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APPROVAL PACKAGE FOR:

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

**Clinical Pharmacology and Biopharmaceutics
Review**

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

sNDA: 20-896/S-011

Date of Submission: July 27, 2001

Drug Name: **Xeloda (capecitabine)**

Formulation: 150 mg and 500 mg Tablets for Oral Administration

Applicant: Hoffmann-La Roche, Inc.
Nutley, NJ

Reviewers: Sophia Abraham, Ph.D.

Type of Submission: Review of a Drug Interaction Study Report
and a Revised Labeling Version

This is a review of the Study No. BP15966 conducted to assess the potential for drug-drug interaction between Xeloda (capecitabine) and warfarin. Based on the results of this study, the Sponsor revised the WARNINGS and PRECAUTIONS sections of XELODA package insert (see Attachment 1).

Xeloda (capecitabine) is an orally administered non-cytotoxic systemic prodrug of 5'-deoxy-5-fluorouridine (5'DFUR) which is converted to 5-fluorouracil. Xeloda is currently approved for the treatment of patients with metastatic breast cancer that is resistant to paclitaxel and an anthracycline-containing regimen or for whom further anthracycline treatment is not indicated. Xeloda is also approved for the first-line treatment in patients with metastatic colorectal cancer.

After oral administration, Xeloda reaches peak blood levels in approximately 1.5 hours (T_{max}) with peak 5-FU levels occurring at 2 hours. Metabolites are 5'-deoxy-5-fluorocytidine (5'DFCR), 5'-deoxy-5-fluorouridine (5'-DFUR), 5-fluorouracil (5-FU), and α -fluoro- β -alanine (FBAL). Capecitabine and its metabolites are predominantly excreted in urine with 95.5% of administered capecitabine dose recovered in the urine. Fecal excretion is minimal (2.6%). The major metabolite excreted in urine is FBAL which represent 57% of the administered dose. About 3% of the administered dose is excreted in urine as unchanged drug. Plasma protein binding of capecitabine and its metabolites is less than 60% and is not concentration-dependent. Capecitabine was primarily bound to human albumin (approximately 35%).

In vitro enzymatic studies with human liver microsomes indicated that capecitabine and its metabolites (5'DFUR, 5'DFCR, 5'FU and FBAL) had no inhibitory effects on substrates of cytochrome P450 for the major isoenzymes

such as 1A2, 2A6, 3A4, 2C9, 2C19, 2D6 and 2E1. Post-marketing safety surveillance in countries where capecitabine has been approved for use in paclitaxel-resistant breast cancer has provided evidence for a possible interaction between capecitabine and coumarin derivatives. Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon.

Warfarin is a hydroxycoumarin derivative, which is commonly used as an oral anticoagulant for the treatment of deep vein thrombosis and pulmonary embolism. It is a racemic mixture of the R- and S-enantiomers. The S-enantiomer exhibits 2-5 times more anticoagulant activity than the R-enantiomer in humans, but generally has a more rapid clearance. Warfarin is completely absorbed after oral administration with peak concentration generally attained within the first 4 hours. Warfarin distributes into a relatively small apparent volume of distribution of about 0.14 L/kg. The elimination of warfarin is almost entirely by metabolism. Warfarin is stereoselectively metabolized by hepatic microsomal enzymes (cytochrome P-450) to inactive hydroxylated metabolites (predominant route) and by reductases to reduced metabolites (warfarin alcohols). The cytochrome P-450 isozymes involved in the metabolism of warfarin include CYP2C9, 2C19, 2C18, 1A2 and 3A4. CYP2C9 is the principal form of human liver P-450 which modulates the in vivo anticoagulant activity of warfarin. The terminal half-life of warfarin after a single dose is approximately one week; however, the effective half-life ranges from 20-60 hours, with a mean of about 40 hours. The clearance of R-warfarin ranges from 37 to 89 hours, while that of S-warfarin ranges from 21 to 43 hours. Studies with radiolabeled drug have demonstrated that up to 92% of the orally administered dose is recovered in urine. Very little warfarin is excreted unchanged in urine. Urinary excretion is in the form of metabolites. Warfarin is highly bound to plasma proteins (~99%).

Protocol No.: BP15966

Title: Effect of capecitabine on the pharmacokinetics and pharmacodynamics of warfarin.

Objectives:

Primary

To investigate the effect of capecitabine on the pharmacokinetics and pharmacodynamics of warfarin.

