CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-896/S-006

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW
AMENDMENT # 1

NDA:	20-896/S-009
Submission Dates:	October 23, 2000
Drug Name:	Capecitabine (XELODA™)
Dosage Form:	150 mg and 500 mg Tablets for Oral Administration
Sponsor:	Hoffmann-La Roche Inc. Nutley, New Jersey
Reviewer:	Sophia Abraham, Ph.D.
Submission Type:	Review of Additional Population PK Analyses

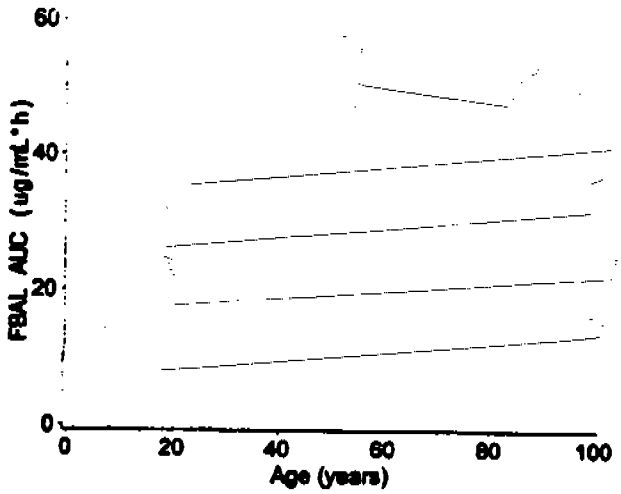
This is an amendment review of additional population PK NONMEM analyses of data from two phase III colorectal cancer studies. The review evaluates the influence of age and creatinine clearance on the Pharmacokinetics of FBAL, one of the main metabolites of capecitabine (XELODA™). This additional analysis was submitted in support of the firm's proposed labeling changes for the use of XELODA™ in renally impaired patients (Original review of the submission of October 23, 2000).

In the submission of September 20, 1999, population PK NONMEM analyses were performed on the pooled plasma data from the pivotal Phase III trials (SO14695 and SO14796) in colorectal cancer patients (n=505) to evaluate the influence of pertinent clinical covariates on the pharmacokinetics of capecitabine and its metabolites. The final PK model was as follows:

Run # CAP7440:

$$CL2 = 1190 \cdot (ALP/140)^{-0.169}$$
$$CL3 = 27.5 \cdot (CLR/80)^{0.615}$$
$$V3 = 73.6 \cdot (CLR/80)^{0.384} \cdot (BSA/1.8)^{0.182}$$

Of the covariates tested, alkaline phosphatase (ALP) levels had a significant influence on 5-FU clearance (CL2) and creatinine clearance (CLR) had a significant influence on FBAL clearance (CL3) and volume of distribution (V3). Age was not a significant covariate affecting the PK parameters of 5'-DFUR, 5-FU, or FBAL. However, a separate regression analysis of the pooled data from the two pivotal Phase III studies (SO14695 and SO14796) revealed that a 20% increase in age results in a 15% increase in exposure to FBAL as measured by AUC (see Figure below).



In the present submission, additional population PK NONMEM analyses were performed using the final PK model that was developed previously (Run # CAP7440) to further evaluate the effect of age on clearance and volume of distribution for FBAL (CL3 and V3). The sponsor included age (AGE) separately as a covariate in the final PK model on CL3 (Run # CAP7490) then on V3 (Run # CAP7491). AGE was then added on both CL3 and V3 to the final PK model (Run # CAP7492). Finally, AGE was included but creatinine clearance was removed from the model on both CL3 and V3 (Run # CAP7493). The results from all these runs are presented in Tables 1-5 (Attachment 1). These models are as follows:

Run # CAP7490:

$$CL3 = 27.6 \cdot (CLR/80)^{0.642} \cdot (AGE/50)^{0.102}$$
$$V3 = 73.6 \cdot (CLR/80)^{0.392} \cdot (BSA/1.8)^{0.810}$$

Run # CAP7491:

$$CL3 = 27.4 \cdot (CLR/80)^{0.601}$$
$$V3 = 74.4 \cdot (CLR/80)^{0.483} \cdot (AGE/50)^{0.236} \cdot (BSA/1.8)^{0.664}$$

Run # CAP7492:

$$CL3 = 27.6 \cdot (CLR/80)^{0.642} \cdot (AGE/50)^{0.102}$$
$$V3 = 74.4 \cdot (CLR/80)^{0.483} \cdot (AGE/50)^{0.236} \cdot (BSA/1.8)^{0.664}$$

Run # CAP7493:

$$CL3 = 27.6 \cdot (AGE/50)^{0.102}$$
$$V3 = 74.4 \cdot (AGE/50)^{0.236} \cdot (BSA/1.8)^{0.664}$$

A 20% increase in age (from 50 to 60 years) results in 2% and 0.3% increase in FBAL clearance (CL3) as shown in Runs # CAP7490 and CAP7492, respectively. FBAL volume of distribution (V3) increased by 4% for both Runs # CAP7491 and CAP7492 with 20% increase in age.

A decrease in the objective function values (OF) was noted when age was added as a covariate in addition to creatinine clearance in the final PK model. This decrease was not significant for Run # CAP7490 ($\Delta OF=0.758$, $p > 0.05$) but was significant for Runs # CAP7491 ($\Delta OF=6.203$, $p < 0.05$) and # CAP7492 ($\Delta OF=6.274$, $p < 0.05$).

When creatinine clearance was removed from the final model and age was included on both CL3 and V3 (Run # CAP7493), the objective function value greatly increased from 2844.378 to 3018.027 ($\Delta OF=173.649$), indicating that creatinine clearance is a significant covariate affecting these parameters. A 20% increase in age (from 50 to 60 years) results in 8% and 3% decrease in FBAL clearance (CL3) and volume (V3) (Run # CAP7493). Age is not an important factor as long as creatinine clearance is accounted for in the model for FBAL clearance and volume of distribution.

Comment to the Medical Reviewer:

FBAL is predominantly eliminated by the kidneys (~50%) and thus, its pharmacokinetics are mostly affected by the degree of renal impairment. It is well known that age is correlated to glomerular filtration rate (GFR) as measured by creatinine clearance. GFR decreases after 40 years of age by approximately 6.0 ml/min/1.73 m^2 per decade. The effect of age on the pharmacokinetics of XELODA™ is primarily due to a decrease in creatinine clearance as the renal function is worsening with age. Elderly patients (> 80 years of age) will be more sensitive to the toxic effects of XELODA™ than younger patients, thus, the warning in the current labeling for patients of > 80 years of age should remain.

RECOMMENDATION

The above Comment is for the Medical Reviewer. No action is indicated.

/S/ 4/12/01

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

/S/ 4/12/01

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

cc: NDA 20-896
HFD-150/Division file
HFD-150/Maureen, Martin
HFD-860/Mehta, Rahman, Abraham
CDR/Biopharm

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

sNDA:	20-896
Dates of Submission:	September 20, 1999 March 6, 2000 June 16, 2000
Type of Submission:	Review of a Supplemental NDA
Drug Name:	***XELODA (Capecitabine)***
Dosage Form:	150 mg and 500 mg Tablets For Oral Administration
Dose:	2500 mg/m^2/day
Applicant:	Hoffmann-La Roche Inc., Nutley, New Jersey
Reviewer: Pharmacometrics Consult:	Safaa Ibrahim, Ph. D. Joga Gobburu, Ph.D.

I. SYNOPSIS

This Supplemental New Drug Application (sNDA) seeks approval for the use of capecitabine (XELODA) tablets in the first-line treatment of patients with advanced and/or metastatic colorectal cancer. XELODA is currently approved for the treatment of patients with metastatic breast cancer resistant to both paclitaxel and for whom further anthracycline therapy is not indicated.

