeloda Taxotere Combination related labeling revisions, from Dr. Alison Martin), 9/4/01 (requesting Phase IV commitment studiesx2), please see the attachment below for a revised Xeloda package insert.

We have accepted most of your labeling recommendations except for few which we would like to discuss at tomorrow's (12-1 PM, 9/6/01) teleconference. Many of our suggestions have been made in order to clarify the PI for better understanding. We would like to discuss in more detail the new section which has been included under Warnings regarding patients >=60 years of age.

We would also like to discuss during the teleconference the FDA position regarding Warfarin/Xeloda interaction as it relates to the Xeloda labeling. We appreciate Division's promptness in reviewing our labeling supplement to add additional Warfarin related Warnings and Precautions to the Xeloda labeling and glad to hear that action letter on Friday (9/7/01) will address both supplements.

Regarding the Phase IV commitment studies and in reference to your September 4, 2001 e-mail the following timelines are anticipated:

1. Phase II 3-arm randomized monotherapy trial: Protocol submission November 2001, Study starts March 2002, Final Study Report December 2003.
2. Pharmacokinetic study of the combination of Xeloda plus docetaxel: Protocol submission December 2001, Study starts March 2002, Final Study Report December 2003.

Please keep in mind that these dates are estimates and may change when the protocols are finalized (e.g., when the final number of patients is determined).

Regards,
Murad

90 pages redacted from this section of the approval package consisted of draft labeling

Pelosi, Maureen A

From: Pelosi, Maureen A
Sent: Tuesday, September 04, 2001 10:08 AM
To: Murad Husain (E-mail)
Subject: Additional Phase 4 request: PK

Importance: High

Dear Murad,

Since your proposed Phase 2 study is not for combination therapy, we recommend that a separate Phase 4 commitment for a PK study be made to study the effect of chronic administration of combination therapy on the PK of capecitabine, it's metabolites, and docetaxel. The accelerated approval study did not meet the PK objectives of data collection in 16 individuals. Only 5 individuals completed the study. This is too few for us to write labeling changes. Below is the formal request:

We recommend that Roche acquire data to determine if long term co administration of capecitabine and docetaxel alters the pharmacokinetics of capecitabine, capecitabine's metabolites, docetaxel, or a combination of these moieties. The performance of the analytical methods and the reporting of the analytical methods for these data should be consistent with FDA's guidance: Bioanalytical Method Validation which is available at http://www.fda.gov/cder/guicance/index.htm.

Pelosi, Maureen A

From: Husain, Murad {PDR~Nutley} [MURAD.HUSAIN@ROCHE.COM]
Sent: Tuesday, August 28, 2001 1:18 PM
To: 'Pelosi, Maureen A'
Subject: RE: Pharmacokinetics Problem

Dear Maureen,

There is no Module X of the clinical study report for So14999. Reference, in fact the whole sentence, is wrong on page 16-5. Sorry about the confusion.

Please let me know if Gene has any other question.

I got your voice message. But I still need to discuss with you today and will call you later.

Regards,
Murad

-----Original Message-----
From: Pelosi, Maureen A [mailto:PELOSIM@cder.fda.gov]
Sent: Tuesday, August 28, 2001 12:42 PM
To: Murad Husain (E-mail)
Subject: Pharmacokinetics Problem
Importance: High

Dear Mura

On page 16-5 of Module I, there is a reference to Module X which we cannot locate. Where in the electronic submission can we find Module X. If there is a Module X and we currently have only Modules I-VI, are we missing (or do we need) Modules VII-IX also?

Maureen

Electronic Mail Message

Date: 7/12/01 11:51:36 AM
From: Husain, Murad PDR~Nutley (MURAD.HUSAIN@ROCHE.COM)
Subject: Xeloda: Dose Reduction for Elderly

Dear Maureen,

As requested, the points below summarize the background and preliminary analyses which support a reduction of the starting dose of capecitabine in elderly patients (>60 years of age) when used in combination with docetaxel 75 mg/sqm. We would propose to submit analyses and propose labeling change indicated below by the last week of July.

The superior time to progression of the capecitabine/docetaxel combination is preserved in the >60 years of age population. A trend for superiority of survival is also observed in this patient group. In the overall population, incidence of adverse events in subsequent treatment may be reduced by aggressive dose modification. In the elderly (>60 years of age) population, the overall safety profile may be further enhanced by an upfront dose reduction of capecitabine, which may allow a greater percentage of the elderly to benefit from the combination therapy with an improved safety profile.

