CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-896/S-006

CORRESPONDENCE

Roche

Pharmaceuticals

April 13, 2001

DUPLICATE

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:

SNC TO SGI-006

Re: NDA 20-896/S-006/ Xeloda® (capecitabine, Ro 09-1978) Tablets
General Correspondence: Rationale for Proposed Indication

Reference is made to the supplemental New Drug Application (S-006) to the NDA 20-896 which provided for a new indication of Xeloda (capecitabine) Tablets for first-line treatment of metastatic colorectal cancer. Reference is also made to the October 30, 2000 resubmission of the aforementioned sNDA in response to the Division's "approvable letter" dated September 20, 2000.

The purpose of this General Correspondence is to provide sponsor's rationale for proposed indication.

The sponsor would propose the following colorectal cancer indication for Xeloda as previously submitted to the agency as an appropriate option: "XELODA is indicated as first-line treatment of patients with metastatic colorectal carcinoma [redacted]" Another option would be the approved European indication, which reads as follows: "Xeloda is indicated for first line monotherapy of metastatic colorectal cancer ". This is based on the following rationale:

- Irinotecan in combination with 5-FU and leucovorin has demonstrated a survival advantage in the treatment of patients with metastatic colorectal carcinoma in the first line treatment setting. Combination therapy with irinotecan, 5-FU and leucovorin is one of the recognized standards of care in this setting [1], in addition to other fluoropyrimidine based regimes[2].
- Debate continues in the US oncology community regarding which patients should receive initial treatment with the combination of irinotecan, 5-FU and leucovorin, e.g. based on baseline characteristics[3].
- Tandem Anticancer Drug and Tumor Audit data, reveals that as of December 2000, approximately 53% of the patients in the US with colorectal cancer are treated with the combination of irinotecan with 5-FU and leucovorin, approximately 39% of the patients will be treated with single agent 5-FU or 5-FU plus leucovorin[4]. This data demonstrates that, despite the survival advantage of the combination of irinotecan, 5-FU and leucovorin, US oncologists do not consider the combination appropriate for all patients who are eligible to receive chemotherapy treatment. This may be based on combination of irinotecan, 5-FU and leucovorin causing grade 3 or 4 toxicity in 53-72% of patients, under lying co-morbid

illness, compromised performance status, patient preference, etc. The majority of patients in this group are currently receiving 5-FU based chemotherapy treatment, additional therapeutic options for this group of patients are needed.

- If the proposed label was to read "XELODA is indicated as first-line treatment of patients with metastatic colorectal carcinoma [redacted] this would be interpreted as meaning that XELODA is indicated as first-line treatment in [redacted] From the irinotecan US package insert "CAMPTOSAR Injection is contraindicated in patients with a known hypersensitivity to the drug.". The sponsor feels that this would not adequately reflect the current practice of oncology in the US nor would it fairly reflect the pending application. The decision by a medical oncologist to recommend to their patient, treatment with the combination of irinotecan, 5-FU and leucovorin or single agent Xeloda as a first line treatment of metastatic colorectal cancer is based on medical judgement. Use of the term [redacted]" would allow the treating oncologist, using their best medical judgement to determine which patients would most likely benefit from the combination of irinotecan, 5-FU and leucovorin and in which patients combination therapy would be medically inappropriate or contraindicated and thus other therapeutic options would be preferred. The clinician and the patient must consider the individual factors of efficacy, toxicity, the patients social situation, and quality of life to arrive at an appropriate therapeutic decision together.

The agency has requested that the following statement be included in the colorectal indication section of the package insert, '[redacted] In the absence of combination data with irinotecan, the sponsor proposes to add the following sentence '[redacted]!" to the precautions section of the package insert. As previously agreed, the sponsor will submit the Xeloda/irinotecan combination phase I clinical trial data to the agency when available.

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

Sincerely,

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

HLR No. 2001-911
Attachments

Dear Maureen,

As discussed with Dr. Allison Martin on April 6 and with you yesterday (April 12), attached is an electronic copy of a General Correspondence to the colorectal sNDA. This letter provides our rationale for the proposed CRC indication. I have included 3 out of 4 the references used in support of the letter. We are sending the same in the mail as well.

As you know, I will be on vacation next week. In case you need something please contact Heather at 973-235-5785.

Happy Easter!

Best regards,

Mayer, R., Moving Beyond Fluorouracil for Colorectal Cancer, The New England Journal of Medicine, Vol. 343, No. 13, 2000, pp. 963-4.

[1] Mayer, NEJM 343 No.13 2000, 963-4
[2] ODAC, March 16, 2000
[3] Knight R et al. First-Line Irinotecan (C), Fluorouracil (F), Leucovorin (L) Especially Improves Survival (OS) in Metastatic Colorectal Cancer (MCRC) Patients (PT) with Favorable Prognostic Indicators. Proc AM Soc Clin Oncol 2000;19 255a (991)

[4] Tandem Anticancer Drug and Tumor Audit Data (see appendix)

Publication Year: 2000

991

First-Line Irinotecan (C), Fluorouracil (F), Leucovorin (L) Especially Improves Survival (OS) in Metastatic Colorectal Cancer (MCRC) Patients (PT) with Favorable Prognostic Indicators. *Robert D Knight, Langdon L Miller, Nicoletta Pirotta, Gary L Elfring, Paula K Locker, Leonard B Saltz, Pharmacia & Upjohn, Peapack, NJ; Memorial Sloan-Kettering Cancer Ctr, New York, NY.*

A randomized, phase III trial (Proc ASCO 1999; 18:223a) of CFL (C125, F500, L20 mg/m^2 wkly x 4 q 6 wk [N=231]) vs FL (F425, L20 mg/m^2 qd x 5 q 4 wk [N=226]) showed that CFL improves response rate (50.2% vs 27.9%, p<.0001) and time to tumor progression (TTP, median 7.0 vs 4.3 mo, p=.004) with a trend for better OS (median 14.5 vs 12.6 mo, p=.097). We report a preplanned analysis of efficacy adjusted for pt characteristics. The major factors retained at p<.05 in the Cox model for better TTP and OS were normal LDH and performance status (PS)=0 (see below); normal bilirubin, WBC, and hemoglobin; and 1 organ site involved. There was an LDH/treatment interaction; CFL pts with normal LDH had more prolonged TTP and an exceptional median 10-mo OS improvement over FL pts (26.4 vs 16.2 mo)(see below). CFL patients with PS=0 also had improved OS. {Table} First-line CFL has greater antitumor activity than FL. MCRC pts with favorable prognostic indicators particularly derive survival benefit from the addition of C to FL, a result that has positive implications for study of CFL in the adjuvant setting.

