- **Chemotherapy after Study Drug**

Sponsor Table 26 presents the number of patients who received additional chemotherapy after study treatment. Data are not available for 6 patients: 4 with missing data and 2 still on study drug at the time the forms were requested. Two of these patients were randomized to capecitabine and 4 to 5-FU/LV. CPT-11 is the only agent that has been shown to prolong survival as second-line treatment of colorectal cancer. Slightly more patients randomized to 5-FU/LV received subsequent CPT-11. No tests of significance are performed.

Sponsor Table 26*
Post-Study Chemotherapy (SO14796)

Post-Study Chemotherapy	Capecitabine (N = 301)	5-FU/LV (N = 301)
Total Receiving Chemorx	50.2%	48.8%
CPT-11	15.9%	21.6%
5-FU	39.9%	27.2%
Oxaliplatin	11.0%	11.6%

*vol. 119, p. 69

Reviewer Comment: *The absence of important details such as dose, specifics of 5FU administration (e.g. with leucovorin or as a continuous infusion), duration of therapy and whether given as second or later treatment, limits any serious analysis. The sponsor submitted additional data on second line chemotherapy in the Four-Month Safety Update. A total of 28 patients on capecitabine and 53 patients on 5-FU/LV received CPT-11, slightly different numbers when compared to the original sNDA data. In either case, no obvious bias in favor of capecitabine is seen since more patients on 5-FU/LV received CPT-11. When compared to S014695, approximately 10% fewer patients received post-study chemotherapy. Of those who did, half as many received CPT-11 and twice as many received oxaliplatin as in the predominantly U.S. study.*

8.2.3.6 Quality of Life

As with S014695, the protocol-specified instrument for measurement of QoL was the EORTC QLQ-C30. Subscales 29 and 30, measuring the global health status, were preselected as the primary outcome of interest over functional and symptoms scales. The timepoint for the primary analysis was day 169 (week 24), chosen to diminish the effect of early dropouts and deaths.

At day 169, 122 (40%) patients on capecitabine and 109 (36%) on 5-FU/LV were evaluated. The QoL global health scores were not statistically different for the two treatments ($p = 0.7095$). Descriptive analyses of the other domains, including appetite loss, fatigue, diarrhea, nausea and vomiting did not indicate a major difference between the treatments.

Reviewer Comment: *Due to both the high percentage of missing data and the different cycle lengths resulting in collection of QoL at different timepoints, these data should be interpreted with caution and be considered as exploratory.*

Major Statistical Issue of sNDA: Testing a Non-Inferiority Hypothesis

As with protocol SO14695, the protocol-specified test of non-inferiority in survival was defined quantitatively by the upper bound of the 95% CI of the HR of capecitabine to 5-FU/LV. If the upper limit did not exceed 1.25 while testing at the 2.5% α-level, non-inferiority would be concluded. Since this definition did not identify the survival benefit conveyed by 5-FU/LV over 5-FU alone, a 10-paper meta-analysis of appropriate randomized trials was undertaken (see Section 7.2.3.4). The following non-inferiority analyses were conducted by the Agency using methodology described in Section 7.2.3.4 and Appendix II.

Table 30 lists vital survival descriptive statistics for S014796 trials for the cutoff dates of January 1999 and May 15, 2000.

Reviewer Table 30: Summary of Relevant Survival Descriptive Statistics (SO14796)

Study	HR(Xeloda/5-FU+LV)	log HR	SE(logHR)
ITT Population			
SO14796 January 1999 cutoff	0.98	-0.0195	0.1019
SO14796 May 15, 2000 cutoff	0.92	-0.0844	0.0867
Standard Population			
S014796 May 15, 2000 cutoff	0.91	-0.0966	0.0921

Reviewer Table 31:
Non-inferiority Survival Analysis for SO14796 (January 1999 Cutoff) using the 10-paper Meta-Analysis and a 0.025 One-Sided Type I Error Rate (Margins and Results are Given)

Study	50% retained	0% retained
ITT Population		
SO14796		
97.5% confidence upper bound = 1.20	1.114[1] NO	1.204[2] YES

[1] Margin is computed using the lower limit of the 30% C.I. for HR(5-FU/5-FU+LV).
[2] Margin is computed using the lower limit of the 48% C.I. for HR(5-FU/5-FU+LV).

A greater than 0% retention of the survival effect due to adding LV to 5-FU for the SO14796 trial was the sole statistically significant result at a 0.025 one-sided significance level.

Table 32 below gives results of 0.025 one-sided type I error rate survival analyses (May 15, 2000 cutoff) using the 10-paper meta-analysis.