* as outlined in Table 138 of Module I of the Clinical Study Report SO14999, the older patients in both treatment groups (Xeloda/Taxotere combination and Taxotere monotherapy) have a decreased tolerance compared to younger patients
* we performed a safety analysis for patients <60 and >60 years of age (as outlined in Table 138). Sixty seven (27%) patients enrolled in the capecitabine plus docetaxel arm were > 60 years of age. As anticipated this analysis is consistent with the data presented in Table 138 and demonstrates for the combination therapy arm, the incidence of all grade 3 and grade 4 treatment related adverse events (87% vs. 75%), grade 3 HFS (27% vs. 23%), grade 3/4 diarrhea (15% vs. 14%), grade 3/4 stomatitis (30% vs. 13%), serious adverse events (45% vs. 28%), withdrawals due to any adverse events (45% vs. 27%) and discontinuations due to related adverse events (36% vs. 21%) were higher in the >60 age group.
* an examination of renal function, which is known to be related to Xeloda safety, did not identify the same clear cut decreased tolerability as did the >60 years age criterion (as outlined in Table 140 of Module 1). This suggests that age should be considered along with renal function in dose recommendation.
* a preliminary analysis evaluating the safety profile of patient subgroups according to age and CrCl did not reveal a clear cut decreased tolerability.
* a preliminary analysis evaluating the safety profile of patients <60 years and >60 years of age by individual treatment cycle (e.g. cycle 1, cycle 2, etc), demonstrates that 21 out of 67 patients (31%) >60 years of age dropped out after the 1st or 2nd treatment cycle mainly due to toxicities vs. 17% in the < 60 age group. The incidence of all and

specific grade 3/4 adverse events in the individual cycle analysis for patients receiving capecitabine (1250 mg/m2) and docetaxel (75 mg/m2) combination was higher in the >60 years age group compared to the <60 years age group. A clinically significant number of patients required interruptions of the Xeloda treatment in both age groups at the full Xeloda dose in treatment cycles 1 and 2.

* a preliminary analysis evaluating the efficacy of patients <60 and >60 years of age who underwent a dose reduction after the first or second treatment cycle does not reveal any major adverse impact on objective response rate, TTP or survival (preservation of the over all trend for superiority). Caution should be used when interpreting the efficacy results of the >60 age group due to the small number of patients.

In the >60 age group, based on the reduced tolerability, the higher number of patients dropping out after 1 or 2 cycles of treatment and the lack of major impact of early dose reductions of capecitabine on efficacy outcomes , we would propose that for patients >60 years of age, the starting dose of Xeloda in combination with docetaxel (75 mg/sqm) should be reduced by 25% from 1250 mg/sqm to 950 mg/sqm twice daily x 14 days, with a one week rest period.

Please advise us on the approach which the division would like to us to take regarding this matter.

Regards,

Murad

Electronic Mail Message

Date: 7/10/01 12:35:14 PM
From: Maureen Pelosi (PELOSIM)
To: Murad Husain (MURAD.HUSAIN@ROCHE.COM)
Subject: Xeloda data sets

Dear Murad,

Please send us (ASAP) the datasets with the dates the investigator determined progressive disease by new lesions or other.

Please tell us the name and location of the field for estrogen receptor status.

Thanks, Maureen

ORIGINAL

Roche

Pharmaceuticals

June 28, 2001

SE1-010
(SU)

Food and Drug Administration
Division of Oncology Drug Products, HFD-150
Office of Drug Evaluation I
Center for Drug Evaluation and Research
1451 Rockville Pike, Woodmont II Building
Rockville, MD 20852-1448

Ladies and Gentlemen:

Re: NDA 20-896/Supplement Number (S-010)
Xeloda® (capecitabine, Ro 09-1978) Tablets
Other: Four Month Safety Update

In accordance with 21 CFR Part 314.50(d) (5) (vi) (b), Hoffmann-La Roche, Inc. herewith submits a Four Month Safety Update for the pending supplemental New Drug Application for Xeloda Tablets, supplement #010 (submitted March 7, 2001). The data presented in this report are consistent with the sNDA and further support the safety profile of Xeloda used in combination with Taxotere for metastatic breast cancer.

The following is provided in this Four Month Safety Update submission:

- Annotated Package Insert
- Four Month Safety Update with a Clinical Cutoff of February 15, 2001
- Four Month Survival Update with a Clinical Cutoff of February 15, 2001

Overall, there were minor safety updates for the Phase III study SO14999. Based on these safety results changes were made to the proposed package insert submitted with the sNDA. New incidence rates have been updated in the ADVERSE REACTIONS section and an updated Kaplan-Meier survival curve is provided in the CLINICAL STUDIES section. The revised version is included with the deleted text stricken, as well as a version with the changes incorporated. Electronic copies of the package insert are included on enclosed disks (Word).

While preparing the annotated package insert an error was found for the ADVERSE REACTIONS section under XELODA and DOCETAXEL in COMBINATION adverse events in ≥5% of patients. The old reference was 8000-13-217-243 and the new reference is 8000-13-[illegible]5-204.