Initial Model		TTP				OS		
Factor	HR	95%CI	P		HR	95%CI	P	
LDH=normal	.60	47-.76	.0001		.48	.37-.62	.0001	
PS=0	.74	59-.93	.0001		.58	.45-.73	.0001	
CFL vs FL	.67	51-.79	.0001		.83	.67-1.04	.1049	
Interaction Model		TTP	(mo)			OS	(mo)	
LDH Value	CFL	FL	HR	P	CFL	FL	HR	P
Normal	9.3	4.7	.46	<.001	26.4	16.2	.58	.007
Abnormal	5.6	3.7	.72	.023	10.7	10.4	.95	.692

04/12/2001

DRUG COMBINATIONS* USED WITH 1ST LINE STAGE D COLORECTAL CANCER PATIENTS

Projected Data

Dec '99 - Jan '01

	Dec '99 Feb '00	Jan '00 Mar '00	Feb '00 Apr '00	Mar '00 May '00	Apr '00 Jun '00	May '00 Jul '00	Jun '00 Aug '00	Jul '00 Sep '00	Aug '00 Oct '00	Sep '00 Nov '00	Oct '00 Dec '00	Nov '00 Jan '01
Base, Patient Records	(133)	(156)	(155)	(152)	(136)	(126)	(128)	(140)	(146)	(143)	(127)	(137)
Avg Monthly Patients	17,700	19,200	19,800	17,700	17,100	16,000	17,100	18,400	20,400	21,200	19,200	19,100
Drugs Utilized	*(%)*	*(%)*	*(%)*	*(%)*	*(%)*	*(%)*	*(%)*	*(%)*	*(%)*	*(%)*	*(%)*	*(%)*
5FU/Leucovorin	68	66	59	52	51	53	51	42	41	38	36	31
5FU/Irino/Leuco	16	15	22	29	32	31	33	39	40	43	47	53
Irinotecan Alone	8	7	4	1	3	6	5	5	5	6	8	8
5FU Alone	6	5	5	6	7	6	4	6	6	6	4	3
5FU/Leuco/Trimetrexate	1	1	3	2	2	1	1	1	1	-	-	1
Capecitabine Alone	-	1	1	2	1	2	2	2	1	1	-	1
5FU/Leucovorin/Oxaliplatin	1	1	1	1	1	1	1	1	1	1	2	1

Major Mentions

* **Drugs used in combination with or without CSFs, Erythropoietin, Means and Protectants**

*** **Less than 0.5 percent**

Source: Tandem Anticancer Drug and Tumor Audit

DRUG COMBINATIONS* USED WITH 2ND LINE STAGE D COLORECTAL CANCER PATIENTS

Projected Data

Dec '99 - Jan '01

	Dec '99 Feb '00	Jan '00 Mar '00	Feb '00 Apr '00	Mar '00 May '00	Apr '00 Jun '00	May '00 Jul '00	Jun '00 Aug '00	Jul '00 Sep '00	Aug '00 Oct '00	Sep '00 Nov '00	Oct '00 Dec '00	Nov '00 Jan '01
Base, Patient Records	(105)	(96)	(90)	(87)	(87)	(84)	(82)	(73)	(71)	(78)	(91)	(83)
Avg Monthly Patients	13,000	11,600	10,800	10,200	10,100	9,700	9,100	8,400	9,100	10,900	11,700	10,500
Drugs Utilized	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Irinotecan Alone	66	66	66	60	60	51	50	42	48	45	46	38
5FU/Irino/Leuco	10	14	15	19	17	25	21	28	23	30	28	32
5FU/Leucovorin	14	13	8	6	5	10	9	11	8	6	6	9
Capecitabine Alone	2	2	1	2	3	5	7	8	8	5	4	3
5FU Alone	3	1	1	1	1	1	2	3	3	5	7	6
5FU/Leucovorin/Oxaliplatin	-	-	-	-	-	-	-	-	3	3	3	3
5FU/Leuco/Mitomycin	1	-	2	2	1	2	1	1	2	2	2	2
Gemcitabine Alone	2	-	-	-	-	1	1	1	-	-	-	-
Mitomycin Alone	1	1	3	3	2	1	1	1	1	1	1	1
5FU/Cisplatin	1	-	-	-	-	-	2	2	2	-	-	-
5FU/Irinotecan	1	1	1	1	1	1	2	2	2	1	1	1

Major Mentions

* Drugs used in combination with or without CSFs, Erythropoietin, Mesna and Protectants

*** Less than 0.5 percent

Source: Tandem Anticancer Drug and Tumor Audit

Electronic Mail Message

Date: 4/5/01 6:39:57 PM
From: Husain, Murad PDR~Nutley (MURAD.HUSAIN@ROCHE.COM)
To: 'Dotti Pease 301-594-5742 FAX 301-5 (PEASE@A1)
To: Husain, Murad PDR~Nutley (MURAD.HUSAIN@ROCHE.COM)
Cc: Maureen Pelosi (PELOSIM@A1)
Subject: Re: Questions from Medical reviewer on 20-896/S006 (colo-rectal)

Dear Dotti and Maureen,

Analysis of all grade 3/4 related and unrelated toxicity is in the Colorectal sNDA,ISS, Volume 33, page 91, Section 5.3.3.4. and Appendix 15; and in 4-month Safety Update (dated 1/21/2000), Volume 1, page 273, Section 4.6.3.2. and Appendix 22.

Analysis of all treatment-related and -unrelated deaths (on study and within 28 days of last dose) is in the Colorectal sNDA,ISS, Volume 33, pages 109-111, Section 5.4 and Table 39, followed by narratives for treatment-related deaths. This was also provided in 4-month Safety Update, Volume 1, pages 274-276, Section 4.7.2. and Table 38.

Analysis of all treatment-related and -unrelated serious adverse events in the Colorectal sNDA, ISS, Volume 33, page 119, Section 5.4.2.3 and Appendix 42; and in 4-Month Safety Update, Volume 1, page 278.

Number of premature withdrawal due to treatment-related AEs is in the Colorectal sNDA, ISS, Volume 33, page 125, Section 5.4.4. and Appendix 45; and in 4-Month Safety Update, Volume 1, pages 278-279 and Appendix 25. A patient listing of AEs leading to withdrawals is in Appendix 26.

Please call me (973-235-5678) or send e-mail if you have additional question.

Regards,
Murad

-----Original Message-----
From: Dotti Pease 301-594-5742 FAX 301-594-0498
[mailto:PEASE@cder.fda.gov <mailto:PEASE@cder.fda.gov>]
Sent: Thursday, April 05, 2001 1:09 PM
To: murad.husain@ROCHE.COM
Cc: Maureen Pelosi
Subject: Questions from Medical reviewer on 20-896/S006 (colo-rectal)
Sensitivity: Confidential

Please see questions below. I will fax also.

Analyses of the clinical safety database are sometimes based on analyses

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301)594-5742 FAX: (301) 594-0498

TO: Murad Husain, Roche
Fax: 973 562-3700/3554

FROM: Dotti Pease, for Maureen Pelosi
Phone: (301) 594-5742

Total number of pages, including cover sheet 2

Date: 4-5-01

COMMENTS: Re: your pending efficacy supplement 20-896/S006 (colorectal cancer), Please see questions below from our medical reviewer.

Analyses of the clinical safety database are sometimes based on analyses of treatment-related toxicities and sometimes on all toxicities regardless of attribution. For completeness and to allow assessment of degree of consistency of analyses, we request the following tables:

Table 4, volume 44.2, currently displays analyses of the overall clinical safety data based on toxicities considered related to treatment however displays treatment withdrawals based on data related and unrelated to treatment. Please provide analyses based on number of all patients with grade 3/4 toxicity, serious

events and deaths on study or within 28 days regardless of attribution.

Table 7, volume 44.2, displays analyses of the phase 3 colorectal data based on treatment-related events regardless of attribution, except in the case of serious events and withdrawals. Please provide analyses on number of patients with grade 3/4 toxicity regardless of attribution, serious events considered related to treatment and number of patients with related events leading to treatment discontinuation. Please also include number of patients with related deaths as well as all deaths on study or within 28 days of treatment.

