

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

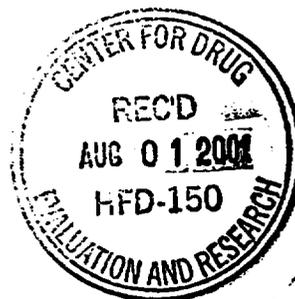
**APPLICATION NUMBER
20-896/S-010/S-011**

Administrative Documents



SUPPLEMENTARY
XP

July 31, 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

Ladies and Gentlemen:

Re: **NDA 20-896/S-010 Xeloda® (capecitabine) Tablets
Patent Information Update**

Pursuant to revised 21 USC 505(b) and 21 CFR 314, Hoffmann-La Roche Inc. herewith submits updated Patent Information for Xeloda® (capecitabine) Tablets, approved under NDA 20-896.

Other than the patents listed in the attachment, Hoffmann-La Roche does not own any additional patents directed specifically to the use of capecitabine in combination with docetaxel for the treatment of patients with metastatic breast cancer.

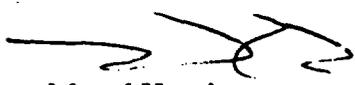
Please note that the United States Patent and Trademark Office has granted a 796 day extension of the term of US Patent No. 4,966,891, covering the above drug product. The new expiration date of the patent is January 13, 2011. The update was submitted to the NDA previously (a copy of the Certificate Extending Patent Term is also attached).

It is our understanding that the above information will be included in the next revision of the Approved Prescription Drug Products List (Orange Book).

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

Sincerely,

HOFFMAN-LA ROCHE INC.



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

Attachments
HLR No.: 2001-1702

Desk-copy (Fedex): US Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Drug Information Services Team
HFD-93 Room #235
Nicholson Lane Research Center
5516 Nicholson Lane, Building A
Kensington, MD 20895

cc: Patent Law Department

PATIENT INFORMATION

1. Active Ingredient(s): capecitabine
2. Strength(s): 150 mg, 500 mg
3. Trade Name: Xeloda®
4. Dosage form and
Route of Administration: Tablet, Oral
5. Application Firm Name: Hoffmann-La Roche Inc.
6. NDA Number: 20-896
7. First Approval Date: April 30, 1998
8. Exclusivity: Subject to patent rights, the first ANDA cannot be submitted until five years after the date of approval of the current NDA.
9. Patent Information:
 - a) Patent number and
Expiration date: 5,472,949 12/14/2013
Type of Patent: product specific claim
Patent Owner: Hoffmann-La Roche Inc.
 - b) Patent number and
Expiration date: 4,966,891 01/13/2011
Type of Patent: product specific claim
Patent Owner: Hoffmann-La Roche Inc.

While this submission was prepared in good faith, no warranty or guarantee is made regarding the accuracy of completeness of the information contained therein.

Trade Name XELODA Tablets Generic Name capecitabine

Applicant Name: Hoffman LaRoche HFD # 150

Approval Date If Known September 7, 2001

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA? YES /___/ NO /X/

b) Is it an effectiveness supplement? YES /X/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE-8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Trade Name XELODA Tablets Generic Name capecitabine

Applicant Name: Hoffman LaRoche HFD # 150

Approval Date If Known September 7, 2001

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a) Is it an original NDA? YES /___/ NO /_X_/

b) Is it an effectiveness supplement? YES /_X_/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE-8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

No, a pediatric waiver was granted for breast cancer

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

NO

If yes, NDA # _____ Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

NO

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO / ___ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-896 _____

NDA# _____

NDA# _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / ___ / NO / X /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____
NDA# _____
NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / X / NO / ___ /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / ___ / NO / X /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / ___ / NO / ___ /

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

SO 14999

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /__X_/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

SO 14999

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # [] YES /_X_/ ! NO /___/ Explain: _____
! _____
!

Investigation #2 !
IND # _____ YES /___/ ! NO /___/ Explain: _____
! _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
YES /___/ Explain _____ ! NO /___/ Explain _____
! _____
! _____
!

Investigation #2 !
YES /___/ Explain _____ ! NO /___/ Explain _____
! _____
! _____
!

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

Preparer: Maureen Pelosi
Project Manager

8-29-01
Date

Concur: Patricia Cortazar, M.D.
Medical Reviewer

08/29/01
Date

Concur: Alison Martin, M.D.

08/29/01
Date

Concur: Richard Pazdur, M.D.
Division Director

08/30/01
Date

cc: Original NDA
HFD-150/Division File
/Pelosi
HFD-93 Mary Ann Holovac
HFD-104/PEDS/T. Crescenzi

Form OGD-011347 Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00



DEBARMENT CERTIFICATION

Hoffmann-La Roche Inc. 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.

CSO NDA LABELING REVIEW OF PACKAGE INSERT

sNDA: 20-896/SLR-011 (Xeloda drug-drug interaction with warfarin)

DATE OF SUBMISSION: July 27, 2001

DATE OF REVIEW: August 24, 2001

DRUG: Xeloda (capecitabine) Tablets

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

The July 27, 2001 submission provides labeling (7/25/01) revisions to the Colorectal label.

It was agreed during the March 5, 1999 teleconference that Roche would conduct a clinical study to investigate potential effects of capecitabine on pharmacokinetics and pharmacodynamics of warfarin. The study has been completed and this supplement proposes revision to the labeling sections for PRECAUTIONS and WARNINGS.

I compared the Warfarin and Colon Cancer labels and the only differences were the addition of the warfarin information to Warnings-Coagulopathy and Drug-Drug Interactions-Coumarin Anticoagulants and Phenytoin Sections. These were expected. There were other minor editorial changes (such as misspellings) and Capecitabine was changed to Xeloda in several places.

The OCBP, Clinical, and Statistical reviewers should determine whether these proposals are acceptable, or if not, what additional changes are required. Additionally, acceptable changes should be incorporated into the SE-7 010 Xeloda-Taxotere label for the pending supplement.



8-24-01

Maureen A. Pelosi
Regulatory Project Manager



18-01

Dotti Pease
Supervisor, Project Manager Staff

CC: Original NDA 20-896 /SLR-011
HFD-150/Div File

/Li /Cheng /Cortazar /Martin /Rahman /Williams, Gene /Abraham,S/ Pelosi

CSO NDA LABELING REVIEW OF PACKAGE INSERT

sNDA: 20-896/SE7-010 (Xeloda in combination with Taxotere for metastatic breast cancer)

DATE OF SUBMISSION: June 11 and June 28, 2001

DATE OF REVIEW: July 5, 2001

DRUG: Xeloda (capecitabine) Tablets

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

The June 11, 2001 submission provides labeling (6/4/01) revisions to the March 7, 2001 labeling submitted with S-010. The June 28, 2001 four month survival and safety update submission provides additional revisions to update the ADVERSE REACTIONS section with new incidence rates and the CLINICAL STUDIES section with a revised Kaplan-Meier survival curve. Additionally, it corrects a reference error in the annotated version of the labeling.

I have reviewed the labeling, compared it with the April 30, 2001 colorectal labeling. I found no changes other than those proposed in this supplement.

The OCBP, Clinical, and Statistical reviewers should determine whether these proposals are acceptable, or if not, what additional changes are required.

TS/ 7-5-01

Maureen A. Pelosi
Regulatory Project Manager

/S/ 7/6/01

Dotti Pease
Supervisor, Project Manager Staff

CC: Original NDA 20-896 /SE7-010
HFD-150/Div File

/Li /Cheng /Cortazar /Martin /Rahman /Williams, Gene /Pelosi

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PID#: D010327

DATE: August 3, 2001

FROM: Lauren Lee, Pharm.D.
Post-marketing Safety Evaluator
Division of Drug Risk Evaluation I, HFD-430

THROUGH: Julie Beitz, M.D., Director
Division of Drug Risk Evaluation I, HFD-430

TO: Richard Pazdur, M.D., Director
Division of Oncology Drug Products, HFD-150

SUBJECT: OPDRA Post-marketing Safety Review
> **Drug:** NDA 20-896 / Applicant: Roche Pharmaceuticals/Hoffmann-La Roche Inc.
Xeloda (capecitabine tablets)
> **Reaction:** Drug interaction with Warfarin

CONFIDENTIAL: CONTAINS / DATA: NOT TO BE USED OUTSIDE OF THE FDA WITHOUT CLEARANCE FROM

I. EXECUTIVE SUMMARY:

This consult is in response to a June 19, 2001 request, by the Division of Oncology Drug Products, to review AERS case reports of a drug interaction between Xeloda and warfarin. This consult is OPDRA's second review of this drug interaction and contains updated information since the last consult, dated June 30, 1999 [PID# 99047/Mary Mease].