This submission consists of 4 CD-ROMs for Case Report Tabulations and Datasets and Patient Case Report Forms. The enclosed Case Report Forms, which were submitted in the sNDA and contain additional information up to February 15, 2001, are only for the patients with updated or new information. The approximate size of the electronic files is approximately [illegible] for Patient Profiles, [illegible] for Dataset related files and [illegible] for Case Report Forms). All electronic files in the submission are provided on CD-ROMs and were scanned for viruses with [illegible] virus update 06-24-2001. No known viruses were found.

Case Report Tabulations and Datasets	1 & 2
Datasets and Patient Profiles	3 & 4

If you have any questions regarding this submission, please feel free to contact the undersigned.

Sincerely,

HOFFMANN LA ROCHE INC.

Murad Husain
Program Director
Drug Regulatory Affairs
Phone: 973-235-4578
Fax: 973-562-3700

HKT/GB
Attachments
HLR No. 2001-1444
Desk Copies: Ms. Maureen Pelosi, Project Manager – HFD-150

Roche

DUPLICATE

June 21, 2001

NDA SUPPLEMENT

PW

Food and Drug Administration
Division of Oncology Drug Products, HFD-150
Office of Drug Evaluation I
Center for Drug Evaluation and Research
1451 Rockville Pike, Woodmont II Building
Rockville, MD 20852-1448

Ladies and Gentlemen:

Re: NDA 20-896-Xeloda™ (capecitabine) Tablets
General Correspondence: Waiver Request for Pediatric Study Requirements

Reference is made to Hoffmann-la Roche Inc.'s approved New Drug Application 20-896 for the treatment of patients with paclitaxel and anthracycline resistant metastatic breast cancer and colorectal cancer applications as well as the agency's September 23, 1999, letter granting a waiver for pediatric studies for metastatic breast cancer and metastatic colorectal cancer. Reference is also made to the June 18, 2001 FDA e-mail requesting information regarding the December 2, 1998 Pediatric Rule (63 FR 66632) for the combination of Xeloda with Taxotere for the treatment of metastatic breast cancer. Based on review of the June 1998 Guidance for Industry: *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug and Cosmetic Act*, the Sponsor hereby requests a waiver for pediatric study requirements due to the following reasons:

1. The current indications for paclitaxel and anthracycline resistant metastatic breast cancer and colorectal cancer are not appropriate indications for the pediatric population, and

2. The proposed indication for the combination of Xeloda with Taxotere for the treatment of metastatic breast cancer is not an appropriate indication for the pediatric population.

If you have any questions regarding this submission, please feel free to contact the undersigned.

Sincerely,

HOFFMANN LA ROCHE INC.

for

Murad Husain
Program Director
Drug Regulatory Affairs
Phone: 973-235-3578
Fax: 973-562-3700

HKT/EMD
HLR No. 2001-1371

Roche

Pharmaceuticals

June 7, 2001

Food and Drug Administration
Division of Oncology Drug Products, HFD-150
Office of Drug Evaluation I
Center for Drug Evaluation and Research
1451 Rockville Pike, Woodmont II Building
Rockville, MD 20852

Re: NDA 20-896/S-010: Amendment to Efficacy Supplement
XELODA® (capecitabine) in Combination with Taxotere® (docetaxel)
in Metastatic Breast Cancer

Ladies and Gentlemen:

Hoffmann-La Roche Inc. as (sponsor of NDA 20-896) is submitting an amendment to Efficacy Supplement S-010, Xeloda® (capecitabine) in Combination with Taxotere® (docetaxel) for treatment of metastatic breast cancer. This submission contains comparative dissolution data requested by the Biopharmaceutics Reviewer.

A comparative assessment of the dissolution profiles of the two strengths of -manufactured drug product used in clinical trial SO 14999, and the same strengths of currently manufactured US commercial drug product are included in this submission. The data used for the assessment are included with a graphical presentation of the profiles. Calculations were performed for both the for the three -manufactured clinical batches of Xeloda Tablets (C189437, C189467 and C189477) vs. market batches of the same strength. All acceptance criteria are met. Testing was performed in accordance with the analytical method currently approved in the NDA.

Please contact me at (973) 562-3519 if you require any additional information.

Sincerely,

HOFFMANN-LA ROCHE INC.

Duane L. Voss

Ms. Duane L. Voss
Program Director
Drug Regulatory Affairs

Telephone: (973) 562-3519
Fax: (973) 562-3700

Attachments
HLR No. 2001-1302

Redacted 5

pages of trade

secret and/or

confidential

commercial

information

Electronic Mail Message

Date: 6/4/01 3:27:38 PM
From: Maureen Pelosi (PELOSIM)
To: Murad Husain (MURAD.HUSAIN@ROCHE.COM)
Subject: Xeloda Drug Interactions

Dear Murad,

I asked Atik how you should handle the Warfarin study results.