Reviewer Table 32:
Non-inferiority Updated (May 15, 2000 Cutoff) Survival Analysis for SO14796 using the 10-paper Meta-Analysis and a 0.025 One-Sided Type I Error Rate (Margins and Results are Given)

Study	50% retained	0% retained
ITT Population		
SO14796		
97.5% confidence	1.111[1]	1.196[2]
upper bound = 1.09	YES	YES
Standard Population		
S014796		
97.5% confidence	1.113[3]	1.199[4]
upper bound = 1.09		

[1] Margin is computed using the lower limit of the 34% C.I. for HR(5-FU/5-FU+LV).
[2] Margin is computed using the lower limit of the 54% C.I. for HR(5-FU/5-FU+LV).
[3] Margin is computed using the lower limit of the 32% C.I. for HR(5-FU/5-FU+LV).
[4] Margin is computed using the lower limit of the 52% C.I. for HR(5-FU/5-FU+LV).

For each population, a greater than 50% retention of the historical survival effect due to adding LV to 5-FU was a statistically significant result at a 0.025 one-sided significance level for the SO14796 trial. For the ITT population, the 97.5% lower bound for the percent of historical survival effect maintained is 61% (29.6% C.I. lower bound of 1.228; cutoff = 1.089). For the standard population, the 97.5% lower bound for the percent of historical survival effect maintained is 62% (26.9% C.I. lower bound of 1.232; cutoff = 1.088).

Using the CBER Method and the 10-paper meta-analysis for analysis of the updated data of May 15, 2000, a greater than 0% retention of the historical survival effect of adding leucovorin to 5-FU can be claimed. For the ITT population, the largest percent maintained if 2.2%. For the standard population, the largest percent of the historical survival effect maintained is 3.3%.

8.2.4 Safety Results

The population evaluable for safety consists of 588 patients: 6 of the 602 randomized patients refused study medication and were not assessed for safety (4 to capecitabine, 2 to 5-FU/LV). The safety aspects of SO14796 are reviewed in the Integrated Review of Safety (ISS; Section 11).

9. Supportive Trial in Colorectal Cancer: SO14797

A open-label randomized phase 2 study comparing the efficacy and safety of continuous therapy with capecitabine, intermittent therapy with capecitabine and intermittent therapy with capecitabine in combination with oral leucovorin in patients with advanced and/or metastatic colorectal carcinoma

9.1 Protocol Review

Study Dates: December 1995 to April 1997

9.1.1 Objectives

Primary:

- "To evaluate the efficacy of capecitabine when administered as continuous therapy, intermittent therapy and when combined with oral leucovorin for 12 weeks at dose levels determined to be one level below the MTD in previously untreated patients with advanced and/or metastatic colorectal carcinoma and to compare the three arms separately."

Secondary:

- To confirm and compare the safety profiles of each of the regimens at these dose levels
- To investigate the effect of food on the PK of capecitabine and its metabolites in patients receiving capecitabine only

9.1.2 Design

The protocol was an open-label, multicenter, multinational phase 2 randomizing patients to one of three treatment groups. Target accrual was 30 patients per arm.

9.1.3 Eligibility Criteria

- Histologically/cytologically confirmed colorectal adenocarcinoma
- Advanced or metastatic disease
- At least one bidimensionally measurable lesion according to WHO criteria
- Minimum size of indicator lesions as follows:
  Liver, soft tissue and masses (CT scan, ultrasound): at least one diameter $\geq$ 20 mm
  Lung (CXR, CT scan): at least one diameter $\geq$ 10 mm
  Skin lesions, nodes: at least one diameter $\geq$ 10 mm
- $\geq$ 18 years of age
- KPS $\geq$ 70%

9.1.4 Exclusion Criteria

- Pregnant or lactating women; women with a positive pregnancy test or no pregnancy test. Sexually active women and men must practice adequate contraception.
- Significant cardiac disease or MI within the past year; CNS metastases or other significant CNS disorder; serious uncontrolled intercurrent infection.
- Other malignancy except basal cell of the skin and in-situ carcinoma of the uterine cervix.
- Patients who have received blood transfusion or growth factors within 2 weeks of start of treatment; XRT within 4 weeks; major surgery to GI tract, liver or kidney that would interfere with oral drug absorption with 4 weeks of treatment start.
- Prior chemotherapy for advanced disease or adjuvant/neoadjuvant therapy within 6 months of treatment start.
- Patients known to be positive for HIV 1, Hepatitis B surface antigen, hepatitis C antibodies

- Patients with the following abnormal laboratory values:
  Hgb < 9.0 g/dl; neutrophils $\leq$ 1.5 x 10^9/l; platelet count < 100 x 10^9/l
  S. creatinine or bilirubin $\geq$ 1.5 x UNL
  ALAT, ASAT > 2.5 x UNL or > 5 UNL in the presence of liver metastases
  Alk phos > 2.5 x UNL or > 5 UNL in the presence of liver metastases or > 10 x UNL in case of bone metastases

9.1.5 Treatment

Patients were randomized sequentially by the sponsor in order of enrollment to one of three treatment groups. All groups received twice daily oral dosing of capecitabine as (1) continuous monotherapy at 1331 mg/m^2/day; intermittent monotherapy with capecitabine at 2510 mg/m^2/day; or (3) intermittent therapy with capecitabine 1656 mg/m^2/day in combination with oral leucovorin 60 mg/day.