As of July 5, 2001, there were 828 total reports in AERS associated with Xeloda. When searches for a drug interaction between Xeloda and warfarin/phenprocoumon were conducted, 72 cases were retrieved. Among these reports, eighteen cases were selected in our case series, three of which were from foreign sources. There were nine 15-day reports, seven periodic reports, and two direct reports. Only one case report specified that it will be published. Seven of fifteen domestic cases occurred after the Xeloda/warfarin interaction was added to the US labeling.

In these cases, three were male and fifteen were female patients with the ages ranging from 40 to 82 years with the mean and median of 67 and 72 years, respectively. The age of one female patient was not specified. Xeloda was used for breast cancer (14), prostate cancer (1), bronchopulmonary carcinoma (1), colon cancer (1), and an unknown indication (1) in these cases. Warfarin was used for the treatment and/or prevention of deep venous thrombosis (3), pulmonary embolism (3), atrial fibrillation (3), port thrombosis (3), subclavian thrombosis (1), jugular vein thrombosis (1), "atrioventricular tachycardia" (1), and for unspecified indications (3). Fifteen patients were taking warfarin, and three patients were taking phenprocoumon prior to the addition of Xeloda therapy. Twelve patients had PT/INR values in the therapeutic range for anticoagulation prior to the administration of Xeloda. No pre-Xeloda PT/INR values were provided for the other six patients. At the time Xeloda was started, warfarin doses ranged from 1 mg to 7.5 mg with the mean of 2.7 mg, and Phenprocoumon doses ranged from 1mg to 3 mg with the mean of 2.3 mg. Xeloda doses ranged from

1300 mg/day to 5000 mg/day, and the mean dose was approximately 3700 mg. Administered doses were not reported in two patients for Xeloda and in one patient for warfarin. The abnormal clotting times were detected within 6 to 61 days (mean: 30.5 days) of starting Xeloda. This information was not available in one case. The duration of warfarin use prior to the addition of Xeloda ranged from 8 days to 5 years with the average of approximately 15 months. The presenting symptoms included loose black or tarry stool (2), hematuria (2), mouth ulcers (2), bleeding gums, spontaneous bruising, stomatitis, and bleeding from a chest wall lesion. Other general symptoms included nausea (3), vomiting (3), weakness (3), fatigue (2), shortness of breath (2), fever (2), tiredness, diaphoresis, headache, dehydration, diarrhea, anorexia, confusion, incontinence, somnolence, septicemia, hand-foot syndrome, and hemiparesis. Diagnoses of gastrointestinal bleed, subdural bleed, and acute cerebral hemorrhage (which resulted in cerebral infarction) were reported in three patients. In seven patients, presenting symptoms were not reported. Elevated INR and/or PT were noted in seventeen patients. INR ranged from 5.2 to 28.7 (average \approx 12.4), and elevated PT ranged from 42.4 to 300 (average \approx 83.3). In seven patients, only the INR levels were available without the PT levels. The exact clotting times were not available in one patient, but the reporter stated that it was elevated. In one patient who was taking phenprocoumon with Xeloda, the Quick's test of $<4\%$ was reported.

In five cases, liver metastases were noted in the reports. However, in one case, "liver investigations were normal." Furthermore, in two other cases, clotting times were within the therapeutic range for anticoagulation prior to the administration of Xeloda. In the last two cases, the status of liver function was not specified, but warfarin was used for 1 year and 3 years, respectively, in these patients, prior to the addition of Xeloda. Concomitant medications were reported in eleven cases, but in three of the cases, the reporter stated that there was no recent change in the regimen of other concomitant drugs. Eight other cases were potentially confounded by the concomitant use of hepatically metabolized drugs. Moreover, since age >60 years, cancer, elevated temperature, poor nutritional status, and/or hepatic impairment are risk factors for increased PT/INR responses to anticoagulation (see Coumadin labeling), then all eighteen cases were potentially at risk for increased PT/INR responses. Outcomes included three deaths, nine hospitalizations, one case requiring intervention, one life-threatening case, and four others that were considered medically relevant.

In conclusion, eighteen cases from AERS suggest a drug interaction between Xeloda and warfarin, and serious outcomes were identified, including two deaths (1 US/1 foreign) that were possibly related to their concomitant use. The current package insert for Xeloda states that a drug interaction can occur when warfarin and Xeloda are used concomitantly. It is noteworthy, however, that in the above cases, the clotting times were greatly elevated despite the relatively low doses of warfarin and recommended doses of Xeloda that were used in these patients. Moreover, despite confounding factors, the temporal association between the addition of Xeloda to warfarin therapy and the increase in clotting times were consistent in these reports. However, seven of fifteen domestic cases occurred after the Xeloda/warfarin interaction was added to the US labeling, and since this labeling change, no deaths were reported. In light of the above findings, we recommend that the current *Warnings* and *Precautions* sections of the Xeloda labeling be revised to reflect the possible dramatic increases in coagulation parameters with the concomitant use of warfarin, especially in patients greater than 60 years old with underlying cancer who may be at a greater risk. Furthermore, coagulation parameters should be closely monitored in patients taking Xeloda and warfarin concomitantly.

II. BACKGROUND

This consult request, from Dr. Atiqur Rahman (clinical pharmacologist, HFD-860), was prompted by the preliminary results of the Warfarin Study (BP15966), which was discontinued after the first four patients demonstrated a definite interaction with capecitabine (per e-mail 6/19/01). The primary

objective of the above study was to investigate the effects of capecitabine on the pharmacokinetics and pharmacodynamics of warfarin in patients with advanced metastatic solid tumors. This study was undertaken to evaluate a possible drug interaction between warfarin and capecitabine that was identified in the spontaneous reports of bleeding and/or alterations in coagulation parameters. The results of this study provided strong evidence that capecitabine inhibits cytochrome P450 (CYP) 2C9. However, warfarin does not appear to have an effect on the pharmacokinetics of capecitabine and its metabolites.

III. INTRODUCTION

Warfarin has two enantiomers that are differently metabolized by CYP enzymes. (R)-enantiomer is primarily metabolized by CYP 1A2, 1A1, and 3A4. (S)-warfarin is the more active enantiomer and is metabolized by CYP 2C9.⁽¹⁾ According to Reigner et al., the lack of a direct inhibition of CYP2C9 by capecitabine or its metabolites and the length of time it takes to observe an increase in coagulation parameters when both drugs are combined suggest that down-regulation of CYP 2C9 is the likely mechanism for the interaction. Another possible mechanism for the potential interaction includes an effect of capecitabine on the pharmacodynamics of warfarin. Furthermore, since capecitabine is a pro-drug of fluorouracil, it is likely that the mechanism involving the suppression of CYP activity may be similar.⁽²⁾

IV. DRUG INFORMATION AND LABELING:

The FDA approved Xeloda (capecitabine tablets) on April 30, 1998. Xeloda is a prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil (5-FU).

According to the latest proposed labeling (HLR 6/27/01), Xeloda is indicated as first-line treatment of patients with metastatic colorectal carcinoma when treatment with fluoropyrimidine therapy alone is preferred. Xeloda in combination with docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior anthracycline containing chemotherapy. Xeloda monotherapy is also indicated for the treatment of patients with metastatic breast cancer resistant to both paclitaxel and anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated.⁽³⁾

Drug Product	NDA	Applicant	FDA Approval	Strength	Supplied
Xeloda (capecitabine tablets)	20-896	Roche/HLR	4/30/98	150 mg & 500 mg	Bottles of 120 and 240 tablets

The recommended dosage is 1250 mg/m² administered orally twice daily for 2 weeks followed by a 1-week rest period given as 3-week cycles. Xeloda should be taken within 30 minutes after a meal.

XELODA PACKAGE INSERT LABELING

A drug interaction between Xeloda and warfarin was added to the labeling on April 26, 1999.

WARNINGS/ PRECAUTIONS (HLR 6/27/01 version): Coagulopathy - altered coagulation parameters and/or bleeding have been reported in patients taking Xeloda concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred within several days and up to several months after initiating Xeloda therapy and, in a few cases, within one month after stopping Xeloda. These events occurred in patients with and without liver metastases. Patients taking coumarin-derivative anticoagulants concomitantly with Xeloda should be monitored regularly for alterations in their coagulation parameters (PT or INR).

ADVERSE REACTIONS (HLR 6/27/01 version): Blood and lymphatics- prothrombin decreased (0.39), coagulation disorder (0.1)

V. MEDICAL LITERATURE SUMMARY:

On 7/10/01, a Medline (*Pubmed*) internet search was conducted to retrieve any published literature cases of a drug interaction between Xeloda and warfarin from years 1966-2000. The search did not reveal any cases citing this drug interaction. However, there were many articles that reported a drug interaction between 5-FU and warfarin.