He said 4 patients are inadequate, that you need to continue with the study as planned (12 patients). The purpose is to determine Xeloda dosing reductions / recommendations for patients on warfarin and that cannot be done with 4 patients.

Maureen

DUPLICATE

Roche

May 25, 2001

NDA SUPPLEMENTS

SE7-010
BM

Pharmaceuticals

Food and Drug Administration
Division of Oncology Drug Products, HFD-150
Office of Drug Evaluation I
Center for Drug Evaluation and Research
1451 Rockville Pike, Woodmont II Building
Rockville, MD 20852

Ladies and Gentlemen:

Re: **NDA 20-896/Supplement Number (S-010)**
Xeloda® (capecitabine, Ro 09-1978) Tablets
(_____) and Data from Analytical Runs for Study SO15304

Reference is made to the FDA's request for information on April 2, 2001. As requested we are providing( ) for Study SO15304 of 20% of patients for capecitabine and its metabolites (day 1 and day 14) and docetaxel (day 1 and day 22) and the Standard and QC Summary Tables.

In this study we measured capecitabine and its metabolites (day 1 and day 14) and docetaxel (day 1 and day 22). There were 3 dosing groups.

- For capecitabine (Ro 09-1978) we have on day 1 in total 30 patients(

- On day 14 we have for capecitabine (Ro 09-1978) in total again 30 patients. The same procedure was used as on day 1 to obtain the extreme profiles.

- For Docetaxel (Taxotere) we have on day 1 in total 26 patients(

- On day 22 we have for docetaxel in total again 26 patients. The same procedure was used as on day 1 to obtain the extreme profiles.

To aid the reviewer in locating the( )Table SO15304 is attached.

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

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

Sincerely,

HOFFMANN-LA ROCHE, INC.

Murad Husain
Program Director
Drug Regulatory Affairs
Phone: (973) 235-4578
Fax: (973) 562-3700/3554

HLR No.: 2001-937

MH/hkt/gb
Attachments

Desk copy: Maureen Pelosi, HFD-150

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

5/24/01

NDA 20-896

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

Attention: Murad Husain
Program Director, Drug Regulatory Affairs

Dear Mr. Husain:

We refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xeloda (capecitabine) tablets.

We have received your submission dated March 7, 2001, regarding the following postmarketing study commitments.

1. A commitment to satisfy the requirements of the accelerated approval regulations (21 CFR 314.510), the proposed Phase 4 study SO14999B entitled, "An open-label randomized Phase 3 study of capecitabine in combination with docetaxel versus docetaxel monotherapy in patients with advanced and/or metastatic breast cancer" will be conducted with due diligence to verify and describe clinical benefit. Clinical benefit could be demonstrated in this study if patients randomized to the capecitabine and docetaxel combination had a clinically and statistically significant improvement in time to progression compared to patients randomized to docetaxel monotherapy. It should be noted, however, that members of the Oncologic Drugs Advisory Committee expressed misgivings at the March 19, 1998 meeting regarding the feasibility of demonstrating net clinical benefit for capecitabine in study SO14999B and recommended that alternative study designs be considered. If study SO14999B does not verify the clinical benefit, capecitabine may be subject to the accelerated approval withdrawal procedures described in 21 CFR 314.530.

   STATUS: Study SO14999 has been completed and the final report submitted March 7, 2001 as S010. This supplement is under review by FDA.

2. A commitment to submit and discuss any alternative studies and/or major amendments to the design of study SO14999B with the FDA prior to enactment.

   STATUS: This commitment is part of #1. See above.

3. A commitment to submit the study "A Phase 2 study of capecitabine in patients who have received previous treatment with paclitaxel or docetaxel for locally advanced and/or metastatic breast cancer" when it is completed.

   STATUS: Study report for was submitted to IND on April 7, 2000 (S-295) and is under review by FDA.

We also refer to your submission dated February 8, 2000, containing protocol to address the following postmarketing study commitment conveyed on our February 25, 1999 supplement request letter.

Clinical commitment to conduct a formal study to investigate the effects of capecitabine on the pharmacokinetics and pharmacodynamics of warfarin (or other coumarin derivative anticoagulants), to fully characterize the mechanism of interaction between capecitabine and coumarin anticoagulants, and to properly provide dosing recommendations. In a March 5, 1999 teleconference, you agreed to conduct the study. FDA requested incorporation of potassium levels, change in intestinal flora.

STATUS: The final protocol for study was submitted to IND on February 8, 2000 and the study is ongoing.

Finally, we remind you of the following commitments outlined in our letter of April 30, 2001 approving S006 and S009.

1. Clinical commitment to update the survival analyses after a total of 1180 deaths have occurred in the two randomized controlled trials, SO14694 and SO14796. The Estimated Updated Survival Analysis submission due date is December 2002.