9.1.6 Schedule of Assessments

Tumor assessments were to be obtained on study day 43 and 85.

9.1.7 Efficacy Criteria and Study Endpoints

The primary efficacy endpoint was RR.

9.1.8 Safety Assessments and Dose Modifications

Dose modification guidelines for toxicity were identical to guidelines used for S014695 and S014796. Patients were evaluated on day one of each cycle; cycle one also required a visit on day 8.

9.1.9 Statistical and Analytical Methods

"The primary efficacy parameter was the best overall response according to the WHO criteria after 12 weeks of treatment. The objective was to demonstrate minimal activity in each treatment arm by testing the hypothesis if the best overall response rate is at least 20% within a treatment arm: H_0: ORR $\geq$ 20% vs. H_1: ORR < 20%

For each treatment arm, a one-sided binomial test with ext distribution and an α-level of 5% was applied and the 95% Pearson-Clopper confidence interval was calculated. Since the nature of the study is exploratory, no adjustment for multiple testing was done.

The analysis was done for the standard and the intent-to-treat population. However, the main conclusion was drawn from the standard population. The result of the intent-to-treat analysis was regarded as supportive."

The standard population excluded patients who did not receive 6 weeks of therapy for other than PD or death, patients who missed more than 7 days of therapy during the first 6 weeks, patients with inadequate information about tumor burden at baseline, and patients with inadequate tumor assessment information.

9.2 Results

9.2.1 Conduct of the Study

The study was conducted according to the principles of the Declaration of Helsinki, or the laws and regulations of the country, whichever was considered to provide greater protection.

9.2.2 Enrollment

Twenty-one centers enrolled 109 patients.

9.2.3 Disposition

Thirty-five patients randomized to intermittent capecitabine with or without leucovorin. Thirty-nine patients randomized to continuous capecitabine. Nineteen patients discontinued treatment due to adverse events including 2 deaths. Patient #16609/0844 died due to PD and patient #16609/0846 due to an MI believed secondary to PD.

9.2.4 Primary Efficacy Endpoint: Response Rate

- **ITT Population**

The response rate in the ITT population is shown below in Sponsor Table 14.

Sponsor Table 14 (Abridged):
Summary of Overall Best Responses, ITT Population*

	Capecitabine + LV N = 35	Continuous Capecitabine N = 39	Intermittent Capecitabine N = 34
RR (CR + PR)	8 (23%)	8 (21%)	8 (24%)
CR	2 (6%)	2 (5%)	1 (3%)
SD	22 (63%)	20 (51%)	21 (62%)
PD	3 (9%)	8 (21%)	3 (9%)
Missing Postbaseline Info	2 (6%)	3 (8%)	2 (6%)

*vol. 41, p. 50

- **Standard Population**

The protocol-specified primary endpoint was RR in the standard population after 12 weeks of treatment. Seven (6.5%) patients were excluded from the standard population (2 in each arm) reducing the denominator in the standard population to 102. RR were 24% for capecitabine + leucovorin, 22% for continuous capecitabine and 25% for intermittent capecitabine.

9.3 Safety

Median duration of treatment was longest on intermittent capecitabine. Types of toxicities were similar across the arms but increased in frequency in the arm including leucovorin and least in the continuous monotherapy arm. Nine of the 10 deaths on study or within 28 days of treatment were considered due to progressive disease. One patient randomized to receive intermittent capecitabine died of non-neutropenic sepsis 12 days after the last dose of capecitabine.

Reviewer Table 33: Summary of Safety

	Capecitabine + LV N = 35	Continuous Capecitabine N = 39	Intermittent Capecitabine N = 34
Median Exposure (days)	130	109	145
Aes Related to Rx	34 (97%)	32 (82%)	29 (85%)
Grade 3-4 Aes Related to Rx	20 (57%)	6 (15%)	13 (38%)
Most Frequent AE			
Diarrhea	21 (60%)	13 (33.3%)	16 (47%)
Hand-Foot Syndrome	19 (54%)	13 (33%)	15 (44%)
Vomiting	14 (40%)	5 (13%)	7 (21%)
Hyperbilirubinemia	3 (9%)	7 (18%)	7 (21%)
Premature Withdrawal due to AE	5 (14%)	6 (15%)	6 (18%)
Death on Study or w/in 28 Days	4 (11%)	2 (5%)	4 (12%)

10. Integrated Summary of Efficacy

The Integrated Summary of Efficacy (ISE) is presented as pooled data from the two open-label, multicenter, parallel group, randomized trials reviewed individually in Sections 7 (SO14695) and 8 (SO14796). The justification for pooling includes that the two protocols were identical and the direction and variance of the HR are approximately the same. The 35 colorectal cancer patients from the phase 2 study who were treated with the phase 3 dose and schedule are not included in the discussion and tables below in order to preserve the ability to assess comparative efficacy of capecitabine vs. 5-FU/LV.