VI. DRUG USE DATA:

VII. SELECTION OF CASE SERIES:

As of July 5, 2001, there were 828 total reports in AERS associated with Xeloda. When searches for a drug interaction between Xeloda and warfarin were conducted, 68 cases were retrieved. Verbatim searches using the term, "phenprocoumon," retrieved four additional cases. In total, 72 cases were reviewed.

Among these reports, eighteen cases were selected in our case series. We excluded the remaining 54 reports based on the following:

Not related to a drug interaction between warfarin and Xeloda	29
Inadequate information/ lacked temporal relationship	21*
Duplicate reports	3
Related to a disease condition	1 (DIC and microangiopathic hemolytic anemia)

**Cases were excluded if warfarin was added to the existing Xeloda therapy or started at the same time without a clear indication that the reported increases in INR/PT were directly related to a possible interaction and not due to the initial titration of warfarin. If there was a history of coagulopathy with warfarin alone or if warfarin doses were increased prior to the addition of Xeloda, we could not exclude the possibility that the reported events were due to the effects of warfarin alone, and therefore, excluded these reports from the case series. Another criterion for exclusion included the lack of temporal relationship in cases where therapy dates of warfarin and/or Xeloda were not reported.*

Given the additional reported cases since OPDRA's previous review of six cases [PID# 99047 (6/30/99)-Mary Mease], two reports (3170413-7, 3194336-2) cited in the former review were excluded according to these stricter exclusion criteria to more accurately identify cases of a true interaction between Xeloda and warfarin. Similarly, among the 22 line listing cases that were submitted by the sponsor on 12/10/98, 12 cases were excluded from our case series due to the lack of sufficient information for inclusion. The remaining 10 cases were duplicate cases that were already retrieved from AERS searches. However, the review of these 22 cases can be found in our prior consult, dated 6/30/99, which is attached to this review.

In total, eighteen cases were included in our case series.

VIII. SUMMARY OF CASES:

The analysis of the selected eighteen cases and their demographic information are as follows:

Age in years:	Range= 40-82, mean= 67, median=72 (unk =1)
Gender:	M (n=3), F (n=15)
Time to ↑ INR/PT:	Range= 6-61 days, mean= 30.5 days, median= 26 days (unk=1)
Dechallenge/Rechallenge (Xeloda):	Pos dec (n=7), Neg dec (n=1), not applicable (n=10) Neg rec (n=2), not applicable (n=16)
Dechallenge/Rechallenge (Warfarin):	Pos dec (n=7), Neg dec (n=1), not applicable (n=10) Neg rec (n=1), not applicable (n=17)
Outcome:	DE (n=3), LT (n=1), HO (n=9), RI (n=1), Other (n=4)
Location:	Foreign (n=3), US (n=15) {Switz (2) & Belgium (1)}
Report type:	15-day reports (n=9), periodic (n=7), direct (n=2)
FDA receipt year:	1998 (n=4), 1999 (n=8), 2000 (n=3), and 2001(n=3)
Reporters:	Physicians (n=10), Pharmacists (n=6), & Nurses (n=2)

In these cases, three were male and fifteen were female patients with the ages ranging from 40 to 82 years with the mean and median of 67 and 72 years, respectively. The age of one female patient was not specified. Since one of the indications for Xeloda is the treatment of advanced breast cancer, it is reasonable that the majority of the patients in this case series are female. Three of eighteen selected cases were received from foreign sources, and only one case report specified that it will be published. Seven of fifteen domestic cases occurred after the Xeloda/warfarin interaction was added to the US labeling.

In addition to breast cancer (14), Xeloda was used for prostate cancer (1), bronchopulmonary carcinoma (1), colon cancer (1), and an unknown indication (1) in these cases. The reports also indicated that warfarin was used for the treatment and/or prevention of deep venous thrombosis (3), pulmonary embolism (3), atrial fibrillation (3), port thrombosis (3), subclavian thrombosis (1), jugular vein thrombosis (1), "atrioventricular tachycardia" (1), and for unspecified indications (3).

Fifteen patients were taking warfarin, and three patients were taking phenprocoumon (3) prior to the addition of Xeloda therapy. Twelve patients had PT/INR values in the therapeutic range for anticoagulation prior to the administration of Xeloda. No pre-Xeloda PT/INR values were provided for the other six patients. Warfarin doses ranged from 1 mg to 7.5 mg with the mean of 2.7 mg. Oral warfarin doses were used in thirteen patients, and in five patients, the dosage form was not specified. Phenprocoumon doses ranged from 1mg to 3 mg with the mean of 2.3 mg. Xeloda doses ranged from 1300 mg/day to 5000 mg/day, and the mean dose was approximately 3700 mg. Administered doses were not reported in two patients for Xeloda and in one patient for warfarin. The abnormal clotting times were detected within 6 to 61 days (mean: 30.5 days) of starting Xeloda. This information was not available in one case. The duration of warfarin use prior to the addition of Xeloda ranged from 8 days to 5 years with the average of approximately 15 months.

The presenting symptoms included loose black or tarry stool (2), hematuria (2), mouth ulcers (2), bleeding gums, spontaneous bruising, stomatitis, and bleeding from a chest wall lesion. Other general symptoms included nausea (3), vomiting (3), weakness (3), fatigue (2), shortness of breath (2), fever (2), tiredness, diaphoresis, headache, dehydration, diarrhea, anorexia, confusion, incontinence, somnolence, septicemia, hand-foot syndrome, and hemiparesis. In three patients (3620204-5, 3319313-X, 3360085-0), diagnoses of gastrointestinal bleed, subdural bleed, and acute cerebral hemorrhage (which resulted in cerebral infarction) were reported, respectively. In seven patients, presenting symptoms were not reported.

All eighteen patients had elevated coagulation parameters. The exact clotting times were not available in one patient, but the reporter stated that it was elevated. The elevated INR ranged from 5.2 to 28.7 (average \approx 12.4), and elevated PT ranged from 42.4 to 300 (average \approx 83.3). In seven patients, only the INR levels were available without the PT levels. In one patient who was taking phenprocoumon with Xeloda, the Quick's test of <4% was reported. In six patients, the elevations in clotting times were noted between intermittent cycles of Xeloda therapy. In the remaining twelve patients, the increase in PT/INR occurred during Xeloda administration. When elevations in clotting times were noted, warfarin or phenprocoumon was initially discontinued in nine patients, and in six patients, both Xeloda and warfarin/phenprocoumon were discontinued. Only Xeloda was discontinued in one patient. This information was unknown in two patients. In four patients, vitamin K was given as part of the treatment. In three patients, both fresh frozen plasma (FFP) and vitamin K were given. In one patient, only FFP was noted, and in another patient, packed red blood cells, FFP, and vitamin K were administered. This information was not reported in the remaining nine patients. No significant negative dechallenge or rechallenge was reported in the above eighteen cases.

In five patients (3208680-3, 3223038-9, 3281062-4, 3472044-8, & 3620204-5), liver metastases were noted in the report. However, in one of the reports (3208680-3), "liver investigations were normal." Furthermore, in two other cases (3223038-9 & 3281062-4), clotting times were within the therapeutic range for anticoagulation prior to the administration of Xeloda. In the last two reports (3472044-8, & 3620204-5), the status of the liver function was not specified, but in these two cases, warfarin was used for 1 year and 3 years, respectively, prior to the addition of Xeloda. Concomitant medications were reported in eleven cases, but in three of the cases, the reporter stated that there was no recent change in concomitant drugs. Eight other cases were potentially confounded by hepatically metabolized drugs such as vinorelbine, nortriptyline, phenobarbital, sertraline, Daypro, fluoxetine, granisetron, paroxetine, paclitaxel, nolvadex, and desipramine. Moreover, since age >60 years, cancer, elevated temperature, poor nutritional status, and/or hepatic impairment are risk factors for increased PT/INR responses to anticoagulation (see Coumadin labeling), then all eighteen cases were potentially at risk for increased PT/INR responses.

Outcomes included three deaths, nine hospitalizations, one case requiring intervention, one life-threatening case, and four others that were considered medically relevant. Among the three death cases, two cases (3319313-X [1999 US] & 3360085-0 [1999 Switzerland]) suggest that a drug interaction between warfarin and Xeloda lead to the death of these patients. In the third case (3223038-9 [1999 US]), however, the underlying disease could have resulted in the death of the patient, but we could not exclude the possibility that an interaction between warfarin and Xeloda could have also contributed to the outcome of this case. All deaths occurred in elderly patients (>75 yrs) and preceded the Xeloda labeling change in the US which addressed a drug interaction with warfarin.