2. Clinical commitment to submit the results of the and clinical trials in advanced metastatic colorectal cancer studying Xeloda in combination with irinotecan when completed. If other trials are initiated with this combination, please submit the results when available. Final Report on Study to be submitted in July 2002; Study to be submitted in January 2003.

3. Clinical commitment to submit the final study report for # "Comparison of the pharmacokinetics of capecitabine in Japanese and Caucasian cancer patients." We note that a retrospective analysis (report) performed on pooled data from seven phase I studies suggested differences between these two populations. Final Report to be submitted by late October 2001.

4. Clinical commitment to identify and submit final study reports for all trials assessing the activity (phase 2) or efficacy (phase 3) of capecitabine as second-line therapy in patients

with colorectal cancer previously treated with a fluoropyrimidine-based therapy. Final Report to be submitted by late October 2001.

If you have any questions, call Maureen Pelosi, Project Manager, at (301) 594-5778.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Electronic Mail Message

Date: 5/22/01 3:18:47 PM
From: Husain, Murad PDR~Nutley (MURAD.HUSAIN@ROCHE.COM)
To: 'Maureen Pelosi 301-594-2473 FAX 30 (PELOSIM@A1)
Subject: Re: Xel/Tax

Maureen,

Yes, there will be a 4-month Safety Update due on July 7. Most significant in the update will be survival update. We expect no significant changes to safety conclusion.

Regards,
Murad

BM_MailData-----Original Message-----
From: Maureen Pelosi 301-594-2473 FAX 301-594-0498 [SMTP:PELOSIM@cder.fda.gov]
Sent: Tuesday, May 22, 2001 3:02 PM
To: Murad Husain
Subject: Xel/Tax
Sensitivity: Confidential

Hi Murad,

Do you know if we will be receiving a safety update for Xeloda? If so, when? The medical officer asked me to inquire.

thanks, Maureen

M10

Electronic Mail Message

Date: 5/17/01 2:39:31 PM
From: Husain, Murad PDR~Nutley (MURAD.HUSAIN@ROCHE.COM)
To: 'Maureen Pelosi 301-594-2473 FAX 30 (PELOSIM@A1)
Subject: Re: Xel/Tax Label

Hi Maureen,

We are working on it and will send the revised PI as soon as it is done.

Regards,
Murad

-----Original Message-----
From: Maureen Pelosi 301-594-2473 FAX 301-594-0498
[mailto:PELOSIM@cder.fda.gov <mailto:PELOSIM@cder.fda.gov>]
Sent: Thursday, May 17, 2001 12:04 PM
To: Murad.Husain@ROCHE.COM
Subject: Xel/Tax Label
Importance: High
Sensitivity: Confidential

Dear Murad,

We are nearing the 3 month review for Xeloda/Taxotere. Please send an updated
label ASAP with the CRC label as the base label so we can start our review.

Please include a disc with a marked up version and a clean version as well as
the hard copy to the sNDA. Additionally, we will need 4 reviewer copies.

Thanks, Maureen

PK

Dear Maureen,

We will submit the following dissolution data on or before June 8, 2001. We will send an official letter with the commitment soon.

Best regards,
Murad

"Evaluation of patients that received drug product manufactured at the site is most straightforward if we can conclude that the manufactured product does not perform significantly differently than the currently marketed US commercial drug product. Relative to the currently marketed US commercial drug product, the site is a Level 3 site change and, in order to evaluate the effect of this change, our current standard (SUPAC-IR) is comparative dissolution data.

Please commit to submitting the following on or before June 8, 2001:

A comparative assessment of the dissolution profiles of the two strengths of manufactured drug product used in trial SO 14999 and the same strengths of currently manufactured US commercial drug product. The raw data for the assessment will be profiles , performed according to current US application/compendial specifications."

-----Original Message-----
From: Maureen Pelosi 301-594-2473 FAX 301-594-0498
[mailto:PELOSIM@cder.fda.gov]
Sent: Tuesday, April 24, 2001 2:36 PM
To: Murad Husain
Subject: Xeloda Ph4 submission
Importance: High
Sensitivity: Confidential

Dear Murad,

Please see the attachment. Clin Pharm is requesting a commitment.

Please send an Email with an initial reply followed by a hard copy.

Thanks, Maureen

4-10-01

Dear Maureen,

Attached is a table listing all investigators for study SO14999 in the format you have requested. Please note that this table was created manually. Names of some investigators were corrected based on their CV/1572s submitted to the capecitabine IND. We have also provided names of both original and replacement investigators where applicable.