- **Protocols**

The protocols were identical in design including objectives, eligibility/exclusion criteria, control arm (Mayo Clinic regimen of 5-FU/LV), dose modifications, schedule of assessments, protocol-specified primary endpoint (response rate) and statistical analyses. Therefore, the total number of patients entered is also (nearly) identical.

Reviewer Table 34:
Comparative Protocol Design and Demographics of S014695 and S014796

Trial	#SO14695	#SO14796
Protocol Comments	•Identical protocols •1° endpoint = RR •eligibility criterion: ≥ 1 bidimensionally measurable lesion	
Countries	61 sites: US, Canada, Brazil, Mexico	59 sites: Italy, England, Scotland, Spain, Germany, Belgium, Russia, Australia, New Zealand, Taiwan
Pts. Entered	605	602
Total Pts. Entered	1207	

- **Demographics**

The distribution of baseline demographics and prognostic factors in the two phase 3 trials were similar except for two factors: race and number of metastatic sites. With regard to race, the population was 84% Caucasian, 8.6% Black and 4% Hispanic in S014695. In S014796, the population was 95% Caucasian, < 1% Black, 0% Hispanic. With regard metastases, liver was the most common site of metastasis, followed by lymph node and lung. The percent of patients with ≥ 2 sites at baseline was 85-86% in S014695 and 65-70% in S014796.

- **Efficacy**

Reviewer Table 35 summarizes the efficacy results for capecitabine vs. 5-FU/LV from studies SO14695 and SO14796. Response rate and TTP are based on the reconciled database with a closure date of September 1998. Survival data is presented using both the September 1998 cutoff and the requested update with a cutoff of May 15, 2000.

Reviewer Table 35:
Individual and Pooled Efficacy Data from SO14695 and SO14796 (ITT Population)

	#14695		#14796	
	Xeloda N = 302	5FU/LV N = 303	Xeloda N = 301	5FU/LV N = 301
[redacted]				
RR ("reconciled")	21%	11% P = 0.0014	21%	14% P = 0.027
TTP				
median ("reconciled")	4.3 mo.* 128 days	4.4 mo. 131 days	4.7 mo. 137 days	4.4 mo. 131 days
95% CI	(120, 136)	(105, 153)	(128, 165)	(102, 156)
HR 95% CI	0.99 (0.84, 1.17)		0.97 (0.82, 1.14)	
Survival				
• Median	12.6 mo. 378 days	13.3 mo. 400 days	13.5 mo. 404 days	12.6 mo. 379 days
95% CI	(318, 432)	(356, 444)	(367, 452)	(338, 434)
# Events	190 (62.9%)	188 (62.0%)	192 (63.8%)	194 (64.5%)
• HR (Xeloda:5-FU/LV) 95% CI	1.13 (0.92; 1.38)		0.98 (0.80; 1.20)	
Pooled Survival				
• Median	13.0 mo. 392 days		13.0 mo. 391 days	
95% CI	(361, 424)		(391, 426)	
• HR (Xeloda:5-FU/LV) 95% CI	1.05 (0.91; 1.21)			
[redacted]				
Survival				
• Median	12.7 mo. 380 days	13.6 mo. 407 days	13.5 mo. 404 days	12.3 mo. 369 days
95% CI	(321, 434)	(366, 446)	(367, 452)	(338, 430)
# Events	260 (86%)	273 (90%)	261 (87%)	272 (90%)
• HR (Xeloda:5-FU/LV) 95% CI	1.00 (0.84, 1.18)		0.92 (0.78, 1.09)	
Pooled Survival				
• Median	13.1 mo. 392 days		13.0 391 days	
95% CI	(366, 426)		(360, 427)	
• HR (Xeloda:5-FU/LV) 95% CI	0.96 (0.85, 1.08)			

* Months calculated by days divided by 30.

- **Exploratory Analysis: Pooled Survival Data using the Standard Population**

Reviewer Table 36 displays survival statistics based on the standard population.

Reviewer Table 36:
Individual and Pooled Efficacy Data from SO14695 and SO14796 (Standard Population)

	#14695		#14796	
	Xeloda (N = 269)	**5FU/LV (N = 266)**	**Xeloda (N = 265)**	**5FU/LV (n = 273)**
Database Closure (January 25, 2009 submitted with NDA)				
Survival				
• **Median**	13.0 mo.* 39 days	14 mo. 419 days	13.7 mo. 411 days	13.0 mo. 391 days
95% CI	(345, 440)	(356, 468)	(373, 458)	(355, 45)
# Events	164 (61%)	161 (60%)	163(61.5%)	174 (63.7%)
• **HR** (Xeloda:5-FU/LV)	1.07		0.96	
95% CI	(0.86; 1.33)		(0.77; 1.19)	
Pooled Survival				
• **Median**	13.4 mo. 401 days		13.3 mo. 400 days	
95% CI	(373; 435)		(366; 434)	
• **HR** (Xeloda:5-FU/LV)	1.01			
95% CI	(0.87; 1.18)			
Requested Updated Survival Analysis – Cut-off Date: May 15, 2010				
Survival				
• **Median**	13.1 mo. 392 days	14.0 mo. 421 days	13.8 mo. 415 days	13.0 mo. 391 days
95% CI	(350; 442)	(366; 468)	(373; 464)	(354; 450)
# Events	231	237	228	245
• **HR** (Xeloda:5-FU/LV)	0.98		0.91	
95% CI	(0.82; 1.17)		(0.76; 1.09)	
Pooled Survival				
• **Median**	13.5 mo. 404 days		13.5 406 days	
95% CI	(379; 440)		(366; 439)	
• **HR** (Xeloda:5-FU/LV)	0.94			
95% CI	(0.83; 1.07)			