Secondary

To investigate the effect of capecitabine on the concentrations of vitamin K1 in plasma.

Study Design:

This was an open-label, multi-center, phase 1, pharmacokinetic (PK) and pharmacodynamic (PD) study in six male and female adult patients with advanced solid cancers. The subjects were dosed according to the schedule below:

Dosing Schedule

| Study Day | Warfarin | Capecitabine | PK Sampling |
|-----------|----------|--------------|-------------|
| 1 | X | | X |
| 8-21 | | X | X* |
| 29-42 | | X | |
| 50-60 | | X | |
| 61 | X | X | X |
| 62-63 | | X | |

*On Day 20

A capecitabine dose of 1250 mg/ m² bid was administered in cycles of 3 weeks (2 weeks on and 1 week off) starting on Day 8.

Warfarin 20 mg was given as a single oral dose on Days 1 and 61.

On the day of concomitant capecitabine and warfarin administration (Day 61), the two treatments were administered at the same time.

Formulation:

Capecitabine Lot Numbers

| Dose | Lot Number |
|--------|------------|
| 150 mg | C198210-06 |
| 500 mg | C198200-06 |

Warfarin was supplied by the Applicant and was used for all patients, except Patient 26598/0003 on Day 1 when the study site's pharmacy's own stock was used in error. Warfarin (Lot number 9HD3WW) was purchased from

Sample Size:

Twelve patients were planned to enter the study. A sample size of 12 patients should demonstrate the lack of a drug-drug interaction between warfarin and capecitabine using the reference region 0.80-1.25 of the reference mean with a power of at least 0.80, if the relative effect of the combined treatment was less

than $\pm 5\%$. The two one-sided test procedure after logarithmic transformation was used at the significance level $\alpha=0.05$.

After six patients had been enrolled, the Applicant, in consultation with the investigators, agreed to stop patient accrual and report the results from these patients based on findings of increased S-warfarin AUC and increased INR values. Of these six patients, five patients completed the study and one patient (Patient 26598/0001) withdrew due to an adverse event. Of these six patients, four had evaluable data for PK and PD on all sampling days (Days 1, 20 and 61).

Sampling:

Pharmacokinetic (PK) Assessment

Blood samples were obtained for capecitabine and metabolites assays prior to and 0.5, 1, 2, 3, 4, 5, 8 and 10 hours following capecitabine dosing on Day 20.

Blood samples were obtained for capecitabine prior to and 2, 4 and 8 hours following capecitabine dosing on Day 61.

Blood samples were obtained for warfarin assay prior to and 1, 2, 4, 8, 12, 24, 32, 48, 72, 96, 120 and 144 hours following warfarin dosing on Days 1 and 61.

Pharmacodynamic (PD) Assessment

Blood samples were obtained for PD analysis prior to and 4, 8, 12, 24, 32, 48, 72, 96, 120 and 144 hours following warfarin dosing on Days 1 and 61.

Vitamin K1 measurements were taken prior to breakfast one day between screening and Day 1 and then on Days 1, 60 and 61.

Assay:

Plasma samples were analyzed for capecitabine and metabolites (5'DFCR, 5'DFUR, 5-FU and FBAL) content using

Calibration curves were linear over the concentration range of $\mu\text{g/ml}$ for capecitabine and 5'-DFCR, $\mu\text{g/ml}$ for 5'-DFUR, $\mu\text{g/ml}$ for 5-FU and $\mu\text{g/ml}$ for FBAL.

Plasma samples were analyzed for S- and R-warfarin using a validated method. The limit of quantification was ng/ml . Precision for the calibration standards and quality control samples, as measured by %CV, ranged from $\%$ for (R)-warfarin and from $\%$ for (S)-warfarin. Accuracy for these samples, as measured by $\%$ ranged from $\%$ to $\%$ for (R)-warfarin and $\%$ to $\%$ for (S)-warfarin.

Plasma samples were analyzed for vitamin K1 using a validated method. The limit of quantification was . ng/ml. Calibration curves were linear over the concentration range of . ng/ml to . ng/ml of vitamin K1. Precision for the calibration standards and quality control samples, as measured by %CV, ranged from . % to . % for vitamin K1. Accuracy for these samples, as measured by % ranged from . % to . % for vitamin K1.