If you have additional request please feel free to call me.
Regards,
Murad

-----Original Message-----
From: Maureen Pelosi 301-594-2473 FAX 301-594-0498
[mailto:PELOSIM@cder.fda.gov]
Sent: Tuesday, April 03, 2001 10:29 AM
To: Murad Husain
Subject: FWD: Xeloda Request
Sensitivity: Confidential

Murad,
Due to time constraints with ODAC and assuming Xeloda is a priority review, would it be possible for Roche to provide a table such as the attached one? I realize we did not request this previously and that Roche is not under a

APPEARS THIS WAY
ON ORIGINAL

Table 1. Xeloda Study SO 99 Clinical Site Information

Study	Country	Patients (n)	Study Sites (n)	Investigators (n)	Investigator Name	Patients Enrolled (n)
SO14999	Australia	40	6	6	Steve Ackland	7
					David Bell	1
					Michael Boyer	6
					Guy Van Hazel	13
					Joe McKendrick	9
					Danny Rischin/Guy Toner*	4
	Brazil	9	2	2	Miguel Jose Froimtchuk	4
					Jose' Luiz Pedrini	5
	Canada	61	11	11	T. Al-Tweigeri/Barbara Walley*	9
					Jean-Pierre Ayoub/Christine Legler*	10
					Bruce Colwell	3
					Paul Goss	3
					Ralph Wong/Shou-Ching Tang*	7
					Ted Vandenberg	7
					Shailendra Verma	7
					Louise Yelle	3
					Amit Oza	5
					Jean Robert	3
					Eva Tomiak	4
	Germany	7	2	2	Roland Mertelsmann	3
					Kurt Possinger	4
	Spain	16	3	3	Moreno Nogueira	6
					Lluch Hernandez	5
					Miguel Martin	5

*Original investigator to enroll patients/Replacement investigator

Table 1. Xeloda Study SO[illegible]99 Clinical Site Information

Study	Country	Patients (n)	Study Sites (n)	Investigators (n)	Investigator Name	Patients Enrolled (n)
SO14999	France	42	5	5	Pierre Fumoleau	5
					Francois Turpin	8
					Louis Mauriac	13
					Dominique Maraninchi	11
					Thomas Bachelot	5
	Great Britain	64	8	8	David Miles	14
					Chris Twelves	9
					Dennis Talbot	4
					Janine Mansi	6
					Susan O'Reilly	2
					Ken O'Byrne	6
					Andreas Makris	7
					Robert Leonard/David Cameron*	16
	Italy	24	6	6	Riccardo Rosso	4
					Pier Franco Conte	7
					Eugenio Villa	3
					Giuseppe Comella	1
					Maurizio Tonato	5
					Armado Santoro	4
	Israel	38	7	7	Moshe Inbar	10
					Sulamith Rizel	11
					Raphael Catane	5
					David Geffen	5
					Biatrice Uzieli	3
					Georgeta Fried	1
					Menachem Ben-Shahar	3

*Original investigator to enroll patients/Replacement investigator

Table 1. Xeloda Study SO 14999 Clinical Site Information

Study	Country	Patients (n)	Study Sites (n)	Investigators (n)	Investigator Name	Patients Enrolled (n)
SO 14999	Mexico	42	4	4	Guadalupe Cervantes	13
					Juan Francisco Gonzalez	9
					Alejandro Silva	7
					Gilberto Morgan-Villela/ Carlos Chan Navarro*	13
	Norway	13	2	2	Bjorn Erikstein	8
					Erik Wist	5
	New Zealand	11	2	2	Michael Findlay	6
					Vernon Harvey	5
	Argentina	4	1	1	Elizabeth Mickiewicz	4
	Taiwan	28	3	3	Tsu-Yi Chao	8
					Ann Lii Cheng	8
					Hwei-Chung Wang/Wing-Yiu Lui*	12
	Russia	65	5	5	August Garin	10
					Michael Lichinitser	10
					Vera Gorbunova	15
					Vladimir Moiseyenko	20
					Vasily Borisov	10
	United States	47	8	8	Svetislava Vukelja	32
					Paul Kaywin	2
					Manuel Modiano	2
					W. Graydon Harker	4
					Edmund Tai	1
					Joan Kroener	3
					Melvin Moore	1
					William David Henner	2

*Original investigator to enroll patients/Replacement investigator

Table 1. Xeloda Study SO. . 99 Clinical Site Information

Study	Country	Patients (n)	Study Sites (n)	Investigators (n)	Investigator Name	Patients Enrolled (n)
SO14999	Australia	40	6	6	Steve Ackland	7
					David Bell	1
					Michael Boyer	6
					Guy Van Hazel	13
					Joe McKendrick	9
					Danny Rischin/Guy Toner*	4
	Brazil	9	2	2	Miguel Jose Froimtchuk	4
					Jose' Luiz Pedrini	5
	Canada	61	11	11	T. Al-Tweigeri/Barbara Walley*	9
					Jean-Pierre Ayoub/Christine Legler*	10
					Bruce Colwell	3
					Paul Goss	3
					Ralph Wong/Shou-Ching Tang*	7
					Ted Vandenberg	7
					Shailendra Verma	7
					Louise Yelle	3
					Amit Oza	5
					Jean Robert	3
					Eva Tomiak	4
	Germany	7	2	2	Roland Mertelsmann	3
					Kurt Possinger	4
	Spain	16	3	3	Moreno Nogueira	6
					Lluch Hernandez	5
					Miguel Martin	5