* Months calculated by days divided by 30.

- **Test of Non-Inferiority in Survival**

Table 37 below lists vital survival descriptive statistics for the two phase 3 trials with cutoff dates of January 1999 and May 15, 2000. Methodology used is as described earlier in 7.2.3.4 and also in Appendix II. Results for the ITT and standard population are included.

Reviewer Table 37: Summary of Relevant Survival Descriptive Statistics

Study	HR(Xeloda/5-FU+LV)	log HR	SE(logHR)
ITT Population			
SO14695 January 1999 cutoff	1.13	0.1220	0.1031
SO14796 January 1999 cutoff	0.98	-0.0195	0.1019
POOLED January 1999 cutoff	1.05	0.0497	0.0724
SO14695 May 15, 2000 cutoff	1.00	-0.0036	0.0868
SO14796 May 15, 2000 cutoff	0.92	-0.0844	0.0867
POOLED May 15, 2000 cutoff	0.96	-0.0432	0.0613
Standard Population			
SO14695 May 15, 2000 cutoff	0.98	-0.0218	0.0926
SO14796 May 15, 2000 cutoff	0.91	-0.0966	0.0921
POOLED May 15, 2000 cutoff	0.94	-0.0590	0.0652

Table 38 below gives results of 0.025 one-sided type I error rate survival analyses for the ITT population (January 1999 cutoff) using the 10-paper meta-analysis. Results are also given for a pooled analysis of the two phase 3 trials.

Reviewer Table 38:
Non-inferiority Survival Analysis (January 1999 Cutoff) using the 10-Paper Meta-Analysis and a 0.025 One-Sided Type I Error Rate (Margins and Results are Given)

Study	50% retained	0% retained
ITT Population		
SO14695		
97.5% confidence	1.114[1]	1.204[2]
upper bound = 1.38	NO	NO
SO14796		
97.5% confidence	1.114[1]	1.204[2]
upper bound = 1.20	NO	YES
POOLED		
97.5% confidence	1.108[3]	1.186[4]
upper bound = 1.21	NO	NO

[1] Margin is computed using the lower limit of the 30% C.I. for HR(5-FU/5-FU+LV).
[2] Margin is computed using the lower limit of the 48% C.I. for HR(5-FU/5-FU+LV).
[3] Margin is computed using the lower limit of the 39% C.I. for HR(5-FU/5-FU+LV).
[4] Margin is computed using the lower limit of the 60% C.I. for HR(5-FU/5-FU+LV).

A greater than 0% retention of the survival effect due to adding LV to 5-FU for the SO14796 trial was the sole statistically significant result at a 0.025 one-sided significance level.

Table 39 below gives results of 0.025 one-sided type I error rate survival analyses (May 15, 2000 cutoff) using the 10-paper meta-analysis. Results are also given for a pooled (Xeloda trials) analysis.

Reviewer Table 39:
Non-inferiority Updated (May 15, 2000 Cutoff) Survival Analysis using the 10-Paper Meta-Analysis and a 0.025 One-Sided Type I Error Rate (Margins and Results are Given)

Study	50% retained	0% retained
ITT Population		
SO14695		
97.5% confidence	1.111[1]	1.196[2]
upper bound = 1.18	NO	YES
SO14796		
97.5% confidence	1.111[1]	1.196[2]
upper bound = 1.09	YES	YES
POOLED		
97.5% confidence	1.104[3]	1.178[4]
upper bound = 1.08	YES	YES
Standard Population		
SO14695		
97.5% confidence	1.113[5]	1.199[6]
upper bound = 1.17	NO	YES
SO14796		
97.5% confidence	1.113[5]	1.199[6]
upper bound = 1.09	YES	YES
POOLED		
97.5% confidence	1.106[7]	1.182[8]
upper bound = 1.07	YES	YES

[1] Margin is computed using the lower limit of the 34% C.I. for HR(5-FU/5-FU+LV).
[2] Margin is computed using the lower limit of the 54% C.I. for HR(5-FU/5-FU+LV).
[3] Margin is computed using the lower limit of the 45% C.I. for HR(5-FU/5-FU+LV).
[4] Margin is computed using the lower limit of the 65% C.I. for HR(5-FU/5-FU+LV).
[5] Margin is computed using the lower limit of the 32% C.I. for HR(5-FU/5-FU+LV).
[6] Margin is computed using the lower limit of the 52% C.I. for HR(5-FU/5-FU+LV).
[7] Margin is computed using the lower limit of the 43% C.I. for HR(5-FU/5-FU+LV).
[8] Margin is computed using the lower limit of the 63% C.I. for HR(5-FU/5-FU+LV).