APPEARS THIS WAY
ON ORIGINAL

. DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-896/S-006

11-4-00

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

Attention: Murad Husain
Program Director

Dear Mr. Husain:

We acknowledge receipt on October 31, 2000 of your October 30, 2000 resubmission to your supplemental new drug application for Xeloda (capecitabine) Tablets.

This resubmission contains the final study report and data for WP15811, revised labeling, and Phase 4 commitments in response to our September 20, 2000 action letter.

With this amendment, we have received a complete response to our September 20, 2000 action letter.

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). If the application is filed, the user fee goal date will be April 30, 2001.

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) 594-5768.

Sincerely,

/S/

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

Roche

Pharmaceuticals

November 2000

Dear Doctor,

Roche Laboratories would like to inform you of important safety-related changes to the prescribing information concerning the use of Xeloda® (capecitabine) in patients with renal impairment at baseline. A copy of the complete revised labeling is included with this letter.

A recently completed clinical pharmacology study evaluated the effects of renal impairment in patients with cancer on the pharmacokinetics of Xeloda. Based on this study and a subsequent safety analysis of the clinical database, the Xeloda labeling has been revised to contraindicate the use of Xeloda in patients with severe renal impairment (calculated creatinine clearance below 30 mL/min). In addition, for patients with moderate renal impairment (calculated creatinine clearance 30-50 mL/min) at baseline, the starting dose of Xeloda should be reduced to 75% of the recommended starting dose (i.e., from 2500 mg/m²/day for 14 days followed by a week rest to 1900 mg/m²/day for 14 days followed by a week rest). Patients with mild renal impairment should be treated with the standard recommended dose of Xeloda with close monitoring. The creatinine clearance was calculated according to the formula of Cockroft and Gault in the majority of patients, and not measured via a 24-hour urine collection.

The analyses of clinical pharmacology study and overall clinical safety data indicated that:

- Patients with severe renal impairment (calculated CrCl <30 mL/min) had a high rate of grade 3-4 and serious adverse events and shorter treatment duration.
- Patients with moderate renal impairment (calculated CrCl 30-50 mL/min) had a greater overall incidence of treatment-related grade 3-4 and serious adverse events relative to patients with normal renal function. The increased incidence of undesirable effects did not impact negatively on the overall benefit for these patients when treated with Xeloda since the tumor response rate was maintained.
- Patients with mild renal impairment (calculated CrCl 51-80 mL/min), although experiencing slightly more serious adverse events and withdrawals due to adverse events than the patients with normal renal function, maintained their overall benefit/risk ratio.

The following lists the labeling changes.

CONTRAINDICATIONS:

Xeloda is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min [Cockroft and Gault]).

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

WARNINGS:

Renal Insufficiency: In patients with moderate renal impairment (creatinine clearance 30-50 mL/min [Cockroft and Gault]) at baseline, a dose reduction to 75% of the Xeloda starting dose is recommended. In patients with mild renal impairment (creatinine clearance 51-80 mL/min) no adjustment in starting dose is recommended. Careful monitoring and prompt treatment interruption is recommended if the patient develops a grade 2, 3, or 4 adverse event with subsequent dose adjustments as outlined in the table in DOSAGE AND ADMINISTRATION.

DOSAGE AND ADMINISTRATION/*Adjustment of Starting Dose in Special Population/ Renal Impairment:*

In patients with moderate renal impairment (creatinine clearance 30-50 mL/min [Cockroft and Gault, as shown below]) at baseline, a dose reduction to 75% of the Xeloda starting dose (from 2500 mg/m^2/day to 1900 mg/m^2/day) is recommended. In patients with mild renal impairment (creatinine clearance 51-80 mL/min) no adjustment in starting dose is recommended. Careful monitoring and prompt treatment interruption is recommended if the patient develops a grade 2, 3, or 4 adverse event with subsequent dose adjustments as outlined in the table in DOSAGE AND ADMINISTRATION. Xeloda is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min [Cockroft and Gault]).

Cockroft and Gault Equation:

$$\text{Creatinine clearance for males} = \frac{(140 - \text{age [yrs]})\ (\text{body wt [kg]})}{(72)\ (\text{serum creatinine [mg/dL]})}$$

Creatinine clearance for females = 0.85 x male value

PATIENT PACKAGE INSERT/Who should not take Xeloda:

- Patients with severe renal impairment. Please inform your doctor if you know of any renal impairment that you may have. Your doctor may either prescribe a different drug or reduce the Xeloda dose.

Please see the accompanying full prescribing information.

Roche Laboratories is committed to providing you with the most up-to-date and accurate information regarding its products. Should you have any questions or require additional information, please contact Roche Professional Product Information at 1-800-526-6367.

Sincerely,

Ted P. Szatrowski

Ted P. Szatrowski, M.D.
Medical Director

ORIGINAL

Roche

Pharmaceuticals

October 30, 2000

Food and Drug Administration
Division of Oncology Drug Products, HFD-150
Office of Drug Evaluation 1
Center for Drug Evaluation and Research
1451 Rockville Pike, Woodmont II Building
Rockville, MD 20852

Ladies and Gentleman:

NDA SUPP AMEND
SE1-006
AZ

Re: **NDA 20-896/S-006, Xeloda® (capecitabine) Tablets**
Amendment: Response to the FDA's Approvable Letter Dated September 20, 2000

Reference is made to our supplemental New Drug Application (S-006) of September 20, 1999 to the NDA 20-896 providing for a new indication of Xeloda for first-line treatment of patients with metastatic colorectal cancer. Reference is also made to the Division's "approvable" letter dated September 20, 2000.

The following are our responses to the Division's conditions for approval.

1. **Provide the final study report, individual patient data, and statistical analysis for the completed study, WP15811 (Effect of Renal Impairment on the Pharmacokinetics of Capecitabine in Cancer Patients). We note that your September 13 and 14, 2000 amendments stated that your preliminary assessment is that contraindications and dose modifications will be necessary in some groups of patients with renal impairment. Please finalize and submit these recommendations to the NDA, accompanied by data sufficient to allow the Agency to confirm the advice.**

Response

The final study report, including individual patient data and statistical analysis for study WP15811 has been submitted to the NDA 20-896 on October 23, 2000, under a "*Supplement – Changes Being Effected*". The supplement provides for revisions to the currently approved Xeloda labeling contraindicating Xeloda in patients with severe renal impairment and recommending dose reduction in patients with moderate renal impairment. This was done in consultation with the Division with an intention to inform the medical community of this new significant safety information, as soon as possible. A draft "Dear Doctor" letter has also been included in the supplement for Division's review, which Roche intends to disseminate to the prescribing physicians upon approval of the supplement.

For your convenience, an identical copy of the set of documents submitted in support of the labeling revisions in the "*Supplement – Changes Being Effected*" submitted on October 23 (volumes 2 to 8), is also provided with this submission. This includes:

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

a. *Rationale for Dose Reduction and Contraindication in Patients with Renal Impairment at Baseline for Xeloda*: This is based on the results from WP15811 and an analysis of the clinical safety database (renal impairment study and six phase II and III breast and colorectal cancer studies) with regard to the impact of creatinine clearance at baseline on the safety profile. This also includes a multivariate analysis of the impact of age and renal function on the safety profile. A disk containing the corresponding data-set is included.

b. Final Study Report for WP15811 (*Effect of Renal Impairment on the Pharmacokinetics of capecitabine in Cancer Patients*), including a disk containing the corresponding PK dataset.

c. *Evaluation of Age and Creatinine Clearance as Covariates in Population Pharmacokinetic Analysis of Capecitabine and its Metabolites*: An analysis of population PK data from two phase III colorectal cancer studies to further evaluate the influence age and creatinine clearance on the Pharmacokinetics of FBAL, one of the main metabolites of capecitabine.