Pharmacokinetic Analysis:

Estimation of the PK parameters was performed according to standard non-compartmental methods. Pharmacokinetic parameters of capecitabine and its metabolites (5'DFCR, 5'DFUR, 5-FU and FBAL) and of R- and S-warfarin were calculated for each patient from the concentration-time data obtained on Day 1 (R- and S-warfarin), Day 20 (capecitabine and its metabolites) and Day 61 (R- and S-warfarin, capecitabine and its metabolites). The parameters C_{max} , t_{max} , AUC_{0-144} , $AUC_{0-\infty}$, $t_{1/2}$, and CL/F were calculated for both R- and S-enantiomers of warfarin. The parameters C_{max} , t_{max} , AUC_{0-t} , $AUC_{0-\infty}$ and $t_{1/2}$, were calculated for capecitabine and its metabolites (5'DFCR, 5'DFUR, 5-FU and FBAL).

Pharmacodynamic Analysis:

Pharmacodynamic parameters included prothrombin time, factor VII activity, and vitamin K1. For prothrombin, baseline corrected AUC_{0-144} for prothrombin time (AUC_{corr}), baseline corrected maximum prothrombin time ($E_{max,corr}$), maximum prothrombin time (E_{max}) and time to reach maximum prothrombin time (t_{max}) were estimated. For factor VII, baseline corrected AUC_{0-144} for factor VII activity (AUC_{corr}), baseline corrected maximum factor VII ($E_{max,corr}$) and time to reach maximum factor VII (t_{max}) were estimated. All PD parameters were calculated using model-independent methods. From the prothrombin time and factor VII activity data, baseline AUCs were estimated by multiplying the baseline measurements by 144. Baseline corrected AUC for prothrombin time, AUC_{corr} , was calculated by subtracting the baseline AUC, $AUC_{baseline}$, from the measured AUC, AUC_{0-t} . Baseline corrected AUC for factor VII, AUC_{corr} , was calculated by subtracting the measured AUC, AUC_{0-t} , from baseline AUC, $AUC_{baseline}$. Maximal prothrombin time (E_{max}) and time to reach E_{max} (t_{max}) was directly read from the observed individual prothrombin time data. Prothrombin time was expressed as INR.

Pharmacodynamic parameters for capecitabine were vitamin K1 obtained on one day between screening and Day 1 and then on Days 1, 60 and 61.

Statistical Analysis:

The primary PK parameter for the assessment of the effect of capecitabine on the PK of warfarin was $AUC_{0-\infty}$ of S-warfarin. The primary PD parameter for the assessment of the effect of capecitabine on the PD of warfarin was baseline corrected AUC_{0-144} of prothrombin time (AUC_{corr}). The AUCs of S-warfarin and of the prothrombin time for the combined treatment relative to the treatment with warfarin alone were estimated and 90% confidence limits were calculated using contrasts from ANOVA on the log-transformed variable. No relevant interaction is concluded if the 90% confidence limits for the ratio of the effects of the combined treatment (warfarin+capecitabine) to warfarin alone would be in the equivalence region of 0.80-1.25. Other PK variables were considered as secondary. All PK parameters are presented by descriptive statistics including means, geometric means, medians, ranges, standard deviations, and coefficient of variations. All comparisons were made at a significance level of $\alpha=0.05$.

Results:

The results of the study are presented in Attachment 2.

The pharmacokinetic results show that the co-administration of capecitabine in 4 patients with warfarin resulted in an increase in $AUC_{0-\infty}$ and $t_{1/2}$ of S-warfarin by 57% and 51%, respectively. The 90% confidence interval for the ratio of Log-transformed AUC was 1.317 to 1.879. The increase in the $AUC_{0-\infty}$ and $t_{1/2}$ of R-warfarin was 13% and 15%, respectively.

Plasma concentrations of capecitabine and its metabolites on Days 20 (without warfarin) and 61 (with warfarin) at times 0, 2, 4 and 8 hours do not appear to be different.

The pharmacodynamic results show that the co-administration of capecitabine with warfarin resulted in a 2.8 fold increase in the baseline corrected AUC of INR (90% CI [1.330; 5.699]) and the maximum observed value of INR was increased by 91%. Three out of four patients received Vitamin K due to an INR >3.0. Baseline corrected AUC of factor VII was 8% lower in the presence of capecitabine. Vitamin K1 concentrations in plasma were below the limit of quantitation of the assay. Baseline corrected AUC of factor VII was similar in the absence or presence of capecitabine, but the baseline values were lower in the presence of capecitabine than in the absence of capecitabine.