Two identical, open-labeled, randomized, well-controlled, multi-center Phase III studies (SO14695 and SO14796) were submitted to support the use of XELODA in the first-line treatment of patients with advance and/or metastatic colorectal cancer.

These two pivotal Phase III trials (SO14695 and SO14796) were prospectively designed to collect sparse plasma samples from patients during the study. Population pharmacokinetic (PK) analyses were performed on pooled sparse plasma data from the two trials using NONMEM modeling program to evaluate the influence of pertinent clinical covariates on the pharmacokinetics of capecitabine and its metabolites. In addition, concentration-effect analyses were also performed to explore the relationship between systemic exposure to capecitabine metabolites and (i) efficacy parameters (e.g., response rate, time to progression, and survival), and (ii) safety parameters (e.g., grade ¾ diarrhea, grade 3 Hand-Foot syndrome, and grade ¾ hyperbilirubinemia).

Population Pharmacokinetic Analyses:

Sparse plasma data from the pivotal Phase III trial in colorectal cancer patients (n=481) combined with the extensive plasma data from the bioequivalence study BP15572 (n=24) were used to develop and validate the population PK model (Total n=505). The final PK model which best described the data was a linear model with first-order absorption and lag time. The **covariates** tested in this model for their potential influence on the main PK parameters (Viz., clearances of 5'-DFUR, 5-FU, and FBAL, and volume of FBAL) included:

- age (AGE), gender (GENDER), race (RACE), body weight (BWT), body surface area (BSA),
- creatinine clearance (CLCR),
- status of liver metastasis (absent versus present),
- Karnofsky Performance Status (KPS),
- albumin (ALB),
- alkaline phosphatase (ALP),
- aspartat aminotransferase (ASAT),
- alanine aminotransferase (ALAT),
- total bilirubin (TB)
- study (STUDY)

Covariates that were found to significantly affect the PK parameters in the final PK model included alkaline phosphatase (ALP) on the clearance of 5-FU, creatinine clearance (CLCR) on the clearance and volume of FBAL, and body surface area (BSA) on the volume of FBAL. A five-fold increase in ALP would result in a 24% decrease in 5-FU clearance. FBAL clearance and its volume of distribution would decrease by 35% and 24%, respectively, when CLCR decreases by 50%; FBAL is excreted primary by the kidneys. FBAL volume of distribution would increase by 24% when BSA increases by 30%.

Although age was not a significant covariate in the final PK model, a separate analysis on the pooled data from the two pivotal studies indicated that a 20% increase in age results in a 15% increase in AUC of FBAL.

As an exploratory analysis, the effect of nine selected comedications on the main PK model parameters (clearances of 5'-DFUR, 5-FU, and FBAL and volume of distribution of FBAL) were examined using the final PK model and the complete data set (n=505). This exploratory analysis revealed that paracetamol (n=20) and morphine (n=14) increased 5-FU clearance by 26% and 41%, respectively and loperamide (n=12) decreased 5-FU clearance by 31%.

Systemic Exposure-Safety/Efficacy Analyses:

Regression analyses of relationships between systemic exposure (AUC, Cmax) to capecitabine metabolites (5'-DFUR, 5-FU and FBAL) after capecitabine dose

of 1250 mg/m^2 and safety/efficacy variables were performed in 481 patients after pooling data from the two pivotal phase III trials in colorectal cancer patients. Systemic exposure was calculated using individual estimates of AUC and Cmax for 5'-DFUR, 5-FU, and FBAL (post-hoc estimates) from the respective population pharmacokinetic analysis. The results of these analyses showed that there was an overlap in systemic exposure to capecitabine metabolites in patients with and without adverse events as indicated by the absence of statistically significant relationships between systemic exposure and adverse events. Most significant relationships found were the increase of related grade ¾ diarrhea with increasing AUC values of FBAL and the increase of hyperbilirubinemia with increasing AUC values of 5-FU.

An overlap was also found between systemic exposure in patients with and without tumor response as indicated by the absence of statistically significant relationships between systemic exposure and tumor response. A positive relationship between Cmax of 5'-DFUR and survival is the most significant relationship. However, the lack of a relationship between Cmax of 5'-DFUR and other efficacy parameters weakens this finding. Negative relationships (i.e., higher systemic exposure with lower probability of response) between plasma AUC of 5-FU and several efficacy parameters (survival, Time-To-disease progression, and tumor response) were found which could not be explained.

Because of the overlap in systemic exposure (AUC and Cmax of 5'-DFUR, 5-FU, and FBAL) between patients with and without grade ¾ adverse effects or with and without efficacy, the Applicant did not use these relationships to optimize capecitabine dose in Phase III trials in colorectal cancer.

II. GENERAL COMMENTS

During the review of the above population PK analyses, the primary reviewer faced with the following QUESTIONS:

1. Although a reliable fit was obtained when the final population PK model was fitted to Index data set (n=321), fitting this model to the complete data set (n=505) produced unrealistic estimates for TLAG (2.02×10^{-4} hours) and its intersubject and intraoccasion variabilities (49498 % and 52915 %, respectively). Is there a need to redevelop the model?

2. Including data from Patient 1005 (Study SO14695) in the Index data set had a major impact on the final population PK model. The covariates identified in the final model without Patient 1005 included the effect of alkaline phosphatase on the clearance of 5-FU, creatinine clearance on the clearance and volume of FBAL, and body surface area on the volume of FBAL. The covariates identified with Patient 1005 included effects of race, gender and study on 5-FU clearance. The effect of alkaline phosphatase was not detected in the model that included Patient 1005. Effects of creatinine clearance on both FBAL clearance and volume and of body surface area on

FBAL volume were present in both models (without or with Patient 1005). Again, is there a need to redevelop the model?

3. As an exploratory analysis, the effect of 'treatment cycle' on the main PK parameters (clearances of 5'-DFUR, 5-FU, and FBAL and volume of distribution of FBAL) was examined using the final population PK model and the complete data set (n=505). There was a significant 'treatment cycle' effect on the clearances of 5'-DFUR, 5-FU, and FBAL and volume of FBAL between Cycle 2 or 4 and single dose administration. This analysis was performed in an exploratory fashion and no definitive conclusion can be drawn.

4. As an exploratory analysis, the effect of nine selected comedications on the main PK model parameters (clearances of 5'-DFUR, 5-FU, and FBAL and volume of FBAL) were examined using the final population PK model and the complete data set (n=505). The results revealed that paracetamol (n=20) and morphine (n=14) increased 5-FU clearance by 26% and 41%, respectively, and loperamide (n=12) decreased 5-FU clearance by 31%. 5-FU is the active moiety for capecitabine. The clinical significance of these interactions is not known. Is there a need to conduct additional drug-drug interactions studies?

Dr. Joga Gobburu (Pharmacometrics Reviewer) addressed the above QUESTIONS as follows:

1. Very small TLag estimate and very large variability: The aim of the pharmacokinetic analysis was to identify influential covariates. The TLag estimates for index data sets CAP7035 and CAP7400 were 0.073 and 0.083 hour, respectively. The estimate of TLag for the complete data set was negligible. Remodeling the data may not lead to a different conclusion. It is so because: (a) The estimate of TLag is about 4.8 min that might not influence the other PK parameters considerably, and (b) The estimates of all clearances and volumes of distribution of all the 3 moieties are similar for the two studies modeled either separately or jointly.