In summary, the small number of patients in the clinical pharmacology study WP15811 does not allow final conclusions for dosing recommendations for patients with mild to moderate renal impairment. Although safety concerns in four (4) patients with severe renal impairment at baseline justifies the recommendation for a contraindication for Xeloda in such patients; this also lead us to analyze the clinical safety database (N = 875 patients from phase II and III breast and colorectal cancer clinical studies) to evaluate the impact of renal impairment at baseline on the safety of patients treated with Xeloda. Based on the analyses of clinical pharmacology study (WP15811) and the clinical safety database, we have proposed in the aforementioned supplement that,

- Patients with severe renal impairment (creatinine clearance < 30 mL/min [Cockroft and Gault]) should not be treated with Xeloda because of unacceptable high rates of grade 4 AEs and of serious AEs.
- Patients with moderate renal impairment (creatinine clearance 30 – 50 mL/min [Cockroft and Gault]) should be treated with a reduced dose of Xeloda (75% of the standard recommended starting dose) to address their greater overall incidence of treatment related grade 3-4 AEs and SAEs relative to patients with normal renal function. The increased incidence of undesirable effects in this group of patients did not impact negatively on the overall benefit.
- Patients with mild renal impairment (creatinine clearance 51-80 mL/min [Cockroft and Gault]) should be treated with standard recommended dose of Xeloda. Although these patients have slightly more SAEs and withdrawals due to AEs than do patients with normal renal function, their overall benefit/risk ratio is maintained.

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

If you have any question regarding this submission, please do not hesitate to call the undersigned.

Sincerely,

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

Desk-copy: Maureen Pelosi, Senior Project Manager

Attachments
HLR No.: 2000-2692

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Cindy Dinella	From: Maureen Pelosi
Fax: **973-562-3700**	Fax: 301-827-4590
Phone: 973-562-3675	Phone: 301-594-5778
Pages, including cover sheet: 2	Date: 15 SEP 00
Re: Xeloda Renal Impairment Clarification	

● Dear Cindy,

Murad is out of the office today and we hope that you might be able to help us. We have a question on the 9/13/00 Renal Impairment document.

On page 6 (attached) Table 2 for Xeloda – are the figures for Xeloda creatinine clearance baselines? If not what do they represent, worse case senario?

Thanks,

/S/

Maureen Pelosi

PRIORITY

Electronic Mail Message

Date: 9/13/00 10:40:54 AM
From: Maureen Pelosi (PELOSIM)
To: Murad Husain (MURAD.HUSAIN@ROCHE.COM)
Subject: Renal Impairment Study WP15811

Murad,

The submission on renal impairment is a preliminary report and contains no individual patient data. With only an interim report we are unable to validate the proposed dosing modifications. When was Study WP15811 completed (we could not find this information in the submission, nor the accrual completion date).

Your submission states that the report will be submitted as a labeling supplement later this year. That is too late to address these significant findings.

Please provide the complete final study report including the raw data and statistical analysis. If you do not have this information, would you explain why not and when it will be available?

Thank you,
Maureen

September 13, 2000

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/S-006/ FDA's E-mails of September 13, 2000
Xeloda (capecitabine, Ro09-1978) Tablets
Renal Impairment Study (WP15811) and Dosing Recommendations

Reference is made to the FDA's two e-mails dated September 13, 2000, requesting (i) the basis of dose adjustment of capecitabine in patients with renal impairment as indicated in our submission Serial No. 307 to the IND( ) and (ii) the status of the Study WP15811 (Effect of Renal Impairment of the Pharmacokinetics of capecitabine in Cancer Patients).

The recommendations for dose reductions and contraindication of Xeloda in patients with renal impairment are based on two sources of information. Clinical safety data of the four groups of patients (according to the degree of renal impairment) in the pharmacology study WP15811 does not allow firm conclusions to be drawn, particularly for patients with mild to moderate renal impairment. This lead us to analyze clinical safety database of two Phase III trials in patients with metastatic colorectal cancer (SO14695 and SO14796) with regard to the effect of creatinine clearance on the safety profile. The analysis of the two data-sets (study WP15811 and the phase III colorectal safety database) indicate that:

- Xeloda should be contra-indicated in patients with severe renal impairment (creatinine clearance below 30 mL/min [Cockroft and Gault]).
- In patients with moderate renal impairment, a dose reduction to 75% of the starting dose of 1250 mg/sqm BID (2500 mg/sqm/day) is recommended.
- No adjustment to the starting dose of Xeloda in patients with mild renal impairment (creatinine clearance 50-80 mL/min) is recommended.

Essential information / background for the dosing recommendations based in the two sources of information is provided as an attachment, as requested.

Regarding the status of the Study WP15811, the last patient completed the study on May 10, 2000 and the clinical database was closed on July 19, 2000, and the PK analysis was completed on August 31, 2000. We will have an abbreviated report (including the text summary, individual data listings and statistical analysis of PK data), in three to four weeks from now.

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

Sincerely,

Murad Husain
Program Director
Regulatory Affairs

Attachment

Desk-copy: Maureen Pelosi, Senior Project Manager

HLR No.: HLR-2000-2281

Electronic Mail Message

Date: 9/11/00 4:07:11 PM
From: Maureen Pelosi (PELOSIM)
To: Murad Husain (MURAD.HUSAIN@ROCHE.COM)
Subject: Xeloda Label Update - Pharm/Tox Review

Dear Murad,

The statistician, Pharm/Tox reviewer, and executive CAC all have determined that doses in the mouse carcinogenicity study were too low to establish absence of carcinogenicity. Thus the study is inadequate to support a label claim.

Now that the Pharm/Tox reviewer has completed his draft review, we recommend that the first paragraph under the section Carcinogenesis, Mutagenesis, and Impairment of Fertility should read as follows:

Carcinogenesis, Mutagenesis and Impairment of Fertility: Capecitabine was not mutagenic in vitro to bacteria (Ames test) or mammalian cells (Chinese hamster V79/HPRT gene mutation assay). Capecitabine was clastogenic in vitro to human peripheral blood lymphocytes but not clastogenic in vivo to mouse bone marrow (micronucleus test). Fluorouracil causes mutations in bacteria and yeast. Fluorouracil also causes chromosomal abnormalities in the mouse micronucleus test in vivo.

Regards, Maureen

Electronic Mail Message

Date: 8/30/00 11:01:08 AM
From: Husain, Murad PDRG-Nutley (MURAD.HUSAIN@ROCHE.COM)
To: 'Maureen Pelosi 301-594-2473 FAX 30 (PELOSIM@A1)
Subject: Re: Xeloda - exclusivity

Maureen,

You are right. We did not request any exclusivity. However, we are preparing one for clinical data exclusivity. It will be filed within next week. Hope this is not too late. Please let me know.