In conclusion, there appears to be an interaction between capecitabine and warfarin. Patient's INR should be monitored closely and warfarin dose adjusted as needed. Other PK variables were regarded as secondary.

OPDRA CONSULT

Review by Lauren Lee, Pharm. D. of Division of Drug Risk Evaluation 1 indicated that there were 828 total Xeloda associated AERS reports as of July 05, 2001. Of the 828 cases, 72 cases were retrieved when searches for concomitant use of Xeloda and warfarin/phenprocoumon were conducted. The review selected 18 cases for detailed analysis. Fifteen patients were on warfarin and three patients were on phenprocoumon prior to the addition of Xeloda. Warfarin doses ranged from 1 mg to 7.5 mg and Phenprocoumon doses ranged from 1 mg to 3 mg. Xeloda doses ranged from 1300 mg/day to 5000 mg/day with the mean dose of approximately 3700 mg/day.

In 17 cases, abnormal clotting times were detected within 6 to 61 days of starting Xeloda therapy. INR ranged from 5.2 to 28.7 (average ~ 12.4) measured in 15 patients. In nine patients, the elevated PT ranged from 42.2 to 300. In 7 patients, only the INR levels were available without the PT levels, and in one patient, only the PT level was available. Various bleeding episodes were reported in the review with these cases, and two deaths were possibly related to the concomitant use of Xeloda and warfarin.

LABELING COMMENTS

1. BOX WARNING

DRAFT

2. The following statement should be added under the **CLINICAL PHARMACOLOGY/Human Pharmacokinetics/Drug-Drug Interactions** section of the package insert for Xeloda:

DRAFT

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

DRAFT

A COMMENT TO THE MEDICAL REVIEWER

1. The sample size is very low (n=4) and not powered to show the lack of a drug interaction between capecitabine and warfarin. Three out of four of the patients required vitamin K due to an INR >3.0. One patient had bleeding episode. In addition post-marketing reports indicated altered coagulation parameters and/or prothrombin time in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants, such as warfarin and phenprocoumon. Therefore, we recommend that a Box warning be added to the current Xeloda package insert. The consequence of adding warfarin to patients while they are on Xeloda is unknown. However, the package insert is expected to address that concern and no formal study is recommended at this time.

RECOMMENDATION

The drug interaction Study BP15966 submitted in this sNDA for XELODA is acceptable to OCPB. The sponsor should incorporate the Labeling changes as outlined in the Comments 1-5 in the package insert for XELODA.

Please forward the above Recommendation and Comments 1-5 to the sponsor and Comment 1 to the Medical Reviewer.

/s/

Team Leader: Atiqur Rahman, Ph.D.
Division of Pharmaceutical Evaluation I

/s/

Reviewer: Sophia Abraham, Ph.D.
Division of Pharmaceutical Evaluation I

cc: sNDA 20-896
HFD-150/Division file
HFD-150/MPelosi, AMartin, PCortazar
HFD-860/MMehta, ARahman, SAbraham
HFD-430/LLee, SLu, JBeitz
CDR/Biopharm

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

pp. 10-29

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

| | |
|--|----------------|
| Submissions & Dates: NDA 20-896, SE7-010 | March 7, 2001 |
| NDA 20-896, SE7-010-B2 | March 28, 2001 |
| NDA 20-896, SE7-010-SNC | April 17, 2001 |
| NDA 20-896, SE-7-010-BM | May 25, 2001 |
| NDA 20-896, SE-7-010-BB | June 7, 2001 |
| NDA 20-896, SE-7-010-BL | June 11, 2001 |

Drug Name: Xeloda[®] (capecitabine)

Dosage Form: 150 and 500 mg tablets

Applicant: Hoffman-La Roche, Inc.

Type of Submission: efficacy supplement in fulfillment of an accelerated approval commitment for NDA 20-896

Recommendations

1. We recommend that the Applicant acquire data to determine if long-term co administration of capecitabine and docetaxel alters the pharmacokinetics of capecitabine, capecitabine's metabolites, docetaxel, or a combination of these moieties. The performance of the analytical methods and the reporting of the analytical methods for these data should be consistent with FDA's guidance: Bioanalytical Method Validation which is available at <http://www.fda.gov/cder/guidance/index.htm>
2. We recommend that the package insert be modified as indicated on page 16 of this review.