For each population, a greater than 50% retention of the historical survival effect due to adding LV to 5-FU was a statistically significant result at a 0.025 one-sided significance level for the SO14796 trial and the pooled analysis, but not for the SO14695 trial. Also for each population, a greater than 0% retention of the survival effect due to adding LV to 5-FU was statistically significant at a 0.025 one-sided significance level for the SO14695 trial (i.e., still able to demonstrate superiority to 5-FU alone, but not able to demonstrate retention of a fraction of the effect on survival when leucovorin is added. It should be noted that the trials are vastly underpowered to demonstrate 50% retention of the survival effect due to adding leucovorin to 5-FU-- see Appendix II, Table 8.)

For the pooled analyses of results based on the ITT population, the 97.5% lower bound for the percent of historical survival effect maintained is 63% (39.1% C.I. lower bound of 1.216; cutoff = 1.08) For the

pooled analyses of results based on the standard population, the 97.5% lower bound for the percent of historical survival effect maintained is 68.5% (31.9% C.I. lower bound of 1.225; cutoff = 1.071).

Using the CBER Method, only a claim of greater than 0% retention of the historical survival effect of adding LV to 5-FU can be claimed for both the ITT and standard population for trial S014796 and the pooled analyses. Trial S014695 would not support a non-inferiority claim by this method (for details, see Appendix 11).

- **Bayesian Analysis to Test the Hypothesis of Non-Inferiority in Survival**

Simon proposed a Bayesian analysis to examine the question of non-inferiority in active control trials. This methodology assumes that a relationship exists between the active control in a non-inferiority trial and evidence of efficacy of the active control over a placebo or previous therapy in a previous trial (or trials). Let *E* represent the experimental treatment (in this case, capcitabine). Let *C* and *P* represent the active control (in this case, 5FU/LV) and a previous standard, respectively. Simon points out that demonstrating that *E* is at least $100k\%$ as effective as *C* is interpretable only to the extent that *C* is effective with respect to *P*. In other words, in evaluating whether $100k\%$ effectiveness relative to *C* represents effectiveness relative to *P*, one must account for the uncertainty in effectiveness of *C* relative to *P*. Symbolically, we will use

$$\beta = \text{log of hazard ratio of } C \text{ to } P,$$
$$\gamma = \text{log of hazard ratio of } E \text{ to } P, \text{ and}$$
$$\beta - \gamma = \text{log of hazard ratio of } C \text{ to } E.$$

Let $y = \alpha + \beta x + \gamma z + \varepsilon$, where y is the response of a given patient and ε is normally distributed random error. The variables x and z are indicator variables as follows: $x = 0$ if the patient's treatment is the experimental agent and $x = 1$ if the patient's treatment is the active control; $z = 1$ if the patient's treatment is the experimental agent and $z = 0$ if the patient's treatment is the active control. The likelihood function for the trial of *E* vs. *C* is given by

$$\pi(D|\alpha,\beta,\gamma) \propto \pi(y_c|\alpha,\beta) \times \pi(y_e|\alpha,\gamma).$$

When the priors for the parameters are given as $\pi(\alpha) \sim N(\mu_\alpha,\sigma_\alpha^2)$, $\pi(\beta) \sim N(\mu_\beta,\sigma_\beta^2)$, and $\pi(\gamma) \sim N(\mu_\gamma,\sigma_\gamma^2)$, the posterior density of $\{\alpha,\beta,\gamma\}$ is $\pi(\alpha,\beta,\gamma|D) \propto \pi(y_c|\alpha,\beta)\,\pi(y_e|\alpha,\gamma)\,\pi(\alpha)\,\pi(\beta)\,\pi(\gamma)$. This posterior may be expressed as a multivariate normal distribution.

In the special case where non-informative priors are specified for α and γ, the conditional posterior distribution for β is $N(\mu_\beta, \sigma_\beta^2)$, the posterior distribution for γ is $N(\mu_\beta + y_c + y_e, \sigma_\beta^2 + 2\sigma^2)$, and the posterior distribution for α is $N(y_c - \mu_\beta, \sigma_\beta^2 + \sigma^2)$.

Simon proposes that a reasonable prior distribution for β is an empirical prior based on a random-effects meta-analysis of historical data, where the studies in the meta-analysis compare *C* versus *P*. For our purposes, the endpoints that would be combined in the meta-analysis are the log hazard ratios of survival. Simon further argues that, generally, the prior distribution for γ will be unknown, and so it is reasonable to choose a non-informative prior for γ. This reflects no quantitative randomized evidence for effectiveness of *E* compared to *C*.