Best regards,
Murad

> ----Original Message-----
> From: Maureen Pelosi 301-594-2473 FAX 301-594-0498
> [SMTP:PELOSIM@cder.fda.gov]
> Sent: Wednesday, August 30, 2000 9:49 AM
> To: Murad Husain
> Subject: Xeloda - exclusivity
> Sensitivity: Confidential

> Murad,
>
> I am filling out the Exclusivity Document that goes with my Action
> Package. It asked "did the sponsor request any exclusivity" and if so,
> "how many years were requested".
>
> I flipped through the desk copies I have and did not find any mention of
> exclusivity. Was anything requested?
>
> Thanks for your help,
> Maureen
>

Fax Cover Sheet

Roche

Pharmaceuticals

To: Maureen Pelosi
Sr. Project Mgr., FDA
Division of Oncology
Drug Products
Fax 301-827-4590

From: Elisa Scordato Mandra
Hoffmann-La Roche Inc
DRA, Bldg 1/2
Tel. (973) 562-3683
Fax (973) 562-3554

Date: August 29, 2000

No. of pages: 3 (incl. coversheet)

RE: Race/Ethnicity Terminology

As requested, see attached terminology from the American Medical Association Manual of Style, 9th edition. pp. 267-268

Regards,

Elisa

Elisa Scordato Mandra
Associate, Labeling Management
and Reporting Group
Drug Regulatory Affairs (PDR)
Tel. +973-562-3683
Fax +973-562-3554/3700

[illegible]house (kăt'hous') n. *Slang.* A house of prostitution.
cat·i·on (kăt'ī'ən) n. [Gk. *kation*, (a thing) going down : *kata-*, [illegible] + *ienai*, to go.] A positively charged ion that in an electrolyte [illegible] toward a negative electrode. —**cat'i·on'ic** (kăt'ī-ŏn'ĭk) *adj.*
cation exchange n. A chemical process used in water softening [illegible] cations of like charge are exchanged equally between a [illegible] zeolite, and a solution, as water.
cat·kin (kăt'kĭn') n. [< obs. Du. *katteken*, dim. of *katte*, cat (from [illegible] resemblance to a cat's tail).] *Bot.* A dense, often drooping flower [illegible] as that of a birch, composed of small scalelike flowers.
cat·like (kăt'lĭk') *adj.* Like a cat : STEALTHY <walked with *catlike* [illegible]>
cat·nap (kăt'năp') n. A short nap. —**cat'nap'** v. (-**napped**, -**nap·ping**).
cat·nip (kăt'nĭp') n. A hairy aromatic plant native to Eurasia, [illegible] *cataria* to which cats are strongly attracted.
cat-o'-nine-tails (kăt'ə-nīn'tālz') n. [So called because it leaves [illegible] like the scratches of a cat.] A whip having nine knotted cords [illegible] to a handle.
ca·top·tric (kə-tŏp'trĭk) *also* **ca·top·tri·cal** (-trĭ-kəl) *adj.* [Gk. *katoptrikos* < *katoptron*, mirror.] Of or relating to mirrors and re[illegible] images. —**ca·top'trics** n.
cat rig n. *Naut.* The rig of a catboat.
CAT scan n. A cross-sectional picture produced by a CAT scanner.
CAT scanner n. A device that produces cross-sectional x-rays of [illegible] body using computerized axial tomography.
CAT scanning n. The act or process of using a CAT scanner.
cat's cradle n. 1. A child's game in which an intricately looped [illegible] is transferred from the hands of one player to the next, result[illegible] succession of different loop patterns. 2. Something likened to [illegible] cradle <*a cat's cradle of intrigues*>
cat-scratch disease *or* **cat scratch fever** n. A disease in [illegible] marked by fever and lymphadenitis and believed to be trans[illegible] by cats.
cat's-eye (kăts'ī') n. 1. Any of various semiprecious gems display[illegible] band of reflected light that shifts position as the gem is turned. [illegible] reflector attached to the back of a vehicle to indicate its [illegible] on the road at night. 3. A marble with eyelike circles.
cat's-paw *also* **cats·paw** (kăts'pô') n. [From a fable about a mon[illegible] used a cat's paw to pull chestnuts out of a fire.] 1. One used [illegible] as a dupe or tool. 2. A light breeze that ruffles small areas [illegible] surface. 3. *Naut.* A hitch in the bight of a rope, on which [illegible] is hooked.
cat·sup (kăt'səp, kăch'əp, kĕch'-) n. *var. of* KETCHUP.
cat·tail (kăt'tāl') n. A marsh plant of the genus *Typha*, esp. *T. lati*[illegible] having long, straplike leaves and a dense cylindrical head of [illegible] brown flowers.
cat·tie (kăt'ē) n. *var. of* CATTY[1].
cat·tle (kăt'l) pl.n. [ME *catel*, livestock, property < Norman Fr. < [illegible] *capitale*, property < Lat. *capitalis*, principal. —see CAPI[illegible]] 1. Animals of the genus *Bos*, esp. those of the domesticated [illegible] *taurus*, raised in many breeds for dairy products and meat. [illegible] beings, esp. when regarded as an unthinking mob.
[illegible] history: *Cattle* and *chattel* are doublets from medieval [illegible] derived from Latin *capitale*, which is also the ancestor [illegible] capital. All three words *refer* to wealth in one form or [illegible] *Cattle* is derived from Norman French *catel* and in medi[illegible] meant "movable property" in general. The word became [illegible] in this sense because livestock was such an important form [illegible]. The further narrowing of *cattle* to refer only to bovine [illegible] occurred in the 19th century. *Chattel* represents the central [illegible] *chatel*. It was adopted in medieval England as a legal [illegible] "movable property," supplanting *cattle*. *Capital*[1] was also [illegible] French in medieval times; it represents not the regu[illegible] development of Latin *capitale* but instead a French rebor[illegible] Latin word. Its original use in English was as an [illegible] meaning "relating to the head" and later meaning [illegible] chief." *Capital*[1] came to denote "wealth" by its use [illegible] a principal substance or property.
cat·tle·man (kăt'l-mən, -măn') n. One who raises or tends cattle.
[illegible] An electrified prod for controlling cattle.
cat·tle·ya ([illegible]lē-ə) n. [NLat. *Cattleya*, genus name, after William [illegible]] An orchid of the genus *Cattleya*, with large rose[illegible] flowers.
cat·ty[1] (kăt'ē) n., pl. -**ties**. [Malay *kati*.] An Asian [illegible] equivalent to 1½ pounds avoirdupois.
cat·ty[2] [illegible] -**ti·er**, -**ti·est**. 1. Catlike. 2. Subtly cruel or mali[illegible] <catty remarks> —**cat'ti·ly** adv. —**cat'ti·ness** n.
cat·ty-cor·nered (kăt'ē-kôr'nərd) *adj.* & *adv.* *var. of* CATER[illegible]
cat·walk [illegible] n. A narrow platform or pathway, as on the [illegible]
Cau·ca·sian (kô-kā'zhən, -kăzh'ən) n. [After the Caucasus, a [illegible] the Soviet Union.] 1. A native or resident of the Caucasus. 2. A member of the Caucasoid ethnic division. —*adj.* 1. Of or relating to the Caucasus region, its people, or their culture. 2. Caucasoid.
Cau·ca·soid (kô'kə-soid') *adj.* 1. Of, relating to, or designating a major ethnic division of the human species having certain distinctive physical characteristics such as skin color varying from very light to brown and fine hair ranging from straight to wavy or curly and regarded as including groups of peoples indigenous to or inhabiting Europe, northern Africa, southwestern Asia, and the Indian subcontinent and persons of this ancestry in other parts of the world. 2. Of, relating to, or typical of Caucasoids. —n. A member of the Caucasoid ethnic division.
cau·cus (kô'kəs) n., pl. -**cus·es** or -**cus·ses**. [Poss. of Algonquian orig.] 1. A closed meeting of the members of a political party to make policy decisions and select candidates for office. 2. *Chiefly Brit.* A committee within a political party charged with setting policy. —vi. -**cused**, -**cus·ing**, -**cus·es** or -**cussed**, -**cus·sing**, -**cus·ses**. To assemble in or hold a caucus.
cau·dad (kô'dăd') *adv.* [Lat. *cauda*, tail + -AD.] *Anat.* Toward the tail or posterior part of the body.
cau·dal (kôd'l) *adj.* [NLat. *caudalis* < Lat. *cauda*, tail.] 1. *Anat.* Of, at, or near the tail or hind parts : POSTERIOR. 2. *Zool.* Taillike. —**cau'dal·ly** *adv.*
caudal fin n. The tail fin of a fish.
cau·date (kô'dāt') *also* **cau·dat·ed** (-dā'tĭd) *adj.* [NLat. *caudatus* < Lat. *cauda*, tail.] Having a tail. —**cau·da'tion** n.
caudate nucleus n. A large ganglion in the lateral ventricle of the brain that functions in motor control.
cau·dex (kô'dĕks') n., pl. -**di·ces** (-dĭ-sēz') or -**dex·es**. [Lat. *caudex*, *caudic-*, tree trunk.] 1. The thickened base of the stem of certain perennials. 2. A woody trunklike stem, as that of a tree fern.
cau·dil·lo (kou-thē'yō, -thē'yō) n., pl. -**llos**. [Sp., leader < LLat. *capitellum*, small head, dim. of Lat. *caput*, head.] A military dictator in Spanish-speaking countries.
cau·dle (kôd'l) n. [ME *caudel* < Norman Fr. < *chaud*, warm < Lat. *calidus*.] A warm beverage of wine or ale mixed with sugar, eggs, bread, and spices, given to sick people.
caught (kôt) v. p.t. & p.p. *of* CATCH.
caul (kôl) n. [ME *calle* < OE *cawl*, basket.] 1. A part of the membrane that surrounds a fetus and that occas. covers its head at birth. 2. The large omentum.
caul·dron (kôl'drən) n. *var. of* CALDRON.
cau·les·cent (kô-lĕs'ənt) *adj.* [Lat. *caulis*, stem + -ESCENT.] *Bot.* Having a stem showing above the ground.
cau·li·cle (kô'lĭ-kəl) n. [Lat. *cauliculus*, dim. of *caulis*, stem.] *Bot.* A small stem.
cau·li·flow·er (kô'lĭ-flou'ər, kŏl'ĭ-) n. [Prob. < Ital. *cavolofiore* : *cavolo*, cabbage (< LLat. *caulus* < Lat. *caulis*) + *fiore*, flower < Lat. *flos*.] 1. A plant, *Brassica oleracea botrytis*, related to the cabbage and broccoli and having an enlarged, edible flower head. 2. The compact whitish flower head of the cauliflower.
cauliflower ear n. An ear deformed by repeated blows.
cau·line (kô'lĭn') *adj.* [NLat. *caulinus* < Lat. *caulis*, stem.] *Bot.* Of, having, or growing on a stem.
caulk *also* **calk** (kôk) vt. **caulked**, **caulk·ing**, **caulks** *also* **calked**, **calk·ing**, **calks**. [OFr. *cauquer*, to press < Lat. *calcare*, to tread < *calx*, heel.] 1. To make (a boat) watertight by packing seams with oakum or tar. 2. To make (e.g., pipes) watertight or airtight by filling in cracks. —**caulk'er** n.
caus·al (kô'zəl) *adj.* 1. Relating to, involving, or being a cause <the *causal* factors of the recession> 2. Indicating or expressing a cause. 3. Originating from a cause. —n. A word or grammatical element expressing a cause or reason. —**caus'al·ly** *adv.*
cau·sal·i·ty (kô-zăl'ĭ-tē) n., pl. -**ties**. 1. The relationship between cause and effect. 2. A causal force, agency, or quality.
cau·sa·tion (kô-zā'shən) n. 1. The act or process of causing. 2. CAUSE 1a. 3. Causality.
caus·a·tive (kô'zə-tĭv) *adj.* 1. Functioning as an agent or cause. 2. Designating a verb or verbal affix that expresses causation. —**caus'a·tive** n. —**caus'a·tive·ly** *adv.*
cause (kôz) n. [ME < OFr. < Lat. *causa*, reason.] 1. a. Something that produces an effect, result, or consequence. b. The person, event, or state responsible for an action or result. 2. A basis for an action or decision : REASON. 3. A goal or principle served with dedication and zeal <"the *cause* of freedom versus tyranny" —Hannah Arendt> 4. The interests of a person or group engaged in a struggle. 5. *Law.* a. A ground for legal action. b. A lawsuit. 6. A subject under discussion or debate. —vt. **caused**, **caus·ing**, **caus·es**. To be the cause of. —**caus'a·ble** *adj.* —**cause'less** *adj.* —**caus'er** n.
✶ *syns:* CAUSE, ANTECEDENT, REASON n. core meaning : that which produces a result or effect <scientists studying the *cause* of sunspots> *ant:* effect
cause cé·lè·bre (kôz' sā-lĕb'rə) n., pl. **causes cé·lè·bres** (kôz' sā-lĕb'rə) [Fr. : *cause*, case + *célèbre*, celebrated.] 1. A notorious legal case. 2. A highly controversial issue.
cau·se·rie (kōz-rē') n. [Fr. < *causer*, to talk < Lat. *causari*, to discuss < *causa*, case.] 1. A chat. 2. A short, informal piece of writing.