2. Patient 1005: The inclusion and exclusion of patient 1005 (study SO14695) changes the selection of influential covariates. This oriental female patient does not seem to demonstrate any obvious differences in the demographic profile from the rest of the patients. During cycle 4, the 5-FU concentrations were about 2.5 times higher over a period of 4 hours than 5'-DFUR values. This trend was not observed during cycle 2 or in other patients. The fact that patient 1005 affect the selection of covariates may suggest highly variable data and weak covariate relationships (1 out of 321 patients). A five–fold change in alkaline phosphatase, for example, is reported to result in a 24% change in 5-FU clearance. Further, the residual variability of the proposed model was 60–70% (CV) for 5-FU. Such a large unexplained variability suggests a not so robust pharmacostatistical model. No exposure–response could be established, although attempted, which makes interpretation of the

24% change in systemic clearance of 5-FU confounding. Such a change in the PK parameter over a broad range of the covariate might not call for a change in the dosing. Nevertheless, the Applicant needs to better substantiate the inclusion and/or exclusion of patient 1005.

3. Treatment cycle effect: Neither the NONMEM control stream nor the model that tested the treatment cycle effect was included with the report of the results. Treatment cycle effect was concluded to be significant for 5'-DFUR, 5-FU and FBAL clearances and the volume of distribution of FBAL. The degrees of freedom were stated to be 3 and it is not clear from the report how that was derived (model not specified). Taking into consideration: (a) the expectation based on physiologic principles (no reason for clearance/volume of distribution being different during different treatment cycles), (b) unexplained variability (~ 60% CV) and (c) the change in the objective function (expecting at least 20 for 2 additional parameters; $p<0.01$), the data do not support a treatment cycle effect on the PK parameters.

4. Drug – drug interactions: The results indicated that paracetamol (26%) and morphine (41%) increase 5-FU clearance and loperamide decreases 5-FU clearance (31%). A priori, based on physiologic principles, no interaction between any of these drugs with 5-FU, 5'-DFUR, or FBAL can be expected. The relationship, again, is weak for all the reasons stated earlier. Further, the number of patients who received these co-medications is less than 4% and thus the results may be an artifact. Drug interactions were concluded to be significant interestingly again for the same parameters as for the treatment cycle effect, 5'-DFUR, 5-FU and FBAL clearances and the volume of distribution of FBAL. The medical reviewer should attempt to compare the clinical end points in these sub-groups to investigate potential effectiveness/ toxicity related issues.

III. LABELING COMMENTS

Draft

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

S

Reviewer: Safaa S. Ibrahim, Ph.D.
Division of Pharmaceutical Evaluation I

ClinPharm/Biopharm Briefing on: July 19, 2000 (Attendees: Drs.: Mehta, Rahman, Ibrahim, Gobburu)

RD/FT S 7/19/00
Team Leader: Atiqur Rahman, Ph.D.
Division of Pharmaceutical Evaluation I

cc: sNDA 20-896
HFD-150/Division file Pelosi
HFD-150/~~Maureen~~, Martin
HFD-860/Mehta, Rahman, Ibrahim
CDR/Biopharm

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V. A Question-Based Review

A. Pharmacokinetics in Colorectal cancer patients

! Has the sponsor adequately described the pharmacokinetics of capecitabine and its metabolites in patients with colorectal cancer?

The sponsor did not conduct a separate study in patients with colorectal cancer. However, as part of the Phase II trial SO14797 (original NDA), eleven patients with colorectal cancer participated in a two-way crossover study to examine the effect of food on the pharmacokinetics of capecitabine and its metabolites. The followings are the mean pharmacokinetics parameters estimated by non-compartmental methods for capecitabine and its metabolites in these patients after single oral administration of 666 mg/m^2 and 1255 mg/m^2 doses 30-minutes after food intake:

Table 1 **Pharmacokinetic parameters of capecitabine and its metabolites in colorectal cancer patients following oral administration of 666 mg/m^2 (n=6) and 1255 mg/m^2 (n=5) doses 30-minutes after *food intake. [C_{max} and AUC values are normalized to a dose of 1255 mg/m^2]**

Parameter	Capecitabine	5'-DFCR	5'-DFUR	5-FU	FBAL
C_{max} (μg/mL)	2.7 (62%)	3.7 (45%)	6.3 (37%)	0.31 (50%)	5.7 (26%)
t_{max} (h)	2.0 (0.5-2.07)	2.0 (1.0-4.0)	2.0 (1.0-4.0)	2.0 (2.0-4.0)	3.0 (2.0-5.0)
$AUC_{0-\infty}$ (μg.h/mL)	6.0 (27%)	9.4 (35%)	14.4 (16%)	0.7 (33%)	31.4 (30%)
$t_{1/2}$ (h)	0.89 (69%)	0.84 (12%)	0.75 (22%)	0.84 (25%)	2.5 (19%)

Arithmetic means (%CV) are reported for C_{max}, $AUC_{0-\infty}$ and $t_{1/2}$. Median values (range) are reported for t_{max}, n=11. * (capecitabine was administered to patients 30 minutes after a standard breakfast during clinical trials)

In addition, the pharmacokinetic parameters were determined using the prospective population PK analysis that was performed on the pooled sparse plasma samples obtained from 481 colorectal patients during the two pivotal Phase III trials. It can be assumed that the sponsor has adequately described the pharmacokinetics of capecitabine and its metabolites in colorectal cancer patients.

B. Population Pharmacokinetic Analyses

! Has the sponsor adequately developed and validated the population PK model for capecitabine and its metabolites?

! What are the covariates tested in the PK model? – Which ones significantly affect the pharmacokinetic parameters of capecitabine and its metabolites?

The basic population PK model developed initially to describe the time course of capecitabine metabolites, 5'-DFUR, 5-FU, and FBAL utilized the plasma data from the bioequivalence study BP15572 (n=24 patients) following a single-dose administration of the to-be-marketed capecitabine formulation (2000 mg). Patients ranged in age from 41 to 80 years. There were 15 males and 9 females. All patients were Caucasians. Extensive PK sampling was applied in this study; a total of 11 samples were taken from each patient pre-dose and at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hr. The structure of the of the basic PK model is depicted below:

Dose of Capecitabine

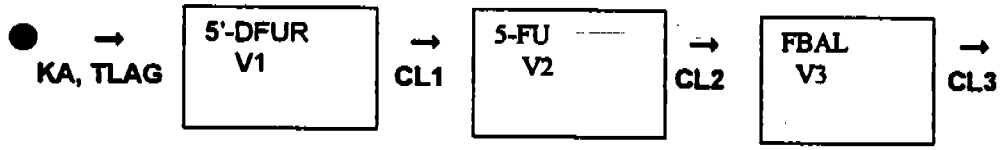


Figure 2. Pharmacokinetic structural model (KA – first-order absorption rate, TLAG – lag time, CL1, C2, CL3 - apparent metabolic clearances, V1, V2, V3- apparent volumes of distribution)

The plasma concentrations of 5'-DFUR, 5-FU, and FBAL were only included in the PK model building to balance the complexity of the model with its clinical relevance. 5'-DFUR and FBAL were considered because of their contribution to safety and 5-FU because it is the active agent following administration of capecitabine and because it is an intermediate between 5'-DFUR and FBAL.

The basic population PK model was then used to analyze the plasma data from the two pivotal Phase III studies in 482 patients colorectal cancer (SO14695 and SO14796). In both studies, patients ranged in age from 27 to 86 years. There were 288 males and 194 females; 431 Caucasians, 22 Blacks, and 29 Others. Data from one patient (Patient 1005, Study SO14695) were excluded from the analysis because of higher 5-FU plasma concentrations compared to those for 5'-DFUR on study days 22 and 64. Patient 1005 was an Oriental female patient, 52 years of age, weighing 77 kg, and having normal values for creatinine clearance, Karnofsky Performance Status, and other physiological parameters (Table 3b, Attachment 2). The complete data set thus included 505 patients (n=481+24) with a range of ages from 27 to 86 years (234 of ≥ 65 years, 7 of ≥ 80 years of age); 303 males and 202 females; 455 Caucasians, 22 Blacks, and 28 Others.