*Original investigator to enroll patients/Replacement investigator

Table 1. Xeloda Study SO[illegible]99 Clinical Site Information

Study	Country	Patients (n)	Study Sites (n)	Investigators (n)	Investigator Name	Patients Enrolled (n)
SO14999	France	42	5	5	Pierre Fumoleau	5
					Francois Turpin	8
					Louis Mauriac	13
					Dominique Maraninchi	11
					Thomas Bachelot	5
	Great Britain	64	8	8	David Miles	14
					Chris Twelves	9
					Dennis Talbot	4
					Janine Mansi	6
					Susan O'Reilly	2
					Ken O'Byrne	6
					Andreas Makris	7
					Robert Leonard/David Cameron*	16
	Italy	24	6	6	Riccardo Rosso	4
					Pier Franco Conte	7
					Eugenio Villa	3
					Giuseppe Comella	1
					Maurizio Tonato	5
					Armado Santoro	4
	Israel	38	7	7	Moshe Inbar	10
					Sulamith Rizel	11
					Raphael Catane	5
					David Geffen	5
					Biatrice Uzieli	3
					Georgeta Fried	1
					Menachem Ben-Shahar	3

*Original investigator to enroll patients/Replacement investigator

Table 1. Xeloda Study SO[illegible]99 Clinical Site Information

Study	Country	Patients (n)	Study Sites (n)	Investigators (n)	Investigator Name	Patients Enrolled (n)
SO 14999	Mexico	42	4	4	Guadalupe Cervantes	13
					Juan Francisco Gonzalez	9
					Alejandro Silva	7
					Gilberto Morgan-Villela/ Carlos Chan Navarro*	13
	Norway	13	2	2	Bjorn Erikstein	8
					Erik Wist	5
	New Zealand	11	2	2	Michael Findlay	6
					Vernon Harvey	5
	Argentina	4	1	1	Elizabeth Mickiewicz	4
	Taiwan	28	3	3	Tsu-Yi Chao	8
					Ann Lii Cheng	8
					Hwei-Chung Wang/Wing-Yiu Lui*	12
	Russia	65	5	5	August Garin	10
					Michael Lichinitser	10
					Vera Gorbunova	15
					Vladimir Moiseyenko	20
					Vasily Borisov	10
	United States	47	8	8	Svetislava Vukelja	32
					Paul Kaywin	2
					Manuel Modiano	2
					W. Graydon Harker	4
					Edmund Tai	1
					Joan Kroener	3
					Melvin Moore	1
					William David Henner	2

*Original investigator to enroll patients/Replacement investigator

Electronic Mail Message

PK

Date: 4/2/01 4:40:06 PM
From: Maureen Pelosi (PELOSIM)
To: Murad Husain (MURAD.HUSAIN@ROCHE.COM)
Cc: Cindy Dinella (cynthia.dinella@roche.com)
Subject: Confirm please

Murad,

Would you please confirm whether or not the current marketed Xeloda tablet dosage form was used in studies S015304 and S014999.

Thanks, Maureen

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-896/S-010

3/26/01

Hoffman-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110-1199

Attention: Murad Husain
Program Director

Dear Mr. Husain:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Xeloda (capecitabine) Tablets

NDA Number: 20-896

Supplement Number: S-010

Date of Supplement: March 7, 2001

Date of Receipt: March 9, 2001

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 31, 2000 in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products,
HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products,
HFD-150
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, call Maureen Pelosi, Project Manager, at (301) 594-5778.

Sincerely,

/S/

Dotti Pease
Chief, Project Management Staff
Division of Oncologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

March 7, 2001

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852

Ladies and Gentlemen:

Re: NDA 20-896 - Xeloda® (capecitabine, Ro 09-1978) Tablets
Efficacy Supplement - Xeloda® (capecitabine) in Combination with Taxotere® (docetaxel) in Metastatic Breast Cancer

In accordance with 21 CFR Parts 314.50 and 314.71, Hoffmann-La Roche Inc. herewith submits an efficacy supplement to NDA 20-896 for the use of Xeloda® (capecitabine) Tablets in combination with Taxotere® (docetaxel) for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior anthracycline containing chemotherapy.

Reference is made to a End-of-Phase 4 meeting between the Division of Oncology Drug Products (HFD-150), CDER and Hoffmann-La Roche Inc. on December 21, 2000 regarding the content and procedure for this submission.