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Murad Husain		Maureen Pelosi
Fax:	**973-562-3700**	Fax:	301-827-4590
Phone:	973-235-4578	Phone:	301-594-5778
Pages, including cover sheet:	1	Date:	07 AUG 00
Re:	Xeloda Request		

● Dear Murad,

We would appreciate an updated survival dataset if possible.

The 4-month safety update refers to survival data with a cutoff date of September 1999. However, the data was not on the disk accompanying the safety update.

Since almost a year has passed, we are wondering if more mature survival data is available for our review. If so, we would like the dataset.

Also, would you format the dataset as Tumasinv.sd2 as in the original NDA for both trials?

I am attending training tomorrow and Wednesday from 8-3:30 but will return to the office around 4 PM.

Regards,

/S/

Maureen A. Pelosi
Senior Regulatory Project Manager

Dear Maureen,

Attached is copy of the fax being sent to you in response to your June 26, 2000 fax regarding liver failure cases.

x Cover Murad to the FDA June 30.doc>>

Please do not hesitate to call me if you have any question regarding this.

Regards,
Murad Husain
Program Director
Regulatory Affairs

From: **Murad Husain,**
Program Director

Hoffmann-La Roche Inc.
Pharma Development Regulatory
Bldg. 1/2 floor
340 Kingsland Street
Nutley, NJ 07110-1199
Tel. 973-235-4578
Fax 973-562-3700/3554

Date: **June 30, 2000**

No. of pages: 2

Dear Maureen,

This is regarding your fax dated June 26, 2000. Please see below our responses to your questions.

1. The study types of the five liver failure reports listed in your fax are as follows.

Manufacturer Control Number	*Study Number**	*Study Type*	Sponsor
MCN 216670	[redacted]	Phase 3	Roche
MCN 207269	[redacted]	Phase 2	Roche
MCN 111552	[redacted]	Phase 3	Roche
MCN 220490	[redacted]	Phase 1	Roche
MCN 222798	[redacted]	Phase 3B	Roche

* M indicates marketing study

BEST POSSIBLE COPY

This ... case where we need sub... on ...