Sparse PK sampling was applied in these studies; a total of three samples were taken from each patient in the pre-determined time frames of 0.5-1 hr, 1.5-3.0 hr, and 3.0-0.5 hr on the first day of cycles 2 (Day 22) and 4 (Day 64) in both studies (SO14695 and SO14796). Plasma samples were analyzed for 5'-DFUR, 5-FU, and FBAL using _____assay methods. The spare data were randomly divided into two sets of data: an index data set (2/3 of all data, n=321) and a validation data set (1/3 of the data, n=160). Study descriptions and baseline demographic data are shown in Tables 2 and 3a, respectively (Attachment 2).

Baseline demographic data for the index and validation data sets are shown in Table 3b (Attachment 2).

Development of the Final PK Model:

The sparse **index data** (n=321) combined with the extensive data from study BP15572 (n=24) were fitted to the **basic** population PK model to estimate the PK parameters of capecitabine metabolites, 5'-DFUR, 5-FU, and FBAL. The extensive data from study BP15572 were added to the sparse index data set in order to obtain a reliable fit.

The residual variability (RV), e.g., assay error, incorrect model specification and incorrect dose and/or sample record, was estimated using a combined exponential and additive error model.

The intersubject variability (ISV) in PK parameters was estimated using an exponential error model.

The interoccasion variability (IOV) on absorption rate constant (KA) and lag time (TLAG) was estimated using an exponential error model.

The following **covariates** were examined for their potential influence on the main PK parameters: clearances of 5'-DFUR (CL1), 5-FU (CL2) and FBAL (CL3), and volume of FBAL (V3):

- age (AGE), gender (GENDER), race (RACE), body weight (BWT), body surface area (BSA),
- creatinine clearance (CLCR),
- status of liver metastasis (absent versus present),
- Karnofsky Performance Status (KPS),
- albumin (ALB),
- alkaline phosphatase (ALP),
- aspartat aminotransferase (ASAT),
- alanine aminotransferase (ALAT),
- total bilirubin (TB)
- study (STUDY)

The influence of continuous covariates (i.e., AGE, BWT, BSA, CLCR, KPS, ALB, ALP, ASAT, ALAT, and TB) on a PK model parameter P (e.g., CL) was examined using a log-linear model.

The influence of categorical covariates (i.e., GENDER, RACE, status of liver metastasis, STUDY) on a PK model parameter (e.g., CL) was examined by multiplying the PK parameter by θ, where θ represents a scale factor quantifying the influence of the covariate on PK parameter.

Each single covariate/PK parameter pair was added, one by one, to the **basic** PK model. The **full** PK model was defined as the model that produced a drop in the NONMEM objective function of 3.84, 5.99, or 7.81 for one, two, or three degrees of freedom, respectively, when compared with the value from the **basic** model at a p-value of < 0.05 assuming a Chi-square distribution.

The **final** PK model was determined by stepwise backward deletion of all covariate relationships from the **full** PK model at a p-value of 0.001. Thus, under the assumption of a Chi-square distribution an increase in NONMEM objective function value of 10.83, 13.82, or 16.27 was required for one, two, or three degrees of freedom, respectively, in order to retain a relationship. At each deletion step only the least significant covariate effect was dropped from the model. This procedure was repeated until no covariate effect with $p<0.001$ was found.

Tables 4, 5, and 6 (Attachment 2) show parameter estimates and variabilities (RV, ISV, and IOV) for the basic, full, and final models, respectively.

After model validation (as outlined below), the final population PK model that was developed using the index data set was then applied to the complete data set (n=505) to yield the final population PK parameter estimates (Table 7a, Attachment 1). The basic PK model was also fitted to the complete data; the results are shown in Table 7b. Diagnostic plots for the final PK model are shown in Figures 4 and 5 (Attachment 2).

The above model building and validation procedures were repeated again with the addition of plasma data from Patient 1005 (Study SO14695) to the database. Patient 1005 was an Oriental female patient, 52 years of age, weighing 77 kg, having normal baseline values for Karnofsky Performance Status, creatinine clearance and other physiological parameters (e.g, albumin, bilirubin, ASAT, ALP... etc.) and without liver metastasis. Results of these analyses are presented in Attachment 3.

As an exploratory analysis, the effect of 'treatment cycle' on the main PK parameters (CL1, CL2, CL3, and V3) was examined using the final population PK model and the complete data set. The 'treatment cycle' effect was modeled as a categorical covariate. Results of this analysis are shown in Table 8 (Attachment 2). Because of its exploratory nature, no validation was considered in this analysis.

Model Validation:

Validation Based on Concentrations: The final PK population model was fitted to the validation data set (n=160). Individual metabolite concentrations ($C_{i,pred}$) for

5'-DFUR, 5-FU, and FBAL were predicted. The predicted metabolite concentrations were compared to the respective observed values ($C_{i,obs}$). For each metabolite, the prediction errors **($pe_{i,con}$)** were calculated as $pe_{i,con} = C_{i,pred} - C_{i,obs}$. The respective mean prediction errors and mean squared prediction errors were calculated over all measurements (see Figures 6-8 and Table 9, Attachment 2).

Validation Based on PK Parameters:

(a) The validation data (n=160) combined with the extensive data from study BP15572 (n=24) were first applied to the basic population PK model and a post-hoc PK parameter estimates were obtained. The extensive data from study BP15572 were again added to the sparse validation data set in order to stabilize the model. The post-hoc PK parameter estimates were used as reference or true ('ref') PK parameter values.

(b) Individual predicted PK parameter estimates were obtained for patients in the validation data set using the final PK model. As a measure of the predictive performance of the final PK model, the prediction error (pe_i) for 'i' metabolite was estimated as the difference between predicted PK parameter and the posthoc 'ref' PK parameter ($pe_i = P_{i,pred} - P_{i,ref}$) .

(c) The predictive performance was evaluated by computing the median prediction error (mde) as a measure of "bias" and median absolute prediction error (mae) as a measure of "precision" (see Table 10, Attachment 2).

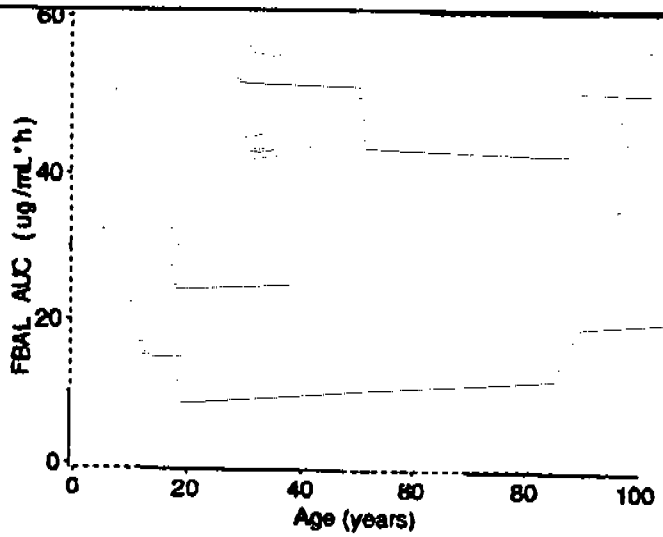
RESULTS

The final PK model (Table 7a, Attachment 2) adequately described plasma profiles of capecitabine metabolites (5'-DFUR, 5-FU, and FBAL) and the relationship between the covariates and PK parameters. The NONMEM objective function value dropped from about 3382 (basic model without covariates, Table 7b) to about 2844 (final model with covariates, Table 7b). The precision (%SE) of PK parameter estimates for the final PK model was reasonable while that for the basic PK model could not be calculated. The NONMEM run for the basic model indicated that R matrix was algorthmically singular and no covariance matrix could be obtained).