/s/

/s/

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Pharmacokinetic Reviewer
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Overall Summary of Findings for the Clinical Pharmacology and Biopharmaceutics Briefing

The current submission is to fulfill commitments made at the time of accelerated approval of Xeloda®.

On April 30, 1998, NDA 20-896 for Xeloda® (capecitabine) was granted accelerated approval for the treatment of patients with metastatic breast cancer resistant to both docetaxel and an anthracycline-containing chemotherapy regimen or resistant to docetaxel and for whom further anthracycline therapy is not indicated.

The below (font change) is reproduced from the approval letter of April 30, 1998.

We remind you of the Phase 4 commitments specified in your submission dated April 16, 1998. These commitments are listed below.

1. To satisfy the requirements of the accelerated approval regulations (21 CFR 314.510), the proposed Phase 4 study SO 14999B entitled, "An open-label randomized Phase 3 study of capecitabine in combination with docetaxel versus docetaxel monotherapy in patients with advanced and/or metastatic breast cancer" will be conducted with due diligence to verify and describe clinical benefit.

Clinical benefit could be demonstrated in this study if patients randomized to the capecitabine and docetaxel combination had a clinically and statistically significant improvement in time to progression compared to patients randomized to docetaxel monotherapy. It should be noted, however, that members of the Oncologic Drugs Advisory Committee expressed misgivings at the March 19, 1998 meeting regarding the feasibility of demonstrating net clinical benefit for capecitabine in study SO14999B and recommended that alternative study designs be considered. If study SO14999B does not verify the clinical benefit, capecitabine may be subject to the accelerated approval withdrawal procedures described in 21 CFR 314.530.

2. Alternative studies, if any, and major amendments to the design of study SO14999B will be submitted to and discussed with FDA prior to enactment.
3. When completed, study NO ` entitled, "A Phase 2 study of capecitabine in patients who have received previous treatment with paclitaxel or docetaxel for locally advanced and/or metastatic breast cancer" will be submitted.

The question-based portion of this review poses three questions. They are reproduced, together with a summary of the respective answers, below.

1. Does the submission accomplish the Clinical Pharmacology and Biopharmaceutics objective(s) of the protocol submitted April 16, 1998?

The sole clinical pharmacology objective in the protocol was to describe the pharmacokinetics of capecitabine in 16 patients in the combination arm. While this information was collected and analyzed per protocol, 5 rather than 16 patients completed the pharmacokinetics portion of the study. We recommend that the Applicant acquire data to determine if long term co-administration of capecitabine and docetaxel alters the pharmacokinetics of capecitabine.

2. Does co-administration of capecitabine and docetaxel alter the pharmacokinetics of either agent?

The effect of co-administration was assessed in Cycle 1 of the safety and tolerance study of the combination and re-assessed for time-dependence (Cycle 4 versus Cycle 1) in the safety and efficacy study. Co-administration had little or no effect on the pharmacokinetics of capecitabine and its metabolites or docetaxel during Cycle 1 of treatment. The results comparing Cycle 4 versus Cycle 1 are difficult to interpret because of the small number of patients contributing Cycle 4 data. We recommend that the Applicant acquire data to determine if long-term co-administration of capecitabine and docetaxel alters the pharmacokinetics of capecitabine.

3. Are the capecitabine drug products used to assess safety and efficacy in clinical trials bioequivalent to the currently marketed products?

Some of the lots of capecitabine used in the safety and efficacy study were produced at a site not used for U.S. commercial manufacture. Using SUPAC criteria, the difference in products is a Level 3 change. Consistent with the Level 3 we requested that the Applicant perform comparative dissolution testing to determine if the drug product was sufficiently similar to current U.S.-manufactured drug product. The Applicant performed this testing and, using the we conclude that the data supports that the drug products used are similar to the currently marketed U.S. drug products.

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Question-based review – Clinical Pharmacology

1. Does the submission accomplish the clinical pharmacology and biopharmaceutics objectives of the protocol submitted April 16, 1998?

A single clinical pharmacology and biopharmaceutics objective is in the protocol of April 30, 1998 (Study SO14999) and is reproduced below (font change):

OBJECTIVES Secondary

To describe the pharmacokinetics of capecitabine in 16 patients randomized to the control arm.