2. Upon review, it was confirmed that only one of the three liver failure cases referred to in the Post-marketing section of the proposed Xeloda package insert was a spontaneous report (see table below).

	Manufacturer Control Number	*Source / Study Number*	*Comments*
1.	*111552*	*Clinical Trial (____*	*Roche-sponsored study*
2.	*204490**	*Clinical Trial (____*	
3.	*201686*	*Spontaneous*	*The initial report was submitted to FDA on March 09, 1999 and follow-ups were submitted on April 30, 1999 and November 30, 1999.*

* MCN 204490 was received from ________ and originated in one of their expanded access program (Protocol ______) with trastuzumab. The report was received at Roche on March 1, 1999 and

... this is a report they ... receiving ... there is no need to ... submission ... what we need ... make very clear ... there was actually only one postmarketing report at the time the label was submitted.

entered in the Roche Drug Safety database (ADVENT) as an "administrative" case since it was thought to have been reported to FDA by ________. Therefore, Roche did not generate any submissions based on this MCN. However, this case was summarized in the Postmarketing Experience section of the Integrated Safety Summary of sNDA 006/NDA 20-896 (Vol 33, page 229-230). It has now been confirmed (on June 29, 2000) that ________ did not submit this case to the authorities since the investigator indicated that the events were not related to trastuzumab. In view of this information, Roche is preparing a MedWatch which will be submitted to the FDA in due course.

Please do not hesitate to call me if you have any questions regarding this.

Regards,

I've asked [redacted] Welwyn can have a MedWatch
available by end of day tomorrow for 204490. I
think it would probably be a good idea to
[redacted] response. See what team
[redacted] think, it's extremely important to
mention [redacted] case summary was included
in [redacted] case that will preclude any

Murad Husain
Program Director
Regulatory Affairs

Electronic Mail Message

Date: 6/30/00 8:27:30 AM
From: Husain, Murad PDRG~Nutley (MURAD.HUSAIN@ROCHE.COM)
To: 'Pelosi, Maureen' (Pelosim@A1)
Subject: Xeloda SNDA-006: Re. Your June 21 e-mail

Dear Maureen,

In reference to your e-mail and fax dated June 21, 2000 please note that the archival copy of the colorectal cancer SNDA contained the correct survival datasets for both studies. These files are titled as follows:

- (data cutoff September 1998)
- (data cutoff January 1999)

were provided for each study separately and for both studies integrated in one dataset. Please note that our survival analysis was based on these datasets, not on , an intermediate dataset created only on the fly by our reporting programs and was therefore added only as an example to facilitate re-analysis.

Please do not hesitate to call me if you have any question regarding s.

Regards,
Murad Husain
Program Director
Regulatory Affairs

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Murad Husain		Maureen Pelosi
Fax:	**973-562-3700**	Fax:	301-827-4590
Phone:	973-235-4578	Phone:	301-594-5778
Pages, including cover sheet:	1	Date:	26 JUN 00
Re:	Xeloda Decision Date		

● Dear Murad,

The Xeloda review team has requested that I inform you that issues regarding non-inferiority are being determined by the Division and Dr. Temple.

At this time, we expect that we will be unable to meet the July 20, 2000 deadline for a 10 month review.

Please phone me if I may of further assistance.

/S/

Maureen A. Pelosi
Senior Regulatory Project Manager

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Murad Husain		Maureen Pelosi
Fax:	**973-562-3700**	Fax:	301-827-4590
Phone:	973-235-4578	Phone:	301-594-5778
Pages, including cover sheet:	1	Date:	26 JUN 00

Re: Xeloda Questions

● Dear Murad,

Please see attached questions on Xeloda.

We have 5 study reports of liver failure with the manufacturer control Numbers that follow:

216670
207269
111552
220490
222798

1. What type of studies were these five reports from? Manufacturer sponsored studies vs. investigator sponsored studies, phase 3, etc.

2. Were the three liver failure cases referred to in the new Postmarketing section of the proposed capecitabine label spontaneous reports? Were they submitted to the FDA? What are the manufacturer control numbers for these 3 reports?

Regards,

Maureen A. Pelosi
Senior Regulatory Project Manager

CC: NDA 20-896 SE-1/006
HFD-150/DIV file

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Murad Husain		Maureen Pelosi
Fax:	**973-562-3700**	Fax:	301-827-4590
Phone:	973-235-4578	Phone:	301-594-5778
Pages, including cover sheet:	2	Date:	21 JUN 00

Re: Xeloda Questions

● Dear Murad,

Please see attached questions on Xeloda. These are identical to those sent earlier by Email, just in case you did not receive them.

Regards,

/S/

Maureen A. Pelosi
Senior Regulatory Project Manager

Please clarify the following issues:

1. Post-Study Chemotherapy, e.g., volume 50, page 71, Table 26, reference to approximately 60% of patients who received post-study chemotherapy on SO14695. Is information on post-study chemotherapy available on all patients on SO14695 and S014796 or is there missing data?

2. Please provide a listing of patients (ID #) and reason for being considered as "missing postbaseline information" when calculating response rate. We are not sure why this number is not the same as the number of patients excluded from the standard analysis. We are also interested in the reconciled assessment of response rate and which patients were excluded.

3. Please characterize the reasons why patients received less than 6 weeks of treatment or less than 50% of treatment during the first 6 weeks. Patient ID and reason for withdrawal from the CRF would suffice or sponsor's interpretation if identified as such.

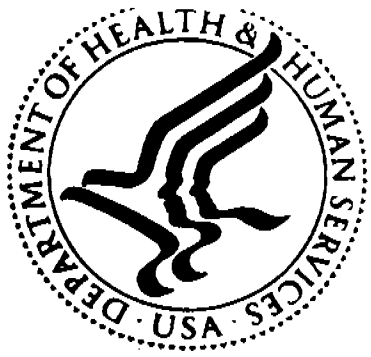
4. The protocol section "Concomitant Medication and Treatment" does not explicitly prohibit other anticancer therapy. The case report form did require listing of all medications. Were other anticancer agents (co-) administered while patients where on study? If so, which ones to which patients?

Did any patient receive radiotherapy while on study?

5. What were the malignancies (other than cured basal cell carcinoma of the skin and in situ carcinoma of the uterine cervix) that resulted in protocol violations? For instance, 11 patients on capecitabine and 7 patients on 5-FU/LV had violations of this eligibility criterion.

6. Why isn't the patient with a major protocol violation counted in the 5-FU/LV arm in your Table 17, volume 50, page 60?

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Murad Husain	Maureen Pelosi
Fax: **973-562-3700**	Fax: 301-827-4590
Phone: 973-235-4578	Phone: 301-594-5778
Pages, including cover sheet: 2	Date: 21 JUN 00
Re: Xeloda Survival Data Questions	

● Dear Murad,

Please see attached Email regarding significant missing data on survival.

Regards,

/S/

Maureen A. Pelosi
Senior Regulatory Project Manager

Electronic Mail Message

Date: 6/21/00 5:01:49 PM
From: Maureen Pelosi (PELOSIM)
To: Murad Husain (MURAD.HUSAIN@ROCHE.COM)
Subject: Xeloda data sets for survival

Dear Murad,

It is my understanding that we were not able to reproduce the survival results because the survival data for Study SO14796 was identical to that of Study S014695. We asked for the correct data for Study S014796.

Please verify that the original archival copy of the NDA contained the correct survival data for both studies.