Intersubject variability (ISV) between the two models remained practically unchanged except for the variability in FBAL volume and clearance; ISV decreased from 37% to 26% and from 47% to 32%, respectively. Residual variability and intraoccasion variability between the basic and final PK models remained also practically unchanged.

Gender, race, liver metastasis, KPS, total billrubin, serum albumin. ASAT, ALAT, and STUDY did not significantly affect the PK parameters of 5'-DFUR, 5-FU, and FBAL.

Age did not significantly affect the PK parameters of 5'-DFUR, 5-FU. However, in a separate analysis on the pooled data from the two pivotal studies revealed that a 20% increase in age results in a 15% increase in AUC of FBAL (see Figure below).



AUC of FBAL as a function of age. The black points are the model predicted individual values of AUC and the line is from the multiplicative model. The AUC values are derived from the individual post hoc estimates of CL and the intended dose of 1250 mg/sqm.

--- Covariates that were found to significantly affect the PK parameters are summarized below:

Statistically significant Effect	Change in independent variable	Effect on the PK parameter	Effect on systemic exposure
ALP on CL of 5-FU	ALP • 5	CL of 5-FU 24% lower	AUC 31% higher
CLCR on CL of FBAL	CLCR • 0.5	CL of FBAL 35% lower	AUC 53% higher
CLCR on V of FBAL	CLCR • 0.5	V of FBAL 24% lower	Cmax 41% higher
BSA on V of FBAL	BSA •1.3	V of FBAL 24% higher	Cmax 19% lower

Effect of Alkaline Phosphatase (ALP) on 5-FU Clearance (CL2):

$$TVCL2 = 1190 \cdot (ALP/140)^{-0.169}$$

For a typical ALP value of 140 U/L, the typical 5-FU clearance (TVCL2) would be 1190 L/hr. In the range of observed ALP values (42-1346 U/L), a five-fold increase in ALP value would result in a 24% decrease in 5-FU clearance.

Effect of Creatinine Clearance (CLCR) on FBAL Clearance (CL3):

$$TVCL3 = 27.5 \cdot (CLCR/80)^{0.615}$$

For a typical CLCR value of 80 ml/min, the typical FBAL clearance (TVCL3) would be 27.5 L/hr. In the range of observed CLCR values (26-261 ml/min), a 50% decrease in CLCR would result a 35% decrease in FBAL clearance. FBAL is excreted primary by the kidneys.

Effect of CLCR and Body Surface Area (BSA) on FBAL Volume of Distribution (V3):

$$TVV3 = 73.6 \cdot (CLCR/80)^{0.384} \cdot (BSA/1.8)^{0.182}$$

For a typical CLCR value of 80 ml/min and a typical BSA value of 1.8 m^2, the typical FBAL volume of distribution (TVV3) would be 73.6 L. In the range of observed CLCR values (CLCR=26-261 ml/min), a 50% decrease in CLCR would result in 24% decrease in FBAL volume of distribution, provided that BSA is unchanged. In the range of observed BSA values (1.19-3.06 m^2), a 30% increase in BSA would result in 24% increase in volume of distribution, provided that CLCR is unchanged.

— When plasma data from Patient 1005 were added to the index data set (n=321+1=322), the final population PK model included the effects of RACE, GENDER, and STUDY on 5-FU clearance (Attachment 3, Table 40). The effect of alkaline phosphatase (ALP) on 5-FU clearance was not significant in the final model when Patient 1005 data were added. Effects of CLCR on both FBAL clearance and volume and of BSA on FBAL volume were present in both models (i.e., with or without data from Patient 1005).

— From Table 8 (Attachment 2), there is a significant 'treatment cycle' effect on PK parameters, CL1, CL2, CL3, and V3, between Cycle 2 or 4 and single dose administration. This analysis was performed in an exploratory fashion and no definitive conclusion could be drawn.

Model Validation:

— Prediction error versus time plots (Figures 6-8, Attachment 2) show that the spread in prediction errors is larger for 5'DFUR and 5-FU than for FBAL. Mean prediction error for FBAL was the lowest (0.004 μg/ml) compared to 0.039 μg/ml and 0.11 μg/ml for 5'-DFUR and 5-FU, respectively (Table 9). Mean prediction errors were not significantly different from zero ($p > 0.05$).

— Table 10 shows that the bias and precision in predicting the PK parameters for the final PK model are less than 10% and 20%, respectively.

In conclusion, a population PK model was adequately developed and validated to fit the plasma data of patients with colorectal cancer during the two pivotal studies.

! **Has the sponsor used the population PK analysis of Phase III plasma data to evaluate any potential for drug-drug interactions in patients with colorectal cancer?**

As an exploratory analysis, the effect of nine selected comedications (Table 11, Attachment 2) on the main PK model parameters (CL1, CL2, CL3, and V3) were examined by adding respective categorical covariate relationships (i.e., comedication present/absent) to the final population PK model and the complete data set (n=505). To reach to the final comedication PK model, one by one deletion was then applied. The results are shown in Table 12 (Attachment 2). Because of its exploratory nature, no validation was considered in this analysis.

The results revealed that paracetamol (n=20) and morphine (n=14) increased 5-FU clearance by 26% and 41%, respectively, and loperamide (n=12) decreased 5-FU clearance by 31%. 5-FU is the active moiety for capecitabine.

Warfarin did not appear to affect the PK of capeciabine metabolites (n=9). However, in the submission of December 10, 1998, the analysis of the safety database for capecitabine revealed that the coadministration of capecitabine with warfarin alter the coagulation parameters (e.g., Prothrombin Time) within several days and up to several months after initiating the therapy. A precaution statement was included in the current package insert for XELODA. A study is undergoing examining the effect of capecitabine on the pharmacokinetics and pharmaco-dynamics of warfarin.

D. Systemic Exposure-Safety/Efficacy Analyses

- **Is there a relationship between systemic exposure and efficacy and/or safety parameters?**

- **Has the relationship between systemic exposure and efficacy and/or safety parameters been used to support dose selection for the pivotal Phase III trials in patients with colorectal cancer?**

The sponsor explored the relationships between systemic exposure (AUC and Cmax) to capecitabine metabolites, 5'-DFUR, 5-FU and FBAL, and measures of safety and efficacy for combined data of two pivotal Phase III studies (SO14695 and SO14796) using regression analyses.

The **safety** measures used in the model were defined as:

SI	All treatment-related (probably, possibly, remotely) grade ¾ adverse events (AE).
S2	Related grade ¾ diarrhea
S3	Grade 3 Hand-Foot syndrome (HFS)
S4	Grade ¾ hyperbilirubinemia (absolute values)

The **efficacy** measures used in the model were defined as:

EI	Time to disease progression (TTP) as assessed by an Independent Review Committee (IRC)
E2	Time to disease progression as assessed by Investigator
E3	Responder/Non Responder as assessed by IRC.
E4	Responder/Non Responder as assessed by Investigator.
E5	Duration of survival

Prediction of Systemic Exposure:

Systemic exposure to 5'-DFUR, 5-FU, and FBAL was predicted using the basic structural PK model derived in STEP 2 (see Figure 3 above). Individual AUC values for 5'-DFUR were calculated as

$$AUC(5'\text{-DFUR}) = \frac{Dose}{CL1} \cdot \frac{MW_{5'\text{-DFUR}}}{MW_{capecitabine}}$$

Where Dose is the amount of capecitabine given to an individual and CL1 is the individual post-hoc estimate of apparent 5'-DFUR clearance. $MW_{5'\text{-DFUR}}$ and $MW_{capecicabine}$ are the molecular weight of 5'-DFUR (MW=246) and capecitabine (MW=359), respectively. Accordingly, for 5-FU and FBAL:

$$AUC(5\text{-FU}) = \frac{Dose}{CL2} \cdot \frac{MW_{5\text{-FU}}}{MW_{capecitabine}}$$

$$AUC(FBAL) = \frac{Dose}{CL3} \cdot \frac{MW_{FBAL}}{MW_{capecitabine}}$$

Cmax values for 5'-DFUR, 5-FU and FBAL were determined by simulation using the basic PK structural model with individual post-hoc parameters estimated from the final population PK model.