The two related death cases are presented below:

1. [3319313-X (1999 US)]

A 76 year old female was hospitalized for prolonged PT and subsequently died due to subdural bleeding during the use of Xeloda for metastatic breast cancer and warfarin. She had a history of atrial fibrillation. On 2/98, warfarin was started (3.75 mg QD), and on 1/99, Xeloda was started. The baseline INR prior to Xeloda was 2.9. On 2/15/99, the patient was hospitalized for vomiting and headache. Head CT revealed multiple subdural bleeds. PT was 49.1 and INR was 17.5. There was no trauma to the head. Several CT scans showed no evidence of a skull fracture. The reporter felt that the subdural bleed was spontaneous and due to the prolonged prothrombin time. Xeloda and warfarin were stopped and the reversal of the anticoagulation treatment was started. As of 2/17/99, there was insufficient information as to the continuation of Xeloda and warfarin. Lab tests revealed PT 16.7 and INR 2. She experienced progressive neurologic deterioration and died on 2/20/99 of subdural bleeds. Further information received on 6/20/00 stated that the patient had pleural and pulmonary parenchymal metastasis and there was no evidence of liver or brain metastasis. The patient's concomitant medications included warfarin, Inderal, Maxzide, digoxin, Percocet, and oxycontin.

2. [3360085-0 (1999 Switzerland)]

An 82 year old female died due to a cerebral hemorrhage during the use of Xeloda for breast cancer and phenprocoumon for thrombosis. In 1995, phenprocoumon 3 mg was started for anticoagulation following a subclavian vein thrombosis. On 2/26/99, Xeloda 4300 mg/day was started. On 3/12/99, Xeloda was stopped. On 3/19/99, Xeloda 4300 mg/day was restarted. On 3/26/99, Xeloda was stopped. On 4/6/99, the patient was hospitalized due to confusion and fever. The patient also experienced incontinence and her neurological status worsened quickly. Left-sided hemiparesis developed and the patient became increasingly somnolent. "Her INR on admission was 6.5, which confirmed the diagnosis of an acute cerebral hemorrhage due to anticoagulation therapy." On 4/15/99, phenprocoumon was stopped. On an unknown date, INR was >7. The patient experienced hemorrhagic cerebral infarction. Due to the poor prognosis, the patient's medication was reduced to analgesics and fluids. On 4/15/99, the patient died. An autopsy was not performed. It was not stated whether fever and increased INR were still persisting at the time of the death. According to the report, the increased INR was suspected to be due to a drug interaction between Xeloda and phenprocoumon.

The above eighteen cases suggest a drug interaction between Xeloda and warfarin when used concomitantly. Despite the confounding factors presented above, the temporal association between the addition of Xeloda to the warfarin regimen and the increase in clotting times were consistent in these reports. The current package insert for Xeloda states that a drug interaction can occur when warfarin and Xeloda are used together. It is noteworthy, however, that in the above cases, the clotting times were greatly elevated despite the relatively low doses of warfarin and recommended doses of Xeloda that were used in these patients. It's also important to note that the above cases may not accurately depict the actual onset time of coagulopathy with the use of these two drugs since it's

impossible to determine when the INR and PT levels started to increase in relation to the elevated levels that were reported in these cases.

IX. CONCLUSION:

Eighteen cases from AERS suggest a drug interaction between Xeloda and warfarin, and serious outcomes were identified, including two deaths (1US/1 foreign) that were possibly related to their concomitant use. However, seven of fifteen domestic cases occurred after the Xeloda/warfarin interaction was added to the US labeling, and since this labeling change, no deaths were reported. In light of the above findings, we recommend that the current *Warnings* and *Precautions* sections of the Xeloda labeling be revised to reflect the possible dramatic increases in coagulation parameters with the concomitant use of warfarin, especially in patients greater than 60 years old with underlying cancer who may be at a greater risk. Furthermore, coagulation parameters should be closely monitored in patients taking Xeloda and warfarin concomitantly.

References

1. Redman AR. Implications of cytochrome P450 2C9 polymorphism on warfarin metabolism and dosing. *Pharmacotherapy*. 2001; 21:235-242.
2. Reigner et al. Clinical pharmacokinetics of capecitabine. *Clin Pharmacokinet*. 2001;40:85-104.
3. Proposed Xeloda® Product Labeling (HLR 6/27/01). Roche Pharmaceuticals/Hoffmann-La Roche Inc., 2001.

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Table 1. Drug interaction between Xeloda and warfarin								
	AERS ISR#s	Yr	Location	Age/ Sex	Xeloda/ warfarin use prior to ↑ in PT/INR	Medical History	Medications	Outcome
1	3732015-0	2001	US	79 M	21 days	Prostate CA, PTCA ('95, '97), A-fib, HTN, CAD, CVA ('97, '98), arthritis, DJD, PVD, cholelithiasis, rising PSA, bypass graft, right hydronephrosis	Warfarin, amlodipine, folic acid, metoprolol, MTV, nitroglycerin, simvastatin, pyridoxine, & loperamide, prochlorperazine	HO
<p>Summary: A 79 yo male with advanced hormone refractory prostate cancer was on chronic warfarin therapy (1/8/01-5/17/01) for pre-existing cardiac problems (a-fib). His baseline PT/PTT/INR were normal. He was started on Xeloda 3300 mg po qd (3/9/01-5/4/01) as part of a clinical trial. His PT/INR increased and he was instructed to decrease his dose of coumadin and have the labs rechecked. His warfarin dose was held on 3/30. However, another physician at an outside facility may have instructed him differently and he became confused regarding his coumadin dose. His warfarin dose increased from 2 mg QD to 6 mg QD on 4/17/01 and adjusted again on 4/20/01 to 3 mg QD. He was hospitalized for observation because of very elevated INR (9.65). This was strictly preventative measure as no bleeding complications had yet occurred. The doses of other medications were not adjusted during this time. Patient is doing fine as of 7/01. He is currently on aspirin and Plavix.</p>								
<p>Labs: PT 20.4, PTT 32.6, INR 1.76 (3/9/01) PT 78.1, PTT 76.6, INR 9.65 (5/15/01) PT 47.4, PTT 41.7, INR 5.2 (3/30/01) PT 13.8, INR 1.7 (6/15/01)</p>								
2	3685823-9	2001	US	72 F	51 days	Metastatic breast CA (bone and skin mets), DVT, & PE	Warfarin, pepcid, MTV, ibuprofen, Senokot-S	HO
<p>Summary: A 72 yo female with recurrent metastatic breast cancer was admitted to a hospital with a 3-day history of weakness, tiredness, fatigue, SOB, and loose black stools. Her history included an infiltrating ductal carcinoma of right breast (dx 3 years earlier). She was initially treated with cytoxan and adriamycin followed by radiation and tamoxifen. After a 2 year recurrence free interval, she developed mets to the skin and bone. Paclitaxel followed by anastrozole provided a progression free interval of 8 months. In 1997, she was diagnosed with PE and was started on heparin followed by warfarin. Two months prior to her admission, her bone scan revealed progressive metastatic disease and she was started on oral Xeloda 2000 mg/m²/day for 3 cycles (10/30/00-1/9/01). She completed 2 full cycles by the time she presented to the hospital. At the time of her admission, she had no recent change in diet or medications. Her warfarin dose was 2.5 mg QD. She was pale, diaphoretic, but no visible signs of purpura or petechia. The patient was admitted to ICU with PT 300 (nl 11-23 no units provided). On 12/20/00, PTT was 146.4 sec (nl 23.5-34.5 sec), PT >100 sec, and INR 13 (nl 2-3). On 12/21/00, patient's temperature was 98.6 F, HR 130, BP 90/60, Hgb 5.6 G/DL (nl 12-16), Hct 16% (nl 37-47), BUN 46 mg/dL, creatinine 0.9 mg/dL, and albumin 2.1 g/dL. LFT's including bili and aminotransferase levels were normal. Patient was treated with IV hydration, FFP, packed red blood cells, and Vit-K. Warfarin, ibuprofen, and Xeloda were discontinued. The elevated INR, black stools, and tiredness resolved. Weakness and Hgb improved. Forty-eight hours after admission, her vitals returned to normal and her INR was therapeutic at 2.2 and her stool was guiac negative. All events resolved and the patient was discharged from the hospital. Several days later, her warfarin was restarted at 2.5 mg/day. She did not receive any more treatment with Xeloda. Her coags remained in therapeutic range since then. The reporter thought that Xeloda had interacted with warfarin.</p>								
<p>Labs: PTT 146.4, PT >100, INR >10 (12/20/00) PT 20.7, INR 2.82 (12/22/00) [PTT nl range: 23.5-34.5 sec, PT nl range: 11-13sec, INR nl range: 2-3] PTT 38.8, PT 38.8, INR 2.23 (12/21/00) PTT 63.8, PT 19.2, INR 2.44 (12/24/00)</p>								
3	3731513-3	2001	US	47 F	14 days	Breast cancer, bone and lung mets, & pleural effusion, DVT, normal liver and renal function	Warfarin, Dyazide, Paxil, Restoril, Oxycontin, Vicodin, aspirin, chlorpheniramine, phenylephrine & Aromasin	LT