The plan for accomplishing this objective was to densely sample patients for capecitabine and metabolites during Cycles 1 (Day 14) and 4 (Day 77). This objective was not altered, nor was the pharmacokinetics data collection and analysis plan altered, between April 30, 1998 and submission of the current submission. However, only 11 patients completed pharmacokinetics assessments for Cycle 1 and only 5 completed for Cycle 4. The data for the completers was collected and analyzed per protocol. Review of the results of Study SO14999 is included in our answer to the next question (Question 2. below)

The answer to this question is clearly “No”. The reason for failure to complete the pharmacokinetics phase of the study is not that patients cannot be observed for 3 full cycles: 62% of the patients that entered the combination arm of Study SO14999 contributed data for an analysis of “Received vs Planned Dose” through 5 cycles (Table 88, Vol 12 p. 12-198). We recommend that Roche study the pharmacokinetics of capecitabine after prolonged co-administration of docetaxel. The exact wording of our recommendation appears in **Recommendations** on page 3 of this review. The purpose of this study will be to provide information for the package insert so that prescribers can consider if altering doses of capecitabine or docetaxel with time is necessary.

2. Does co-administration of capecitabine and docetaxel alter the pharmacokinetics of either agent?

Docetaxel is metabolized predominantly by Cytochrome P450 3A4. Capecitabine and 5-FU are not Cytochromes P450 substrates. Based upon these *in vitro* data, no interaction would be predicted.

The pharmacokinetics of capecitabine and docetaxel when used together has been investigated in two clinical studies. Study SO15304 is a Phase I study in 26 patients with the pharmacokinetic objective of investigating the interaction between capecitabine and docetaxel. Study SO14999 is the pivotal Phase III study and pharmacokinetics has been investigated in a subset of 5 patients with the objective of describing the pharmacokinetics of capecitabine in the combination arm on Days 14 and 77 to learn if the pharmacokinetics of capecitabine are altered by several cycles of combination treatment.

The dosing and pharmacokinetics sampling scheme for Study SO15304 are presented below as Table 1.

| Table 1. Dosing and PK Sampling -- Study SO15304¹ | | | | | | | |
|---|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|-------------------------------------|
| | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 |
| docetaxel dose | 75 – 100 mg/m ² | | | | | | |
| capecitabine dose | 1650 – 2500 mg/m ² |
| docetaxel PK (h) | dense | 0, 6 | 0 | | | | |
| capecitabine PK (h) | dense | | | | | | |
| | Day 8 | Day 9 | Day 10 | Day 11 | Day 12 | Day 13 | Day 14 |
| docetaxel dose | | | | | | | |
| capecitabine dose | 1650 – 2500 mg/m ² |
| docetaxel PK (h) | | | | | | | |
| capecitabine PK (h) | | | | | | | dense |
| | Day 15 | Day 16 | Day 17 | Day 18 | Day 19 | Day 20 | Day 21 |
| docetaxel dose | | | | | | | |
| capecitabine dose | | | | | | | |
| docetaxel PK (h) | | | | | | | |
| capecitabine PK (h) | | | | | | | |
| | Day 22 | Day 23 | Day 24 | Day 25 | Day 26 | Day 27 | Day 28 |
| docetaxel dose | 75 – 100 mg/m ² | | | | | | |
| capecitabine dose | | | | | | | |
| docetaxel PK (h) | dense | 0, 6 | 0 | | | | |
| capecitabine PK (h) | | | | | | | |
| ¹ PK comparisons: docetaxel w/capecitabine (Days 1-3) vs docetaxel alone (Days 22-24) capecitabine w/docetaxel (Day 1) vs capecitabine alone (Day 14) | | | | | | | |
| *note: When treating patients the Cycle is 3 weeks; for Study SO15304 a second cycle was not initiated on Day 22 (no capecitabine was dosed) to allow for measurement of docetaxel in the absence of capecitabine | | | | | | | |

The results of Study SO15304 are presented below.