Systemic Exposure/Safety Analyses:

A logistic regression analysis (PROC LOGISTIC, SAS Software) was performed on all safety parameters (S1-S4) with the dependent variable being occurrence (yes/no) of the respective event over the entire study period and the independent variable being systemic exposure (i.e. AUC or Cmax) to 5'-DFUR, 5-FU and FBAL.

As the first step in the analyses, univariate logistic regression was performed with each dependent variable (SI-S4) on each of the six independent variables (AUC and Cmax of 5'-DFUR, 5-FU, and FBAL).

Results are shown in Tables 13-20 and Figures 13-16 (Attachment 4).

Systemic Exposure/Efficacy Analyses:

Two types of regression analyses were performed for efficacy, depending on whether the dependent variables were considered as time-to-event variables or binary variables:

Cox regression analysis (PROC PHREEG, SAS Software) was used in the analysis of systemic exposure and time-to-event data (TTP assessed by IRC (E1), TTP assessed by Investigator (E2), and duration of survival (E5)). The Cox proportional hazard model was applied to investigate the relationship between exposure and these efficacy criteria.

As the first step in the analyses, univariate Cox regression was performed with each dependent variable (El, E2, E5) on each of the six independent variables (AUC and Cmax of 5'-DFUR, 5-FU, and FBAL). All independent variables which were significant at $p \leq 0.05$ were combined with those covariates which were found to have a significant impact on the particular efficacy parameter in previous clinical subgroup analyses. Results are shown in Tables 21-24 (Attachment 3).

Systemic exposure versus duration of survival analyses are shown in Tables 29 and 30 (Attachment 3).

- A logistic regression analysis (PROC LOGISTIC, SAS Software) was used in the analysis of systemic exposure and the **binary variable,** tumor response, as assessed by IRC (E3) and by Investigator (E4). No multivariate models were explored in this case.

Results are shown in Tables 25-28 and Figures 17 and 18 (Attachment 3).

RESULTS

Systemic Exposure/Safety:

- There was an overlap in systemic exposure in patients with and without related grade ¾ adverse events (Table 13).

- No statistically significant relationships were found between systemic exposure measures and all related grade ¾ adverse events ($p > 0.05$, Table 14).

- AUC of FBAL was the only statistically significant exposure measure with respect to related grade ¾ diarrhea ($p=0.035$, Table 16). With increasing FBAL AUC values, the probability for a related grade ¾ diarrhea also increases.

- There were no statistically significant relationships between systemic exposure measures and grade 3 Hand-Foot Syndrome ($P > 0.05$, Tables 17 and 18).

- The probability of hyperbilirubinemia increased with increasing AUC values of 5-FU (Slope=0.21, $p=0.025$); while it decreased with increasing Cmax of FBAL (Slope=-0.28, $p=0.014$), as shown in Table 20.

Systemic Exposure/Efficacy:

- The highest Hazard Ratio was obtained with 5-FU AUC and Time to Disease Progression (TTP) as assessed by Investigator. Higher exposure (AUC) to 5-FU in plasma leads to higher risk of disease progression, $p=0.0056$ and 0.0094 for univariate and mulitvariate Cox models, respectively (Table 22).

- The highest Hazard Ratio was obtained with 5-FU AUC and TTP as assessed by IRC, $p=0.045$ using univariate Cox model (Table 24).

- There was an overlap in systemic exposure in patients with and without tumor response as assessed by Investigator and IRC (Tables 25 and 27).

- There were no statistically significant relationships between systemic exposure measures and tumor response as assessed by Investigator ($P > 0.05$, Table 26).

- AUC of 5-FU was the only statistically significant exposure measure with respect to tumor response as assessed by IRC, p=0.012 (Table 28).

- Cmax of 5'-DFUR was the only statistically significant systemic exposure variable for survival, showing a positive association with survival (p= 0.0048 and 0.032 for univariate and multivariate Cox models, respectively, Table 30).

In summary,

- There was an overlap in systemic exposure to capecitabine metabolites in patients with and without adverse events as indicated by the absence of statistically significant relationships between systemic exposure and adverse events. Most significant relationships found were the increase of related grade ¾ diarrhea with increasing AUC values of FBAL and the increase of hyperbilirubinemia with increasing AUC values of 5-FU.

- An overlap was also found between systemic exposure in patients with and without tumor response as indicated by the absence of statistically significant relationships between systemic exposure and tumor response. A positive relationship between Cmax of 5'-DFUR and survival is the most significant relationship. However, the lack of a relationship between Cmax of 5'-DFUR and other efficacy parameters weakens this finding. Negative relationships (i.e., higher systemic exposure with lower probability of response) between plasma AUC of 5-FU and several efficacy parameters (survival, TTP, and tumor response) were found which could not be explained.

- Because of the overlap in systemic exposure (AUC and Cmax of 5'-DFUR, 5-FU, and FBAL) between patients with and without grade ¾ adverse effects or with and without efficacy, the Applicant did not use these relationships to optimize capecitabine dose in Phase III trials in colorectal cancer.

VI. *In Vitro* Cytochrome P450 Inhibition Studies

The effects of capecitabine and its three metabolites (5'-DFCR, 5-FU and FBAL) on the inhibition of human cytochrome P450 enzymes was investigated. These studies were conducted using human liver microsomes and known specific probe substrates for each individual P450 isoform: CYP1A2 (ethoxyresrufin), CYP2A6 (coumarin), CYP 2C9 (tolbutamide), CYP2C19 (S-mephenytoin), CYP2D6 (bufuralol), CYP2E1 (chlorzoxazone), and CYP3A4 (midazolam). The results indicate that capecitabine, 5'-DFCR, 5-FU and FBAL have no inhibitory effect on the major cytochrome P450 enzymes.

APPEARS THIS WAY
ON ORIGINAL

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

(pp. 22-41)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:	20-896/S-006
Submission Date:	August 25, 2000
Drug Name:	**Capecitabine (XELODA™)**
Dosage Form:	150 mg and 500 mg Tablets For Oral Administration
Sponsor:	Hoffmann-La Roche Inc. Nutley, New Jersey
Reviewer:	Safaa Ibrahim, Ph.D.
Type of Submission:	Review of a Labeling Supplement

This is a review of the revised version of the package insert for Xeloda™.

The following minor corrections have been made to the CLINICAL PHARMACOLOGY/Human Pharmacokineties/Special Populations section of the package insert for Xeloda™.

DRAFT

Recommendation

Corrections made in the package insert are acceptable to OCPB. No action is necessary.

/S/ 10/11/00
Team Leader: Atiqur Rahman, Ph.D.
Division of Pharmaceutical Evaluation I

/S/
Reviewer: Safaa S. Ibrahim, Ph.D.
Division of Pharmaceutical Evaluation I

cc: NDA 20-896
HFD-150/Division file
HFD-150/Maureen, Martin
HFD-860/Mehta, Rahman, Ibrahim
CDR (Biopharm)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA:	20-896/S-006
Submission Dates:	September 12, 2000 September 13, 2000
Drug Name:	Capecitabine (XELODA™)
Dosage Form:	150 mg and 500 mg Tablets for Oral Administration
Sponsor:	Hoffmann-La Roche Inc. Nutley, New Jersey
Reviewer:	Safaa Ibrahim, Ph.D.
Submission Type:	Review of a Study Report

This submission contains a brief summary of the safety and pharmacokinetic data obtained from a study entitled "Effect of Renal Impairment on the Pharmacokinetics of Capecitabine in Cancer Patients" (Protocol WP15811). These data were submitted upon FDA's request in the fax of August 22, 2000.