The problem of specifying a formal definition for non-inferiority has been considered at length. Based on the guidelines for non-inferiority trials in the ICH E9 document, if *E* and *C* are equivalent, we want high probability (e.g. 0.80) of concluding that E is effective relative to P and at least $100k\%$ as effective as *C*, where $0 < k < 1$ and is the minimal efficacy difference tolerable to show non-inferiority. If $k = 0$, then *E* is non-inferior to *C* simply because *E* is superior to *P*. If $k = 0.50$, then for *E* to be non-inferior to *C*, *E* must be superior to *P* and *E* must be at least 50% as effective as *C*.

Reviewer Table 40: Non-inferiority Analysis for Survival using Simon's Method

Population	Non-inferiority* (Yes/No) Jan. 1999 cut-off data	Non-inferiority* (Yes/No) May, 2000 cut-off data
SO14695	No (Prob=0.82)	Yes (Prob=0.98)
SO14796	Yes (Prob=0.98)	Yes (Prob>0.99)
Pooled	No (Prob=0.97)	Yes (Prob>0.99)

*to beat placebo

Results of the Bayesian analysis provide supportive evidence for this noninferiority analysis. The major concerns, besides those related to the on meta-analysis, are selection of a prior and choosing a standard for posterior probability (similar to 0.025 type one error for non-inferiority test using frequentist methods). In addition, definitions of the Proportion of Effect Retained Based on Hazard Ratios are different between Simon (1999) and Hasselblad and Kong (1999) compared to CBER & CDER's methods

The geometric definition of the proportion of effect retained, δ, is given by

$$\delta = \frac{\log HR(P/C) - \log HR(T/C)}{\log HR(P/C)}$$ when HR(P/C) > 1. Simon (1999) and Hasselblad and Kong (1999) have used this definition.

The arithmetic definition of the proportion of effect retained, δ, is given by

$$\delta = \frac{HR(P/C) - HR(T/C)}{HR(P/C) - 1}$$ when HR(P/C) > 1. CBER and CDER have used this definition.

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ON ORIGINAL

11. Integrated Summary of Safety (ISS)

11.1 Overview of ISS

Capecitabine received accelerated approval for breast cancer in April of 1998 and subsequently in other countries (see Section 13). The safety database for the original label was based of 570 patients treated with a dose and schedule identical to what was used in the two phase 3 colorectal trials. The mean duration of treatment for the breast cancer indication was 4 months.

Additional safety data submitted with this sNDA is based on 875 patients, 630 on colorectal cancer trials and 245 on breast cancer trials. The cut-off date for the safety analysis was September, 1999. The median duration of treatment is 127 days, i.e. approximately 4.2 months, nearly identical to duration supporting the original indication. (The mean duration will not be used since the sponsor counts days of actual treatment rather than the cycle length with rest periods. This leads to a mean six times greater for patients on capecitabine.)

The sponsor submits ISS data as the "overall Safety Database" consisting of 875 patients and as the "Capecitabine Phase 3 CRC Pool. It was agreed prior to sNDA submission that the ISS would pool safety data from the two phase 3 trials, i.e., 596 of the 875 patients reported, in order to preserve the integrity of the comparative incidences of important toxicities in the pertinent population for the requested indication. Furthermore, it was agreed that for the integrated phase 3 colorectal cancer data would collapse specific adverse event terms: (1) mucosal , stomatitis, and mouth ulceration were collapsed into stomatitis all; (2) diarrhoea NOS, diarrhoea aggravated were collapsed into diarrhoea.

It should be noted, however, that the majority of exposure to capecitabine lies in the body of post-marketing data. A consult was submitted to OPDRA regarding potentially serious treatment-related adverse events (see summary below and Appendix III). In conclusion, spontaneous reporting of AEs did support the need to modify the original label, which the sponsor recognized in its suggested modifications to the label.

Finally, the latest literature on the topic of capecitabine having been labeled at too high a dose is discussed in this section. The abstract by Dr. Joyce O'Shaughnessy summarized below and supported by the sponsor is in some sense contradictory to the proposed marketing presentation that capecitabine is safer than 5-FU/LV.

11.2 Pooled Safety Date from the Phase 3 Colorectal Trials: S014695 and S014796

- **Extent of Exposure**

The median duration of treatment was similar, 138.5 days for capecitabine and 140 days of 5-FU/LV. Patients on capecitabine took a mean of 84% of the planned dose and patients on 5-FU/LV took a mean of 89% of the planned dose.

The sponsor claims that dose modifications were more frequent in patients receiving 5-FU/LV.