Table 2. Study SO15304 – Effect of Co-administration on the PK of Capecitabine and Docetaxel¹

| PK parameter | Ratio: Co-administration/Alone | 90% Confidence Interval |
|------------------------------------|--------------------------------|-------------------------|
| AUC _{0-inf} of Docetaxel | 0.96 | 0.88 - 0.104 |
| Cmax of Docetaxel | 0.98 | 0.9 - 1.06 |
| AUC _{0-t} of capecitabine | 0.97 | 0.77 - 1.22 |
| Cmax of capecitabine | 1.1 | 0.67 - 1.53 |
| AUC _{0-t} of 5'DFCR | 0.99 | 0.8 - 1.23 |
| Cmax of 5'DFCR | 1.04 | 0.76 - 1.41 |
| AUC _{0-inf} of 5'DFUR | 1.05 | 0.93 - 1.18 |
| Cmax of 5'DFUR | 1.06 | 0.81 - 1.38 |
| AUC _{0-inf} of 5-FU | 0.74* | 0.57 - 0.96 |
| Cmax of 5-FU | 0.79 | 0.53 - 1.38 |
| AUC _{0-inf} of FBAL | 1.02 | 0.88 - 1.18 |
| Cmax of FBAL | 0.96 | 0.79 - 1.16 |

¹values taken from Applicant's calculations

*possibly a result of 5-FU inducing it's own metabolism rather than an effect of co-administration (14 days of capecitabine monotherapy decreases AUC of 5-FU by 10 – 60%).

The dosing for Study SO14999 (the pivotal Phase III study) was similar to that of Study SO15304 (see Table 1. on p. x above) except that

1. the starting doses did not vary: 75 mg/m² for docetaxel and 2500 mg/m² for capecitabine, and
2. Cycles were 3 weeks long (dosing of capecitabine was performed on Days 22 – 35). The Pharmacokinetic sampling for Study SO14999 is only for capecitabine and occurs on Days 14 (last dose of capecitabine for Cycle 1) and 77 (last dose of capecitabine for Cycle 4). The pharmacokinetic results are reproduced from the Applicant's submission and are presented on the following page.

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Table 149 Descriptive Statistics of the Pharmacokinetic Parameters of Capecitabine and Its Metabolites Estimated on Days 14 and 77 after the Morning Administration of Capecitabine.

| Pharmacokinetic Parameter | Day 14 | Day 77 |
|--|------------------|------------------|
| N | 5 | 5 |
| Capecitabine | | |
| C_{max} ($\mu\text{g/mL}$) | 3.02 (59%) | 6.88 (66%) |
| t_{max} (h) | 2.00 (1.00-3.18) | 1.00 (0.52-4.02) |
| $AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{h/mL}$) | 5.41 (26%) | 8.21 (19%) |
| $t_{1/2}$ (h) | 0.64 (90%) | 0.54 (58%) |
| 5'-DFCR | | |
| C_{max} ($\mu\text{g/mL}$) | 3.35 (44%) | 5.02 (91%) |
| t_{max} (h) | 2.00 (1.00-3.18) | 1.01 (0.52-4.02) |
| $AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{h/mL}$) | 7.80 (45%) | 9.90 (78%) |
| $t_{1/2}$ (h) | 0.98 (71%) | 0.71 (36%) |
| 5'-DFUR | | |
| C_{max} ($\mu\text{g/mL}$) | 6.40 (60%) | 9.15 (74%) |
| t_{max} (h) | 2.00 (1.00-3.18) | 1.03 (1.02-4.02) |
| $AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{h/mL}$) | 15.0 (28%) | 17.4 (39%) |
| $t_{1/2}$ (h) | 0.71 (70%) | 0.86 (61%) |
| 5-FU | | |
| C_{max} ($\mu\text{g/mL}$) | 0.364 (37%) | 0.414 (111%) |
| t_{max} (h) | 2.00 (1.00-3.18) | 1.03 (1.02-4.02) |
| $AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{h/mL}$) | 0.786 (42%) | 0.779 (74%) |
| $t_{1/2}$ (h) | 0.75 (71%) | 0.70 (16%) |
| FBAL | | |
| C_{max} ($\mu\text{g/mL}$) | 5.21 (26%) | 5.73 (39%) |
| t_{max} (h) | 3.00 (2.00-7.02) | 3.03 (2.00-5.02) |
| AUC_{0-12} ($\mu\text{g}\cdot\text{h/mL}$) | 25.7 (32%) | 25.2 (35%) |
| $t_{1/2}$ (h) | 2.95 (44%) | 2.43 (12%) |

- Geometric means (geometric CV) are reported for C_{max} , $AUC_{0-\infty}$ or AUC_{0-12} .
- Median values (min-max) are reported for t_{max} .
- Arithmetic means (CV) are reported for $t_{1/2}$.
- Since some patients were dose reduced between day 14 and day 77, AUC and C_{max} values on both days were normalized to a dose equal to the starting dose.
- Patients 20014/6105, 19962/6204, 19962/6209, 19963/6307, and 19963/6309 had evaluable PK samples on day 14 as well as on day 77.