Summary of the Study Report:

This was an open-label, parallel design, phase I study in 27 cancer patients. There were 4 groups with varying degrees of renal function, as follows:

Group	N	Males/ Females	Creatinine Clearance
A (normal renal function)	6	3/3	> 80 ml/min
B (mild renal impairment)	8	3/5	51-80 ml/min
C (moderate renal impairment)	9	1/8	30-50 ml/min
D (severe renal impairment)	4	1/3	< 30 ml/min

Creatinine clearance (CLcr) was estimated using serum creatinine and patients' demographics (age, sex and body weight) by Cockroft and Gault formula. Patients were administered 1250 mg/m^2 capecitabine twice a day for 2 weeks followed by 1 week off. The pharmacokinetics of capecitabine and its metabolites were assessed on study days 1 and 14.

Results are presented in Tables 1-13 (Attachment 1).

Safety Results:

The safety results (Table 2) indicate that:

- Patients with severe renal impairment (Group D) had the highest incidence of adverse events (AE's) with Grade 3-4 or serious adverse events (SAE's) (100%, N=4/4) than other groups.
- The incidence of SAE's was higher than in Groups C and B than the normal group (Group A), 89% (N=8/9), 62.5% (N=5/8), and 50% (N=3/6), respectively.
- The incidence of Grade 3-4 AE's was 100% (N=6/6) in Group A, 87.5% (N=7/8) in Group B, and 89% (N=8/9) in Group C.
- Of the 27 patients enrolled, 4 patients died during the study, one with mild renal impairment from (Group B), one with moderate renal impairment (Group C) and 2 with severe renal impairment (Group D). According to Table 3, the cause of death was not related to the drug except for Patient 44 (Group D). Five additional death cases occurred after the last dose of capecitabine; the cause of death as assessed by the sponsor was from progressive disease (4 cases) or unknown (1 case).

Pharmacokinetic Results:

Pharmacokinetic data (Tables 4-13) were reported as mean (%CV) of pharmacokinetic parameters for capecitabine and its metabolites on Days 1 and 14. No individual data or statistical analyses were submitted. Percent change in pharmacokinetic parameters in renal groups compared to the normal group is shown in the table below:

Parameter	(Mild/Normal)		Moderate/Normal		Severe/Normal	
	Day 1 (N=8/6)	Day 14 (N=7/6)	Day 1 (N=6/6)	Day 14 (N=6/6)	Day 1 (N=4/6)	Day 14 (N=2/6)
Cmax						
Capecitabine	--	--	--	--	--	--
5'-DCFR	--	--	--	--	↑ 20%	--
5'-DFUR	--	--	↑ 21%	--	↑ 84%	--
5-FU	--	--	--	--	--	--
FBAL	--	↑18%	--	↑ 39%	↑ 50%	↑189%
AUC0-∞						
Capecitabine	--	--	↑ 25%	↑ 19%	↑ 25%	--
5'-DCFR	--	--	↑ 16%	--	--	--
5'-DFUR	--	--	↑ 42%	↑ 29%	↑ 70%	↑ 17%
5-FU	--	--	--	--	↑ 23%	--
FBAL	--	↑ 20%	↑ 85%	↑69%	↑ 258%	315%

From the above table it appears that renal impairment greatly influenced the

pharmacokinetics of FBAL followed by 5'-DFUR and capecitabine. Renal impairment had less effect on the pharmacokinetics of 5'-DCFR and 5-FU. For example, on Day 1 of therapy, patients with moderate renal impairment had a higher exposure (as assessed by AUC0-∞) to capecitabine, 5'-DFUR, and FBAL than normal patients (25%, 42%, and 85%, respectively). The corresponding values in severe renal patients were 25%, 70%, and 258%, respectively. On Day 14, exposure to capecitabine was slightly increased (19%) in patients with moderate renal impairment, but not in patients with mild and severe renal impairment. Exposure to 5'-DFUR and FBAL was 29% and 69% respectively, higher in moderate renal patients and 17% and 315%, respectively, higher in severe renal patients than normal patients.

Based on these safety and pharmacokinetic data, the sponsor recommends that

- XELODA™ should be contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min).
- In patients with moderate renal impairment, a dose reduction to 75% of the starting dose of 2500 mg/m^2/day) is recommended.
- No adjustment to the starting dose of XELODA™ in patients with mild renal impairment (creatinine clearance=50-80 ml/min) is recommended.

Since a summary of the data was submitted in this study with no individual data or statistical analysis, proper assessment of the effect of renal impairment on the pharmacokinetics of capecitabine and its metabolites and proper dosing recommendations for the use of XELODA™ in renal patients could not be made.

RECOMMENDATION

The sponsor should submit the final report for Study WP15811 to the FDA for review as soon as it is completed.

Please convey the above Recommendation to the sponsor.

S 9/18/00

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

S

Reviewer: Safaa S. Ibrahim, Ph.D.
Division of Pharmaceutical Evaluation I

cc: NDA 20-896
HFD-150/Division file
HFD-150/Maureen, Martin
HFD-860/Mehta, Rahman, Ibrahim
CDR/Biopharm

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

sNDA:	20-896/SE1-006 and SLR-009
Submission Dates:	October 23, 2000 October 30, 2000 November 6, 2000
Drug Name:	Capecitabine (XELODA)
Dosage Form:	150 mg and 500 mg Tablets for Oral Administration
Applicant:	Hoffmann-La Roche, Inc. Nutley, New Jersey
Reviewer:	Safaa Ibrahim, Ph.D.
Submission Type:	Review of a Renal Impairment Study Report and a Revised Version of the Labeling

This is a review of a study report (WP15811) evaluating the effect of renal impairment on the pharmacokinetics of capcitabine and its metabolites (Submissions of October 23 and November 6, 2000). Based on the results of this study, the Applicant proposed a revised a package insert for XELODA (see Attachment 1). The submission dated October 30, 2000 contains the Applicant's responses to the Division's approvable letter dated September 20, 2000.

Capecitabine (Ro 09-1978) is a novel antineoplastic agent (prodrug) belonging to the fluoropyrimidine carbamate class. It is rationally designed as an orally administered precursor of 5'-deoxy-5-fluorouridine (5'-DFUR) which is activated to the cytotoxic moiety, 5-fluorouracil (5-FU), by thymidine phosphorylase. XELODA is approved for the treatment of metastatic breast cancer. The sNDA is seeking approval for the first-line treament of patients with metastatic colorectal cancer when XELODA is administered as 1250 mg/m^2 twice daily in cycles of three weeks, two weeks on treatment and one week off.

The original NDA for XELODA (submission of October 28, 1997) did not contain a formal pharmacokinetic study in renally impaired patients. However, the meta-analysis of data from the Phase I studies of the original NDA indicated that creatinine clearance might have an impact on the pharmacokinetics of 5-FU and FBAL. Systemic exposure to 5-FU and FBAL would increase by 45% when creatinine clearance decreases by 50%. A population PK analysis of the data from the Phase III trials in colorectal cancer patients of the submission of September 20, 1999 indicated that FBAL clearance would decrease by 35% when creatinine clearance decreases by 50%. Both the meta-analysis and

population PK analysis are exploratory in nature and could not strongly support any dosing recommendations to be made in the labeling for the use of XELODA in renally impaired patients.