This supplemental NDA satisfies the last remaining Phase 4 commitment (Commitment #1, Approval Letter for NDA 20-896, dated April 30, 1998) and the requirements of accelerated approval regulations (21 CFR 314.510).

The safety and efficacy data in support of this supplement are based on the results of "An open-label randomized Phase III study of capecitabine in combination with docetaxel versus docetaxel monotherapy in patients with advanced and/or metastatic breast cancer" (Study Protocol SO14999). A total of 511 patients with locally advanced or metastatic breast cancer resistant to, or recurring after an anthracycline-containing chemotherapy, or relapsing during or recurring within two years of completing an anthracycline containing adjuvant therapy were randomized to either combination (n=255) or monotherapy (n=256) treatment groups in this multinational study. The patients in the combination group received Xeloda (1250 mg/m^2 twice daily for 14 days followed by one week without treatment) and docetaxel (75 mg/m^2 as a one hour intravenous infusion) in three-week cycles. The patients in the monotherapy group received docetaxel (100 mg/m^2 as a one hour intravenous infusion) in three-week cycles.

We believe that this large adequate and well-controlled phase 3 clinical trial provides substantial evidence of efficacy and safety, as compared to docetaxel monotherapy, to support the use of Xeloda in combination with docetaxel in patients with locally

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

Roche

advanced and/or metastatic breast cancer, after failure of prior anthracycline containing chemotherapy.

Request for Priority Review:
In accordance with the Prescription Drug User Fee Act and FDA's "Guidance for Industry: Standards for the Prompt Review of Efficay Supplements, Including Priority Efficacy Supplements (May 1998)", Hoffmann-La Roche Inc. requests a priority review of this sNDA. We believe that the proposed new indication of Xeloda in combination with docetaxel would be a significant improvement in the treatment of patients with locally advanced and/or metastatic breast cancer, compared to marketed products and/or treatments.

This Supplement is organized as follows:

Overall NDA Supplement Content	Volume Number
Section 1 - Index	1
Section 2 - Labeling	2
Section 3 - Application Summary	3
Section 4 - Chemistry, Manufacturing and Controls	N/A
Section 5 - Nonclinical Pharmacology and Toxicology	N/A
Section 6 - Human Pharmacokinetics and Bioavailability	4-11
Section 7 - Microbiology/Virology	N/A
Sections 8/10 - Clinical and Statistical	12-70
Section 11 - Case Report Tabulations and Datasets	1 & 2
Section 12 - Patient Case Report Forms	2 - 5

This submission consists of an archival copy of , paper volumes for Sections 1, 2, 3, 6, 8, and 10 and 5 CD-ROMs for Sections 11 and 12. The approximate size of these electronic files is for Patient Profiles. for SAS transport files and for Case Report Forms). All electronic files in the submission are provided on CD-ROMs and were scanned for viruses with No known viruses were found. An electronic review aid of Sections 1-12 will be provided separately at a later time.

Patent Information:
There is no patent information provided with this submission.

User Fee:
Following this letter is Form FDA 3397 and a copy of the check for the User Fee payment for this sNDA and a copy of the cover letter, which accompanied our payment. The User Fee Number assigned to this application is 4087.

Financial Disclosure:
In conformance with 21 CFR Parts 54.3 and 54.4, we certify the absence of financial interests by our clinical investigators for the covered clinical study SO14999. Form 3454 and a list of clinical investigators are enclosed.

Debarment Information:
In conformance with FD&C Act 306 (k)(l), the Sponsor hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Roche Contacts:
In order to facilitate the review, we encourage the Division to contact us to clarify any issues or address any questions. Please contact Murad Husain (973-235-4578) with any questions or issues.

The information contained in this New Drug Application is CONFIDENTIAL and should not be disclosed outside the Food and Drug Administration without the prior notification to, and written consent of Hoffmann-La Roche Inc.

If you have any question regarding this submission, please contact the undersigned at (973)235-4578.

Sincerely,

HOFFMANN-LA ROCHE INC.

Murad Husain
Program Director
Drug Regulatory Affairs
Phone: 973-235-4578
Fax: 973-562-3700

MH/emd

HLR No.: 2001-548

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-896

SEP 23 1999

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

Attention: Candice Shepherd, Pharm.D.
Program Director

Dear Dr. Shepherd:

Reference is made to your correspondence dated September 9, 1999, requesting a waiver for pediatric studies under 21 CFR 314.55(c).

We have reviewed the information you have submitted and agree that a waiver is justified for Xeloda for metastatic breast cancer and metastatic colorectal cancer for the pediatric population.

Accordingly, a waiver for pediatric studies for this application is granted under 21 CFR 314.55 at this time.

If you have any questions, please contact Maureen A. Pelosi, Project Manager at (301) 594-5778.

Sincerely yours,

/S/

9/23/99

Robert Justice, M.D.
Acting Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research