These data are inconclusive because of the small number of patients studied (n = 5). Nonetheless, the mean behavior shows a 120%, 50% and 43% increase in C_{max} for capecitabine, 5'-DFCR and 5'-DFUR. Correspondingly there are 53%, 27% and 16% increases in AUC for these moieties. These changes reinforce our recommendation that the Applicant acquire data to determine if pharmacokinetics are altered with time (see Recommendations, page 3).

Question-based review – Biopharmaceutics

1. Is the capecitabine drug product used to assess safety and efficacy in clinical trials bioequivalent to the currently marketed product?

The submission did not specify that the capecitabine drug product used was the currently marketed U.S. drug product. For this reason FDA requested that Roche submit information regarding the drug products used. The full texts of the FDA information requests and Roche's responses are reproduced as Appendix 2 (page 50) of this review.

Some of the formulations used in the Safety and Efficacy study were manufactured at a facility not approved for manufacture of drug product for the U.S.

Relative to the site of U.S. manufacture, use of the site is a Level 3 SUPAC change. Consistent with a Level 3 change FDA requested comparative dissolution data using the currently approved procedure for Xeloda tablets. The procedure is USP Apparatus 2 at rpm in mL deionized water at °C. This testing was performed and the results are on the following three pages of this review (reproduced without edits from Roche's submission). Based on the values obtained () we conclude that the capecitabine drug product used to assess safety and efficacy is bioequivalent to the currently marketed product.

**APPEARS THIS WAY
ON ORIGINAL**

Question-based review -- Analytical Methods

1. Clinical Pharmacology

In both studies, concentrations of capecitabine and its metabolites (5'-DFCR, 5'DFUR, 5-FU and FBAL) were measured by using the same method previously used during the development of capecitabine. Docetaxel was measured using a validated method.

Details of the performance of the analytical methods can be found in Appendix 6 of this review which begins on page 80.

2. Biopharmaceutics

A summary of the analytical methods for the comparative dissolution testing has been submitted and is included as Appendix 3 of this review (page 57).

**APPEARS THIS WAY
ON ORIGINAL**

Detailed labeling recommendations

A claim that pharmacokinetics are not changed by capecitabine and docetaxel co-administration has been added to the label. It is reproduced below (font change).

Draft

We recommend that the words " " be substituted for the words " " to make clear that chronic dosing has not been studied. The revised section is produced below (font change).

~~XXXXXX~~ **Draft**

**APPEARS THIS WAY
ON ORIGINAL**

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

pp. 17-49

Appendix 2 – Roche’s Response to FDA’s Requests for Information of April 2, 2001 and April 10, 2001: Formulations used during development

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REPLY TO FDA QUESTION OF APRIL 2, 2001

FDA Question #1: Would you please indicate if the current marketed tablet was the Xeloda dosage form used, and the only Xeloda dosage form used, in studies SO 15304 and SO 14999?

Sponsor Reply: All tablets used in clinical studies SO 15304 and SO 14999 are fully representative of the currently marketed tablets. All batches used in clinical study SO 14999 have the same quantitative composition as the currently marketed tablets. The batches used in clinical study SO 15304 also have the same composition for the tablet as the currently marketed tablets but the color of these tablets was different (tan).

SO 14999

All batches used in clinical study SO 14999 have the same quantitative composition as the currently marketed product. Tablets used at the initiation of the clinical study were manufactured for clinical use but they are identical to the currently marketed product.

These tablets differed from the currently marketed product only in the embossing on the tablets or the site of manufacture. Subsequent supplies, also identical to the current marketed tablet, were taken from process validation and commercial production batches.

SO 15304

The composition of the of the clinical tablets for study SO 15304 are identical to the tablet of the current commercial product. Tablets used in this study (C-183025 and C-183035) contained a tan colorant in the film coat rather than light peach (150 mg) or peach (500 mg). The amount of film coating on these tan 150-mg tablets was slightly less than what was used on subsequent batches of light peach 150-mg tablets. The manufacturing equipment and scale were the same as those of subsequent batches.

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pages of trade

secret and/or

confidential

commercial

information