<p>Summary: A 47 yo female experienced life-threatening increased INR/PT while receiving warfarin (3/20/00-5/25/00) and Xeloda (5/11/00-10/25/00). She had a history of breast cancer, lung/bone mets, and pleural effusion. She was taking warfarin for a blood clot in her right leg, and the dose was not adjusted when Xeloda was started. Doses of her other medications were not changed during the time that warfarin and Xeloda were used together, but Aromasin was started the same day as Xeloda. Baseline coags prior to Xeloda were normal. The patient noticed bleeding from gums when brushing her teeth. On 5/25/00, patient's INR and PT were 16.9 and 50, respectively. Warfarin was stopped and the increased INR and PT abated. Xeloda was restarted at 1500 mg BID. Warfarin was not restarted since DVT resolved by this point. Increased INR and PT did not reoccur. Aromasin was not considered a cause of this reaction and was discontinued in 10/00. The reporter had stated that the INR/PT increase was definitely related to Xeloda and warfarin.</p>								
<p>Labs: PT 50, INR 16.9 (5/25/00) [PT nl range: 10-13.8, INR nl range: 2-3]</p>								
4	3472044-8	2000	US	63 F	21 days	Breast cancer w/ mets to liver and bone (dx 6/98), fluid retention, & thrombosis	Warfarin, Adriamycin, Taxol, Tamoxifen, Neurontin, desipramine, HCTZ, milk thistle, & co-enzyme Q-10	HO
<p>Summary: A 63 yo female was hospitalized due to increased PT/INR levels following the use of Xeloda. Her medical history included breast cancer w/ liver and bone mets (dx 6/98), mild fluid retention, and a blood clot in a mediport that traveled to the carotid artery (9/98), for which she was treated with warfarin 5 mg QD and the clot resolved. Warfarin was maintained. On 9/7/99, Xeloda was started at 3000 mg po QD and on 9/28/99 Xeloda was increased to 3500 mg po QD. During the second course of Xeloda therapy, the patient experienced elevated INR=15 and elevated PT= 42.4. The patient was hospitalized and warfarin was discontinued for 3 days. Warfarin was restarted at 4 mg QD. Xeloda was discontinued. On 10/18/99, warfarin was discontinued. Patient started Plavix and aspirin to replace coumadin therapy. At the time of the report (10/27/99), the events improved and Xeloda was expected to be restarted within 2 weeks. Further follow-up on 11/1/99 indicated that she developed grade 3 hand/foot syndrome and Xeloda was reduced to 3000 mg QD. The hand/foot syndrome resolved. The patient's tumor markers had dropped. On 11/18/99, INR and PT levels were normal.</p>								
<p>Labs: PT 42.4, INR 15 (9/28/99) PT 32.4, INR 8.5 (10/18/99)</p>								
5	3472041-2 3361314-x	2000	US	56 F	26 days	Breast CA, PE, DVT	Warfarin	Other
<p>Summary: A 56 yo female experienced elevated INR during the use of Xeloda (8/29/99-9/26/99) and warfarin (6/15/98-9/26/99). Pt's history included PE and DVT. In 1998, she started warfarin 2.5 mg QD. On 8/99, she started palliative radiation for the treatment of progressive scleroderma. On 8/29/99, she started Xeloda 1500 mg q12. On 9/24/99, INR of 5.82 was noted and a drug interaction was suspected with warfarin. On 9/26/99, the patient presented with a malignant pleural effusion and lab test showed INR 6.3, CBC w/ diff nl, Alb 3.1, SGOT 27, Alk Phos 94, SGPT <4, Bili 0.4/0.2. Warfarin and Xeloda were discontinued. Patient was treated w/ vit-k to improve coagulopathy in order to insert chest tube for pleural effusion. Increased INR and drug interaction abated. Xeloda was not restarted after 9/26/99. On follow-up, the patients INR resolved, chemo was discontinued, and the patient was on palliative care only.</p>								
<p>Labs: INR 5.62 (9/24/99) INR 6.76 (9/27/99) INR 6.3 (9/26/99)</p>								
6	3620204-5	2000	US	60 F	40 days	Breast CA with liver mets, DM, HTN, gout, & depression	Warfarin, Daypro, Lasix, atenolol, Paxil, Tylox, glucophage, & potassium	HO
<p>Summary: A 60 yo female was hospitalized with a GI bleed and also experienced nausea, vomiting, diarrhea during the use of Xeloda (2/15/00-3/28/00) for metastatic breast cancer. Patient was concomitantly taking warfarin (12/16/96- continuing as of 11/30/00). On 2/15/00 Xeloda was started at 2500 mg BID and the first course was finished on 2/29/00. The second course started on 3/1/00. On 3/27/00, the patient was admitted to a hospital with black, tarry, guaiac-positive stools with low Hgb. Patient was diagnosed with a GI bleed. Her INR was increased (no value available). On 3/28/00, Xeloda was stopped due to progression of breast cancer. Prior to discharge, her GI bleed resolved, and her INR was below 1.3 with vitamin K and FFP.</p>								
<p>Labs: INR 1.3</p>								
7	3413661-0	1999	US	58 M	36 days	Metastatic colon CA, allergy to PCN, no alcohol/tob	Warfarin, ranitidine, granisetron,	HO

<p>Summary: A 58 yo male was hospitalized for increased INR during the use of Xeloda for metastatic colon cancer and warfarin (6/15/98-10/1/99) for recurrent DVT. In '98, she started warfarin 2 mg QD. On 8/9/99, her INR was 1.86. On 8/25/99, Xeloda 650 mg BID was started as an intermittent therapy. On 9/7/99, her INR was 3.11. On 10/1/99, her INR was >20 and warfarin was discontinued. She was treated with vit-k (5 mg) and was hospitalized. On 10/4/99, her INR was 2.84. The reporter thought that the increased INR could be due to a drug interaction between Xeloda and warfarin.</p>							
Labs: INR 1.86 (8/9/99)		INR >20 (10/1/99)					
INR 3.11 (9/7/99)		INR 2.84 (10/4/99)					
8	3319313-X	1999	US	76 F	31 days	Breast CA, A-fib	Warfarin, Inderal, Maxzide, digoxin, Percocet, DE, HO oxycontin
<p>Summary: 76 yo female was hospitalized for prolonged PT and subsequently died due to subdural bleeding during the use Xeloda (1/15/99-2/15/99) for metastatic breast cancer and warfarin (2/15/98-2/15/99). She had a history of a-fib. On 2/98, warfarin was started (3.75 mg QD). On 1/99, Xeloda was started. The baseline INR prior to Xeloda was 2.9. On 2/15/99, the patient was hospitalized for vomiting and headache. Head CT revealed multiple subdural bleed. PT was 49.1 and INR was 17.5. There was no trauma to the head. Several CT scans showed no evidence of skull fracture. The reporter felt that the subdural bleed was spontaneous and due to prolonged PT. Xeloda and warfarin were stopped and reversal of anticoagulation treatment was started. As of 2/17/99, there was insufficient information as to the continuation of Xeloda and warfarin. Lab tests revealed PT 16.7 and INR 2. On 2/20/99, she experienced progressive neurologic deterioration and died of subdural bleeds. Further information received on 6/20/00 stated that the patient had pleural and pulmonary parenchymal mets and there was no evidence of liver or brain mets.</p>							
Labs: INR 2.9 (1/99)		INR 2, PT 16.7 (2/17/99)					
INR 17.5, PT 49.1 (2/15/99)							
9	3223038-9	1999	US	77 F	21 days	Breast CA w/ lung, liver, bone mets, and PE (1/5/99)	Warfarin DE, HO
<p>Summary: A 77 yo female was hospitalized for elevated INR, weakness, septicemia w/ fever, leukopenia, thrombocytopenia, dehydration, stomatitis with bleeding mouth ulcers during the use of Xeloda (1/26/99-2/16/99) for breast cancer (lung {stable fxn}, liver, and bone mets). Her history includes PE in 1/99. Her baseline PTT was 16.8 and INR of 1.9 with warfarin 7.5 mg QD. Warfarin was used between 1/15/99-2/16/99. On 1/26/99, Xeloda 2500 mg BID was started. On 2/9/99, the patient took the last dose of Xeloda for this cycle. On 2/12/99, she experienced sores in her mouth. On 2/16/99, she presented to the ER with stomatitis with bleeding mouth ulcers, sepsis, fever, dehydration, and weakness. Labs showed PLT 31, WBC 0.5, PTT 61.8, INR 28.7. She received IV fluids, blood transfusions, Timentin, Neupogen, and magic mouthwash. Warfarin was stopped. The next cycle was not started. On 2/17/99, labs showed PLT of 39, PTT 27.4, INR 5.3, and WBC 0.7. On 2/19/99, she died of progression of neoplasia, SVT, pancytopenia, mucositis, and septicemia. Drug relationship was listed as related to elevated INR.</p>							
Labs: PTT 16.8, INR 1.9 (1/25/99)		PTT 27.4, INR 5.3 (2/17/99)					
PTT 61.8, INR 28.7 (2/16/99)							
10	3219363-8	1999	US	40 F	56 days	Metastatic breast CA, cerebral palsy	Warfarin, Aredia, Pepcid, Ativan, Librax, Other Prozac, and Vicodin
<p>Summary: A 40 yo female developed increased PT/PTT with spontaneous bruising, hand-foot syndrome, diarrhea, and abdominal pain during the use of Xeloda (8/17/98-10/8/98) for metastatic breast cancer and warfarin (5/15/98-10/12/98) for anticoagulation. She has mets to the bone and brain. She also has cerebral palsy and is wheelchair bound. She has a central line placed for venous stasis. On 5/98, her PT and PTT were 11.9 and 26, respectively. Warfarin 1 mg QD was started on 5/15/98. On 8/17/98, Xeloda was started at 1800 mg BID. The patient developed hand-foot syndrome, abdominal pain, and diarrhea. On 10/12/98, she reported spontaneous bruising and developed increasing levels of PT(44.5) and PTT (159.5). Warfarin was discontinued. On 10/13/98, PT and PTT were 94 and 91.4, respectively. She received 10 mg Vit-k. On 10/14/98, her PT and PTT were 20.4 and 36.1. Xeloda had not been rechallenged and warfarin was restarted. Abdominal pain, diarrhea, and hand-foot syndrome improved. Her labs showed PT 12.4, PTT 39.5, and INR of 1.11.</p>							
Labs: PTT 26, PT 11.9 (5/98)		PTT 91.4, PT 94 (10/13/98)					
PTT 159.5, PT 44.5 (10/12/98)		PTT 36.1, PT 20.4 (10/14/98)					
11	3208680-3	1999	US	79 F	23 days	Breast CA with mets to bone, lung, and liver, chronic a-fib, thrombosis	Warfarin Other