The Agency requested the Applicant to conduct a prospective study in renally impaired patients. Accordingly, Hoffmann-La Roche submitted a protocol (WP15811) on August 28, 1998 under IND ( ) to evaluate the effect of renal impairment on the pharmacokinetics of capecitabine and its metabolites in cancer patients with varying degrees of renal impairment. During the ongoing study for this protocol, analysis of the MedWatch of November 23, 1999 (S-281) showed that a 70 years old female patient from United Kingdom with chronic renal failure was hospitalized with stomatitis, diarrhea, and hypotension. The patient developed sepsis and acute on chronic renal failure and then died. The cause of death was stated to be a combination of sepsis, acute on chronic renal failure, and progression of neoplasia. The Agency strongly recommended the sponsor in the submissions of November 23, 1999 and February 16, 2000 (IND ( ) respectively) to submit for review all individual safety and pharmacokinetic data for Study WP15811 as soon as the report was completed. The following is the review of Study WP15811:

Protocol No.: WP15811

Title: **Effect of Renal Impairment on the Pharmacokinetics of Capecitabine in Cancer Patients**

Objectives:

- To investigate the effect of renal impairment on the pharmacokinetics of capecitabine in cancer patients.
- To explore the effect of renal function on safety.

Study Design:

This was an open-label, parallel design, steady-state, phase I study in 27 cancer patients. There were 4 groups with varying degrees of renal function, as follows:

Group	N	Males/ Females	Creatinine Clearance
A (normal renal function)	6	3/3	> 80 ml/min
B (mild renal impairment)	8	3/5	51-80 ml/min
C (moderate renal impairment)	9	1/8	30-50 ml/min
D (severe renal impairment)	4	1/3	< 30 ml/min

Creatinine clearance was estimated using serum creatinine and patients' demographics (age, sex and body weight) by Cockroft and Gault formula.

Of the 27 patients, three patients in the moderate group (Group C) were excluded from the pharmacokinetic evaluation (see Table 10, Attachment 1 for more details). All patients were administered 1250 mg/m^2 capecitabine orally twice a day for 2 weeks within 30-minutes after a meal. The pharmacokinetics of capecitabine and its metabolites were assessed on study days 1 and 14.

Sampling:

Blood samples were collected at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours following dosing on days 1 and 14. Total urine was collected on a cumulative basis during 0-12 and 12-24 hours post dose on days 1 and 14.

Analytical Methods:

Plasma and urine samples for capecitabine and its metabolites (5'-DFCR, 5'-DFUR, 5-FU, and FBAL) were analyzed using validated [redacted]

Pharmacokinetic Evaluation:

Estimation of the pharmacokinetic parameters was performed according to standard noncompartmental methods. The pharmacokinetic parameters of capecitabine and its metabolites (5'-DFCR, 5'-DFUR, 5-FU and FBAL) were calculated for each patient from the concentration-time data obtained on days 1 and 14. The following parameters were estimated: maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), apparent half-life ($t_{½}$), area under the plasma curve from time 0 to infinity ($AUC_{0-\infty}$). From urine data, percentage of dose excreted in urine as unchanged drug and metabolites (5'-DFCR, 5'-DFUR, 5-FU, and FBAL) were calculated.

Results:

Detailed results are presented in Attachment 2. Descriptive statistices on the pharmaco-kinetic parameters are shown in Tables 12-21. Percent of dose excreted in urine as parent drug and its metabolites is shown in Tables 22 and 23. Safety results are shown in Tables 30 and 31.

Pharmacokinetic Results:

From Tables 12-21 (Attachment 2), the percent change in C_{max} and $AUC_{0-\infty}$ on Days 1 and 14 in renal groups (mild=Mi, moderate=Mo, severe=S) compared to the normal group (normal=N) was calculated (by the reviewer) and presented in the table in the next page:

n/Group Ratio	% Change in C_{max} Compared to the Normal Group					
	Mi/N 8/6	Mo/N 6/6	S/N 4/6	Mi/N 8/6	Mo/N 6/6	S/N 2/6
	Day 1			Day 14		
Capecitabine	--	16%	--	-10%	--	25%
5'-DFCR	--	--	20%	-12%	-50%	-47%
5'-DFUR	--	20%	84%	-27%	-15%	--
5-FU	-50%	-40%	--	-25%	-50%	-29%
FBAL	-12%	--	50%	20%	37%	189%
	% Change in $AUC_{0-\infty}$ Compared to the Normal Group					
Capecitabine	--	26%	25%	--	19%	-42%
5'-DFCR	--	16%	--	--	-26%	-37%
5'-DFUR	--	42%	71%	-19%	29%	16%
5-FU	-34	-10%	23%	-25%	-20%	--
FBAL	--	85%	258%	19%	69%	315%

-- = Unchanged

From the above table, it appears that renal impairment greatly influenced the pharmacokinetics of FBAL, this is expected since this moiety is primary excreted in urine (about 50%). For example, on Day 1 of therapy, patients with moderate and severe renal impairment had 85% and 258%, respectively, higher systemic exposure to FBAL (as assessed by $AUC_{0-\infty}$) than patients with normal renal function. The corresponding values on Day 14 were 69% and 315%, respectively. Systemic exposure to 5'-DFUR on Day 1 was 42% and 71% higher in moderately and severely renally impaired patients, respectively, than in normal patients; however, similar increases were not observed on Day 14. On Day 1, systemic exposure to capecitabine was about 25% higher in both moderately and severely renally impaired patients than in normal patients. There is no evidence of an effect of renal impairment on the systemic exposure to 5'-DFCR and 5-FU.

Safety Results:

From Table 31 (Attachment 2), the incidence of at least one severe (Grade 3) adverse event was 100 %, 87.5%, 89%, and 100% in the normal, mild, moderate, and severe renal groups, respectively. The incidence of at least one life-threatening (Grade 4) adverse event was 50% in the severe renal group and 11% in the moderate renal group. No Grade 4 event occurred in the normal or mild renal group. A summary is shown below for the intensity of adverse events in patients who experienced at least one adverse event during the study:

Degree of Renal Impairment	Normal	Mild	Moderate	Severe
Total N	6	8	9	4
Grade 1 (Mild)	6 (100%)	8 (100%)	9 (100%)	4 (100%)
Grade 2 (Moderate)	6 (100%)	7 (87.5%)	9 (100%)	4 (100%)
Grade 3 (Severe)	6 (100%)	7 (87.5%)	8 (89%)	4 (100%)
Grade 4 (Life-threatening)	–	–	1 (11%)	2 (50%)

Based on the results from the above study (WP15811), the sponsor concluded the following recommendations for the use of XELODA in renally impaired patients:

- XELODA should be contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min [Cockroft and Gault]).

- In patients with moderate renal impairment (creatinine clearance=30-50 ml/min [Cockroft and Gault]), a dose reduction to 75% of the starting dose of 1250 mg/m^2 BID (2500 mg/m^2/day) is recommended.

- No adjustment to the starting dose of XELODA in patients with mild renal impairment (creatinine clearance=51-80 ml/min [Cockroft and Gault]) is recommended.

The above recommendations are acceptable.

LABELING COMMENTS

Reference is made to the Applicant's revised package insert for XELODA (Attachment 1) under:

DRAFT

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(pp. 67)

RECOMMENDATION

The renal impairment Study WP15811 submitted in this sNDA for XELODA is acceptable. The Applicant should incorporate the Labeling changes as outlined in the Comments above in the package insert for XELODA.

Please forward the above Recommendation and Comments 1-4 to the sponsor.

/S/

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

/S/

Reviewer: Safaa S. Ibrahim, Ph.D.
Division of Pharmaceutical Evaluation I

cc: sNDA 20-896
HFD-150/Division file
HFD-150/Maureen, Johnson, Martin
HFD-860/Mehta, Rahman, Ibrahim
CDR/Biopharm

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pages of trade secret and/or confidential commercial information