If the archival copy is not correct, please send the corrected survival data as an amendment, not new correspondence and provide an archive copy in addition to the review copy we have already received. Your 6/16 title "request for additional data sets" is misleading.

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301)594-5742 FAX: (301) 594-0498

TO: Candice Shepherd, Roche 973 562-3695
Fax: 973 562-3554 or 3700

FROM: Dotti Pease, Project Manager
Phone: (301) 594-5742

Total number of pages, including cover sheet 1

Date: 6-13-00

COMMENTS: Re: your pending supplement for Xeloda for colon cancer, the statistician has the following request:

Because we are unable to reproduce your survival results for the NDA 20-896, we have examined the datasets submitted in the NDA and found that your survival data for Study SO14796 is the identical copy of the survival data set for Study SO14695. Please submit the right survival dataset for study SO14796 as soon as you can. The specific dataset name is: Because the short review time left, could you send that dataset via email to us at CHENGA@CDER.FDA.GOV as well as a diskette to the NDA by courier.

If possible, we would like to have this by Friday. Thanks
Dotti for Maureen

/S/

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Tom Watson	Maureen Pelosi
Fax: **973-562-3700**	Fax: 301-827-4590
Phone: 973-235-4578	Phone: 301-594-5778
Pages, including cover sheet: 1	Date: 04 – 05 – 00
Re: Xeloda	

● Dear Tom,

The clinical pharmacology/biopharm reviewer is searching for the SAS data files for report B-164837.

Please inform us where we might locate these files in the electronic reviewers aid. If not included, please provide the files on a disc/CD as a biopharm amendment to the NDA.

Regards,

/S/

Maureen A. Pelosi
Regulatory Project Manager

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Candice Shepherd	Maureen Pelosi
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Pages, including cover sheet: 2	Date: 1 – 10 – 00
Re: NDA 20-896 SE-1/006 BAYESIAN Teleconf.	

● Candice,

David Smith forwarded Uli's comments to Rich Simon. Attached is the reply we received from Dr. Simon. We may have to revisit the issues once more??

Regards,

/S/

Maureen A. Pelosi
Regulatory Project Manager

Dear David,

I've looked at the question you raised about the possibility that equation (5) in my paper contains a typo and I am sure that the equation is correct as published. I think, however, that Dr. Burger is miss-reading the equation. The equation gives an expression for the mean of the posterior distribution of the vector (beta, gamma). It does **not** indicate that the posterior distribution of gamma is normal with mean y+g' where " g' is a prior information for g". I'm not sure what Dr. Burger means by that statement. I repeat, equation (5) is an expression for the mean (eta_{beta}, eta_{gamma}) of the posterior distribution of (beta, gamma). The variances of the posterior distribution are obtained by inverting the symmetric Λ matrix where the components of this matrix are specified just above (5).

If you solve (5) explicitly in the special case where there is no prior information on gamma (i.e. $\sigma_{gamma} = \infty$), you get that eta_{gamma} equals y + the prior mean of beta. Note, I said the prior mean of beta. Even though the right hand side of the second equation of (5) does not have a term containing the prior mean of beta, the solution for eta_{gamma} does. If you invert the matrix Λ in this special case, you get that the variance of the posterior distribution of gamma is $\sigma^2 + \sigma^2_{beta}$. I had that result in the first two drafts of the manuscript submitted to Biometrics but they made me cut it to save space. Dr. Burger noticed, however, that it was part of my presentation to the ODAC a couple of weeks ago.

The general solution of (5) for the mean of the posterior distribution of gamma is num/denom where

$$num = w_b(y+\mu_b) + w_g(1+w_b/w)\mu_g$$

$$denom = w_b + w_g + w_b w_g/w$$

$$w = 1/\sigma^2, \quad w_b = 1/\sigma^2_{beta}, \quad w_g = 1/\sigma^2_{gamma}.$$

I hope that this clarifies things. Please don't hesitate to get back to me if it doesn't.

Rich Simon

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

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Pages, including cover sheet: 8	Date: 1 – 5 – 00
Re: NDA 20-896 SE-1/006 BAYESIAN Teleconf.	

- Candice,

Attached are the finalized 12/22 telecon minutes regarding the bayesian analysis for Xeloda.

Regards,

/S/

Maureen A. Pelosi
Regulatory Project Manager

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

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5600 Fishers Lane, Rockville, MD 20857

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Pages, including cover sheet: 2	Date: 12 – 22 - 99
Re: NDA 20-896 SE-1/006	

● Candice,

Attached is the table we promised to fax you

Regards,

Maureen Pelosi

UC

AUTHOR & CIT.	# OF PTS
Erlichman 1988 JCO	130
Poon 1989 JCO	140
Meta-Analysis** 1992 JCO	1381
Pallavincini 1993 J Chemo	150
Borner 1998 Ann Onc	309
Doroshow 1990 JCO	79
Labianca 1991 Ann Onc	182
DiCostanzo 1992 Ann Onc	181
Leichman 1995 JCO	174

FOOD AND DRUG ADMINISTRATION
OFFICE OF DRUG EVALUATION I

DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

PHONE: (301)594-5742 FAX: (301) 594-0498

TO: Candice Shepherd (973) 562-3695
Fax: 973 562-3700 or 3554

FROM: Dotti Pease for Maureen Pelosi
Phone: (301) 594-5742

Total number of pages, including cover sheet 7

Date: 12-10-99

COMMENTS: Please see attached requests from our statisticians re: capecitabine carcinogenicity data.

CC: Orig. NDA 20-896
Div. File
M. Pelosi

FOR EXPEDITED STATISTICAL REVIEW OF CARCINOGENICITY DATA PLEASE PROVIDE THE FOLLOWING:

Three (3) ASCII files, one for the tumor codes and names, one for the organ codes and names, and one for the animal data allowing for SAS list input, e.g. input values have to be separated from each other by at least one blank (by at least two blanks for character input values with one or more single imbedded blanks), and periods rather than blanks for missing values. The period should always be separated by two blanks. The format is know as the old 'OEB' format (attached) and is similar to the one specified in the Electronic Submission Guidance with the exception that the tumor and organ names are not with the animal data but in separate files.

At the end of each line of organ/tumor code and names there should be a string of blanks, so that there will be no wrap around when reading the data into SAS.

When an animal has no tumors and all organ/tissues were examined, there should be only one record for this animal.

For animals with tumors, there should be as many records as there were tumor/tissue combinations.

In addition, there should be one record for each organ/tissue that was 'unusable examined' or 'unexamined'.

The codes for the variables should be exactly those specified in the OEB format.

Please provide the results of a PROC CONTENTS run.

Please perform at least the following statistical analyses: Survival trend tests, adjusted Cox and Kruskal-Wallis tests, all pair-wise comparisons of groups (adjusted Cox and Kruskal-Wallis), and Kaplan Meier survival curves. Weigh doses by actual dose levels used. Tumor analysis: Perform exact permutation trend tests and exact pair-wise comparisons on fatal, incidental or palpable tumors as defined by Peto and asymptotic tests when fatal and incidental tumors fall in the same time interval. We suggest the following fixed time intervals: weeks 0-52, 53-78, 79-91, 92-104. If there are two control groups, perform the tests

with each control group separately and combined (if control groups are identical). Certain tumors should also be grouped and analyzed, according to McConnell et al (1986) or through discussion with reviewing pharmacologist.

For questions please call Ms. Kelly (301) 827-1547.

Attachments: File formats, references.