Summary: A 79 yo female developed increased INR, mouth ulcers, diarrhea, nausea, anorexia, weakness and fall during the use of Xeloda (6/8/98-7/11/98) for breast cancer. Her history included breast cancer with mets to bone, lung, liver over 18 years. She had taken anticoagulation therapy since 1993 for chronic a-fib/thrombosis with warfarin (6/15/93-8/4/98). On 6/8/98, Xeloda was started at 2000 mg BID. On 6/22/98, she experienced mouth ulcers, diarrhea, nausea, and anorexia. On 6/28/98, all events resolved. On 7/1/98, her INR and PT were 14.51 and 44.5, respectively. On 7/7/98, the anorexia and diarrhea reoccurred. Her PT and INR were 44.5 and 4.7, respectively. Warfarin was stopped. On 7/8/98, the anorexia and diarrhea resolved again. On 7/9/98, Xeloda dose was decreased to 1500 mg BID. On 7/11/98, the patient was taken to the ER with weakness after falling. No injuries occurred. Xeloda was stopped. On 7/12/98, warfarin was restarted at 2.5 mg QD. Xeloda was restarted at 1500 mg BID. On 7/29/98, the increased INR resolved (PT 15.5, INR 1.5). Xeloda was continuing and warfarin was stopped. On 8/11/98, her PT and INR were 30.8 and 6.83, respectively. Xeloda was discontinued at an unknown date. On 10/26/98, she complained of red palms and burning paresthesias on her feet. She developed sore mouth, bleeding from chest wall lesion. Her PT and INR were 23.9 and 4.08, respectively. On examination, she was noted to have a-fib. She was in no respiratory distress. A chest wall lesion was 2 cm with notable bleeding. Some regrowth of tumor appeared to be present underneath the lesions. A diagnosis of recurrent carcinoma of the breast to chest wall and chronic a-fib was made. On 10/29/98, she continued to experience red blisters and burning sensations on her feet. Diarrhea was experienced 3 times that day. Liver investigations were normal. On 12/17/98, PT and INR were 13.3 and 1.23, respectively.

Labs: PT 44.5, INR 14.51 (7/1/98)	PT 30.8, INR 6.83 (8/11/98)
INR 4.07 (7/7/98)	PT 23.9, INR 4.08 (10/26/98)
INR 1.5 (7/29/98)	PT 13.3, INR 1.23 (12/17/98)
INR 4.2 (8/4/98)	

12	3194958-9	1999	US	76 F	Not reported	Metastatic breast CA, h/o port thrombosis	Warfarin	HO
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Summary: A 76 yo female with metastatic breast cancer was chronically taking warfarin 1mg/day for prophylaxis against port thrombosis. The actual pre-Xeloda INR not known but MD states it was approximately 1 and normal. She started Xeloda on an unknown date. The INR on 8/12/98, following the start of Xeloda was 12.9 with PTT >200 sec. Patient was admitted to a hospital and was given FFPx1 and vit-k 10mg sq x2 with marked improvement.

Labs: PTT >200, INR 12.9 (8/12/98)	INR 1.4 (8/14/98)
INR 3.9 (8/13/98)	

13	3382275-3	1999	Belgium	72 F	6 days	Breast CA, atrioventricular tachycardia	Phenprocoumon	HO
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Summary: A 72 yo female with breast cancer was hospitalized for hematuria during participation in a study during the use of Marcoumar (phenprocoumon) for atrioventricular tachycardia. On 7/19/99, phenprocoumon 1 mg QD was started. On 10/1/99, Xeloda 4000 mg/day was started as intermittent therapy. On 10/6/99, the patient experienced macroscopic hematuria during the night. On 10/7/99, she was hospitalized for the event. Her Hgb was 11.6 G/dL (nl: 11.5-16.5 G/dL), erythrocytes 3.98 million/mm³ (nl: 4-5 million/mm³), Hct 34% (nl: 37 to 47 %), leucocytes 3.8 x 10³/mm³ (nl: 4-10x 10³/mm³), neutrophils 64% (nl: 40-75%), thrombocytes 146 x 10³/mm³ (nl: 150 to 400 x 10³/mm³), prothrombin index <7% (therapeutic range: 12-30), INR >6 (therapeutic range: 2-4), LDH 811 U/L (nl: 313-618 U/L) and CA marker 223.3 U/mL (nl: 0-28). Phenprocoumon was stopped (10/7/99) and vitamin K supplement was started. On 10/8/99, the event resolved. The patient was discharged from the hospital. The investigator listed hematuria as related to Xeloda and phenprocoumon.

Labs: INR >6 (10/7/99)

14	3360085-0	1999	Switz	82 F	39 days	Breast CA, subclavian vein thrombosis	phenprocoumon	DE, HO
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Summary: A 82 female experienced a drug interaction leading to an increased INR and died due to cerebral hemorrhage during the use of Xeloda for breast cancer and phenprocoumon for thrombosis. In 1995, phenprocoumon 3 mg was started for anticoagulation following a subclavian vein thrombosis. On 2/26/99, Xeloda 4300 mg/day was started. On 3/12/99, Xeloda was stopped. On 3/19/99, Xeloda 4300 mg/day was restarted. On 3/26/99, Xeloda was stopped. On 4/6/99, the patient was hospitalized due to progressing confusion and fever on admission. The patient also experienced incontinence and her neurological status worsened quickly. Left-sided hemiparesis developed and the patient became increasingly somnolent. Her INR on admission was 6.5, which confirmed the diagnosis of an acute cerebral hemorrhage due to the anticoagulation therapy. On 4/15/99, phenprocoumon was stopped. On an unknown date, INR was >7. On an unknown date, the patient experienced hemorrhagic cerebral infarction. Due to the poor prognosis, the patient's medication was reduced to analgesics and fluids. On 4/15/99, the patient died. An autopsy was not performed. It was not stated whether fever and increased INR were still persisting at the time of the death. According to the report, the increased INR is suspected to be due to a drug interaction between Xeloda and phenprocoumon.

	Labs: INR > 7 INR 6.5 (4/6/99)							
15	3281062-4	1998	US	75 F	39 days	Breast CA w/ bone, lung, liver, and heart mets	Warfarin, monopril, Aredia	HO
	<p>Summary: A 75 yo female was hospitalized with increased PT and INR during the use of Xeloda (7/3/98-8/8/98) for breast cancer. She has a history of mets to bone, lungs, liver, and pericardium. She was receiving warfarin 1 mg po QD (6/25/98-8/11/98) for a probable PE revealed by ventilation/perfusion scan before the start of chemotherapy. On 7/3/98, Xeloda 2150 mg BID was started. On 7/10/98, she developed decreased appetite and diarrhea which resolved in a week. On 7/21/98, her PT and INR were 11.8 and 1.1, respectively. This was considered to be normal. During the second cycle of Xeloda, she developed nausea, vomiting, fatigue, SOB, and hand/foot syndrome. On 8/11/98, her PT and INR were 77.6 and 5.8, respectively. Warfarin was stopped. On 8/12/98, her PT and INR were 114.9 and 12, respectively. She was hospitalized and received FFP and vit-k. She had no visible signs of bleeding. On 8/14/98, her PT and INR were 13.5 and 1.4, respectively. She was discharged but Xeloda and warfarin were not restarted.</p>							
	<p>Labs: PT 11.8, INR 1.1 (7/21/98) PT 114.9, INR 12 (8/12/98) PT 77.6, INR 5.8 (8/11/98) PT 13.5, INR 1.4 (8/14/98)</p>							
16	3151496-7	1998	US	F	61 days	Coagulation disorder	Warfarin	Other
	<p>Summary: A female patient of unknown age experienced increased INR and PT during the use of Xeloda for an unknown indication and warfarin for a coagulation disorder. In 1/98, warfarin 1 mg QD was started. In 5/98, her PT and PTT were 11.9 and 26, respectively. On 8/98, Xeloda 3600 mg daily was started for an unstated indication. On 10/98, she experienced increased INR of 8.7 and PT 94, and PTT 91.4. The reporter thought that the increased INR and PT were due to a drug interaction between warfarin and Xeloda. At the time of the report (10/16/98), warfarin and Xeloda were maintained.</p>							
	<p>Labs: PTT 26, PT 11.9 (5/98) PTT 91.4, PT 94, INR 8.7 (10/98)</p>							
17	3128622-9	1998	US	67 F	25 days	Breast CA w/ mets to lung, seizure, hx chemo, allergy to PCN, & smoker	Warfarin, nortriptyline, Zoloft, phenobarbital, and Zantac	RI
	<p>Summary: A 67 yo female developed hematuria and elevated PT/INR while taking Xeloda (7/6/98-8/3/98). She has a history of breast cancer metastatic to the lung and seizure disorder. She was also receiving nortriptyline, sertraline, ranitidine, and phenobarbital. She was a smoker, but did not drink alcohol. She also had a hx of allergy to PCN. Years ago (at an unknown date), warfarin was started at an alternating dose of 2.5 mg and 5 mg daily. On 1/98, warfarin dose was changed so that she would receive 5 mg for 2 days followed by 2.5 mg on the third day repeating continually. On 7/6/98, she started Xeloda 4300 mg QD. On 7/13/98, her INR was 2 (nl: 0.8-1.1), which is the baseline level for the original dosage of warfarin since 1/98. The second cycle of Xeloda was started on 7/27/98. On 7/29/98, she developed hematuria. On 8/1/98, she went to the ER complaining of hematuria and her PTT and INR were >100 (nl: 23.32) and 9.93, respectively. She received 2 units of FFP. Warfarin was discontinued. On 8/3/98, hematuria recurred and Xeloda was discontinued. On 8/14/98, patient was rechallenged on Xeloda (2150 mg/day). Hematuria and elevated PT did not reappear. In 1/98, her underlying condition had worsened and she was placed on Gemzar.</p>							
	<p>Labs: INR 2 (7/13/98) PTT >100, INR 9.93 (8/1/98)</p>							
18	3164193-9	1998	Switz	63 M	9 days	Bronchopulmonary carcinoma (4/98), cataracts, neuropathy, thrombocytopenia, prior chemotherapies	Marcumar (phenprocoumon), Navelbine,	HO
	<p>Summary: A 63 year old male, with a history of bronchopulmonary carcinoma (4/98), cataracts, and neuropathy of the feet and thrombocytopenia due to several previous chemotherapy regimens, began phenprocoumon 3mg daily on 4/25/98 due to thrombosis of the jugular vein. On approximately 5/25/98 a Quick's test was 33%. On an unspecified date the phenprocoumon was reduced to the 0.75mg dosage form (exact dosage not specified). The patient was hospitalized on 9/18/98 for pneumonia, was treated with antibiotics, and discharged on 9/25/98. Capecitabine 4000mg/day and vinorelbine 40mg on days 1 and 8 of a 14 day cycle was started on 10/26/98. The Quick's test on 10/26/98 was 33%. On 11/4/98 the Quick's test was <4% and the phenprocoumon was reduced to 0.5mg/day. On 11/6/98 the Quick's test was 22% and the prothrombin time resolved. On an unspecified date, but after the start of capecitabine and vinorelbine, the patient presented with hepatic damage. The sponsor was unable to obtain additional information regarding the hepatic damage but the capecitabine and vinorelbine were continuing.</p>							

Labs: Quick's Test 25-33% (5/98)	Quick's Test <4% (11/4/98)
Quick's Test 33% (10/26/98)	Quick's Test 22% (11/6/98)

TELECONFERENCE MINUTES

MEETING DATE: 06 SEP 01 **TIME:** 12 PM **LOCATION:** Conference Rm B

NDA 20-896 SE-7 #010 & SLR-011 **DRUG:** XELODA (capecitabine) Tablets

SPONSOR/APPLICANT: Hoffman La Roche **TYPE of MEETING:** Teleconference

FDA PARTICIPANTS: Richard Pazdur, M.D., Division Director
Alison Martin, M.D., Team Leader
Patricia Cortazar, M.D., Medical Reviewer
Atik Rahman, Ph.D., OCPB, Team Leader
Sophia Abraham, Ph.D., OCBP Reviewer
Ning Li, Ph.D., Biometrics Reviewer
Maureen Pelosi, RPh, Project Manager

INDUSTRY PARTICIPANTS: Alex Zukiwski, M.D.
Marty Huber
Bruno Ousterwalder, M.D.
Markus Abt, Ph.D.
Dan Zabrowski
Murad Husain, R.Ph., Regulatory Affairs

BACKGROUND: The Division is finishing the sNDA review of the Xeloda-Taxotere combination and the labeling supplement for warfarin. We have requested a black box warning for Xeloda-warfarin interactions. Roche has requested an opportunity to speak with the Division to discuss our rationale for the black box as well as to propose alternatives.

QUESTIONS for DISCUSSION:

- 1. Roche: The standard procedure has been to monitor the activity and then take an appropriate step. This was done with Roche's Dear Doctor Letter and then a statement in the WARNINGS section in 1999. There has been no change in the signals. Why does FDA want to add a black box warning?**

FDA Response:

- FDA's goal is zero incidents. This is a preventable adverse event that is very serious. Better physician education is required.
- There is valid evidence in the PK data. The study was closed after enrolling 4 patients who had dramatic PK and PD changes.
- Post-marketing reporting has stabilized but our goal is 0%. A boxed warning increases the chance that the information will be read. Cancer patients are different in

that they have metastatic liver disease, a terminal illness, patients older than 60 are at increased risk, and Xeloda is a toxic drug that has a significant interaction with warfarin.

- The Division has spoken with Dr. Temple who supports the black box warning.

2. Roche: The sponsor believes that a black box warning would hinder direct advertising to the consumer and wishes to propose alternatives.

FDA Response:

- Please send us your suggestions later today. This application is due tomorrow.

The teleconference concluded at 1 PM.

/s/

/9-6-01

Concurrence Chair:

/s/

/9-7-01

Maureen Pelosi
Project Manager

Patricia Cortazar, M.D.
Medical Officer

TELECONFERENCE MINUTES

MEETING DATE: 04 SEP 01 **TIME:** 8:15 AM **LOCATION:** Conference Rm 2025B

NDA 20-896 SE-7 #010 & SLR-011 **DRUG:** XELODA (capecitabine) Tablets

SPONSOR/APPLICANT: Hoffman La Roche **TYPE of MEETING:** Teleconference

FDA PARTICIPANTS: Julie Beitz, M.D., OPDRA Director (by phone)
Susan Lu, OPDRA Team Leader
Lauren Lee, OPDRA Reviewer
Alison Martin, M.D., Team Leader
Patricia Cortazar, M.D., Medical Reviewer
Atik Rahman, Ph.D., OCPB, Team Leader
Sophia Abraham, Ph.D., Reviewer
Maureen Pelosi, RPh, Project Manager

BACKGROUND: The Division is finishing the sNDA review of the Xeloda-Taxotere combination to grant full approval and is concerned about the Drug-Drug Interaction between Xeloda and Warfarin. The Division would like to add a black box warning to the label.

QUESTIONS for DISCUSSION:

- 1. OPDRA: There have been 15 warfarin reports, 8 during the first year after approval and 3 deaths prior to adding coagulopathy to the label in April, 1999. Since then, there have been 2 reports and no deaths. Therefore there has been no spike in incidents to signal a new concern. Is the black box warning truly necessary?**

Division Response:

- The goal is to have zero incidents. The interaction is preventable and the outcome is possibly life threatening.
 - Physicians may not read the whole label.
 - Physicians do not read Dear Doctor letters carefully.
 - There is a concern for the elderly patients that might be lost as an interaction warning.
 - A black box warning is more effective. We could also ask for detailing material to address the problem since face to face interaction is also highly effective in impacting the physician behavior.

TELECONFERENCE MINUTES

MEETING DATE: 23 AUG 01 **TIME:** 12:30PM **LOCATION:** Conference Rm B

NDA 20-896 SE-⁷8 #010

DRUG: XELODA (capecitabine) Tablets

SPONSOR/APPLICANT: Hoffman La Roche **TYPE of MEETING:** Teleconference

FDA PARTICIPANTS: Richard Pazdur, M.D., Division Director
Alison Martin, M.D., Team Leader
Patricia Cortazar, M.D., Medical Reviewer
Maureen Pelosi, RPh, Project Manager

INDUSTRY PARTICIPANTS:

Alex Zukiwski, M.D.
Jan Fagerberg, M.D.
Bruno Ousterwalder, M.D.
Markus Abt, Ph.D.
Murad Husain, R.Ph., Regulatory Affairs

BACKGROUND: The Division is finishing the sNDA review of the Xeloda-Taxotere combination and is generally concerned that the Xeloda dose may be too high. There was a 65% dose reduction in combination with Taxotere. Therefore, the Division wants to speak with Roche and discuss plans for exploring dose and schedule in future development.

QUESTIONS for DISCUSSION:

- 1. FDA: There is some concern regarding the 65% dose reduction with the combination therapy. This is most likely associated with Xeloda. Are you aware of this and what are your plans for further development?**

Roche Response:

- Roche representatives stated that they are aware of the situation and are concerned. They cited three examples of protocols ongoing or planned with Xeloda monotherapy that might satisfy the Division regarding exploring varied doses and schedules.

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- Roche also mentioned plans to further study the Xeloda combination:

FDA Response:

- We are considering requesting a Phase 4 commitment for a randomized Phase 2 study to compare various doses and schedules of Xeloda. Response would be the endpoint which is appropriate in a refractory population similar to the population studies for accelerated approval.
- Have you considered a sequential design such as a comparison of Xeloda followed by docetaxel versus the Xeloda-Taxotere combination as a way to decrease toxicity and test preservation of survival?

2. Roche Question: Why are you suggesting a randomized Phase 2 trial?

FDA Response:

- We believe this may be a way to link decreased toxicity to efficacy, but the population has to be appropriate to reply on a surrogate endpoint of response rate.

ACTION ITEM(S):

1. Please send us details about the above plans and any others of which you are aware.
2. Roche will discuss these issues further and send us information early next week.

The teleconference concluded at 1 PM.

 /S/ /8-29-01
Maureen Pelosi
Project Manager

Concurrence Chair: /S/ /8-29-01
Patricia Cortazar, M.D.
Medical Officer

MEETING MINUTES

MEETING DATE: 12/21/00 **TIME:** 3 PM **LOCATION:** Conf Rm C (3004)

IND/NDA **IND[** **]** **Request Submission Date:** 10/25/00 (N-310)
Briefing Document Submission 11/22/00 (N-311)

DRUG: XELODA (capecitabine) tablets

SPONSOR/APPLICANT: Roche

TYPE of MEETING:

1. **End of Phase 4**
2. **Proposed Indication: Xeloda in combination with docetaxel in the treatment of locally advanced or metastatic breast cancer (final indication to be proposed)**

PURPOSE: To discuss the results of the Phase 3 study SO14999 and fulfillment of accelerated approval commitments for NDA 20-896 and Xeloda labeling update.

To answer specific questions from the sponsor.

FDA PARTICIPANTS:

Richard Pazdur, MD, Division Director
Alison Martin, M.D. Team Leader
Patricia Cortazar, MD, Medical Officer
Ning Li, Ph.D., Biometrics Reviewer
Safaa Ibrahim, PhD, OCBP Reviewer
Maureen Pelosi, R.Ph., Project Manager

ROCHE PARTICIPANTS:

Bruno Osterwalder, MD, Clinical Science
Alex Zukiwski, MD, Clinical Science
Jan Fagerberg, MD, Clinical Science
Lucille Donatucci, M.S., Clinical Science
Bruno Reigner, Ph.D., Clinical Pharmacology
Markus Abt, Ph.D., Biometrics
Olga Rutman, M.S., Biometrics
Peter Teuber, Ph.D., Project Leader
Richard Peck, Ph.D., Regulatory Affairs
Murad Husain, R.Ph., Regulatory Affairs

BACKGROUND AND MEETING OBJECTIVES:

The NDA, 20-896, for Xeloda® (capecitabine) Tablets was approved under accelerated approval regulations (21 CFR 314.510, Subpart H) on April 30, 1998 for the treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and or for whom further anthracycline therapy is not indicated. The accelerated approval of the NDA was based on an open-label, single arm, phase II clinical study demonstrating anti-tumor activity in terms of response rate.

To satisfy the requirements of the accelerated approval regulations it was agreed that a Phase IV study SO14999 entitled "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" will be conducted to verify and describe clinical benefits.

The results of so14999 demonstrate that capecitabine in combination with docetaxel (Taxotere®) is statistically significantly superior than Taxotere® monotherapy with respect to median time to disease progression ($p=0.0001$), median survival ($p=0.0119$), and response rate ($p=0.007$). The safety results of the study are in line with the adverse events listed in the current Xeloda labeling, with some increases in frequency for certain adverse events in combination arm, compared to monotherapy.

- To briefly present the results of study SO14999
- To discuss and agree upon the regulatory procedure on how to submit the necessary data to fulfill the accelerated approval commitment and change the existing Xeloda labeling to include the combination treatment regimen
- To gain concurrence on the content of the submission
- To understand the regulatory process which will take place and its related timings

**APPEARS THIS WAY
ON ORIGINAL**

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Regarding the Xeloda™ (capecitabine) Breast/ EOP4 sNDA filing:

The questions for the meeting with the Division are as follows:

1. Does the Division have any questions regarding the efficacy or safety data presented in the briefing package?

FDA Response: We have the following comments:

- **The patient population must be well described to allow assessment of potential bias between the arms. Please provide the number of patients per arm in each of the four eligibility categories listed on page 2 (along with patient ID). Provide the definition of locally advanced disease including definition by stage; description of previous therapy including treatment dates and doses; and details on previous treatment failure.**
 - **How many patients were previously treated with paclitaxel (include patient ID and doses received). Please include as a Cox regression model a binary variable of whether patients were previously treated with paclitaxel. This will be an exploratory analysis.**
 - **How many survival analyses have been done and what are the timings?**
 - **Please provide information on treatment after study therapy and “crossovers.”**
 - **Please provide toxicity information on patients with hyperbilirubinemia and/or elevated transaminases.**
2. Does the Division agree with our proposal for not _____ in the briefing document?

FDA Response:

- **You will need to reconcile only the tumor response data. It may be to your advantage to have a strong secondary endpoint. FDA will review TTP data derived from the investigator datasets. Please clarify the meaning of “TTP utilizing the on treatment approach.”**

3. Does the Division agree with the content of the proposed submission to meet the two objectives which are to fulfill the accelerated approval commitment and to modify the Xeloda labeling to include the combination treatment regimen? The following documents will be submitted in support of the proposal:

- Phase 1 clinical study report
- Phase 3 pivotal clinical study report
- All Case Report Forms for the pivotal clinical study report (electronically)
- SAS datasets for the pivotal clinical study
- Proposed labeling changes

FDA Response:

Yes, we agree with the content of the submission. Datasets should be in SAS transport files. Please also provide the following information:

- **Analyses of TTP, RR and survival in the subset of patients treated by country and North America versus the Rest of the World**
- **Detailed description of datasets used for efficacy analysis.**
- **Please follow the Guidance for electronic submissions (FDA CDER web page).**
- **Include PK data from the Phase 1 Clinical Study SO15304.**

Biometrics Comments: Please include the following in the sNDA:

- **Both the electronic and hard copy of the SAS codes used for the final data analyses (i.e. those reported in the final NDA for the controlled trial). The sponsor will work together with the reviewer(s) after submission.**
- **Electronic SAS data files with the first 10-20 lines printed (hard copy)**
- **Hard copy of the SAS PROC CONTENTS for the data files for the final data analysis**

4. How should Roche submit the above data? Do we file solely to the IND? If yes, what would be the timing to complete the review?

FDA Response:

- **You may file to the NDA as a supplement. The timing to complete the review will be determined when you submit the sNDA, but is usually 6 to 10 months.**