Reviewer Comment: *The conclusion that dose modifications were more frequent in patients receiving 5-FU/LV could be an artifact of how dose modification guidelines were written in the protocol (see Section 7.1.8).*

1. *For the first appearance of a grade 2 toxicity, the protocol specified treatment cessation, resumption of 100% dosing and use of preventative medication for patients on capecitabine. Treatment interruption followed by an 80% reduction once toxicity resolved was specified for first appearance of grade 2 toxicities due to 5-FU/LV. Sponsor data from Table 37, volume 33, p. 107 states the number of patients with treatment interruption on capecitabine was 308 (51.7%) and on 5-FU/LV was 38 (6.4%). Sponsor Table 38 (volume 33, p. 108) displays information on dose modification* ***and/or treatment***

interruption. The percentage of patients requiring dose reduction and/or treatment interruptions due to adverse events was 56.7% on capecitabine and 46.5% on 5-FU/LV. Differences are highlighted in bold type.

Sponsor Table 38:
Summary of Most Frequent AEs (≥5%) Leading to Dose Reduction and/or Treatment Interruption

	Capecitabine N = 596		5-FU/LV N = 593	
Diarrhea	96	16.1%	91	15.3%
Stomatitis	24	4.0%	135	22.8%
Vomiting	34	5.7%	20	3.4%
Hand-and-Foot Synd.	182	30.5%	3	0.5%
Neutropenia	6	1.0%	35	5.9%

2. *The meaning of fewer dose modifications is uncertain since patients on capecitabine took a mean of 84% of the planned dose and patients on 5-FU/LV took a mean of 89% of the planned dose.*

Reviewer Table 41: Examples of Dose Modifications for a 1.7 m^2 Person

	Capecitabine (2500 mg/day)	5-FU/LV (425 mg/day)
Initial Dose	4300	722.5
75% Reduction	3225	542
50% Reduction	2150	361
80% of Original Dose	3440	578
70% of Previous Dose	2408	404

- **Overall Incidence and Severity of Adverse Events**

Overall, most patients experienced an adverse event of any cause (96.3% on capecitabine and 94.3% on 5-FU/LV) and an adverse event coded as related (probably, possibly or remotely) to treatment (89% on both arms). The incidence of grade 3 events was slightly higher in patients on capecitabine when considering events due to all causes and treatment related. Grade 4 events were slightly higher in patients on capecitabine when considering events due to all causes, but not when considering those related to treatment.

Reviewer Table 42:
Incidence, Severity and Relationship of Adverse Event to Study Drug

	Capecitabine N = 596	5-FU/LV N = 593
[redacted]		
• **All Grades**		
No. of pts with at least one AE	574 (96.3%)	559 (94.3%)
Total No. of AEs	4919	4890
• **Grade 3**		
No. of pts with at least one AE	312 (52.3%)	268 (45.2%)
Total No. of AEs	612	512
• **Grade 4**		
No. of pts with at least one AE	54 (9.1%)	53 (8.9%)
Total No. of AEs	73	83
[redacted]		
• **All Grades**		
No. of pts with at least one AE	532 (89.3%)	528 (89.0%)
Total No. of AEs	3009	3310
• **Grade 3**		
No. of pts with at least one AE	227 (38.1%)	202 (34.1%)
Total No. of AEs	342	350
• **Grade 4**		
No. of pts with at least one AE	18 (3.0%)	30 (5.1%)
Total No. of Aes	27	46

Vol.33, p.82 and Appendix 15 in vol. 34

- **Deaths**

A total of 82 patients died on study or within 28 days after receiving study drug: 50 (8.4%) on capecitabine and 32 (5.4%) on 5-FU/LV. The sponsor presents the data as six (1%) on each treatment arm were considered related to treatment – see Reviewer Table 43 below.

Reviewer Table 43:
Deaths on or within 28 Days of Treatment: By Relationship to Treatment as Coded by Investigator

	Capecitabine N = 596	5-FU/LV N = 593
Total	**50 (8.4%)**	**32 (5.4%)**
Assessed as Treatment-Related	**6 (1.0%)**	**6 (1.0%)**
Cardiac Failure/MI	1	1
GI: Enterocolitis, GI Necrosis, GI Hemorrhage	2	1
PE	1	-
Infection: Pneumonia, Sepsis, URI	1	2
Renal Tubular Necrosis	-	1
Hyperosmolar State	-	1
Unknown Cause	1	-
Assessed as Unrelated to Treatment	**44 (7.7%)**	**26 (4.4%)**
PD	26	16
Cardiac Arrest, MI, Cardiac Failure, CAD	5	1
CVA	3	-
Cerebral hemorrhage, UGI hemorrhage	2	-
Septicemia, sepsis	4	2
ARDS, Respiratory Failure	-	2
PE	2	3
Intestinal obstruction, Large Intestinal Obstruction	-	2
GI Necrosis	1	-
Hypokalemis	1	-

Reviewer Comment: *In a randomized and unblinded trial, it may be more valid to look at the epidemiology of death by treatment arm and avoid what may be investigator bias. The following table lists patients by whether they died on study, i.e., investigator had not determined the risk/benefit ratio favored stopping therapy, vs. deaths within 28 days. Deaths within 28 days are balanced with 31 and 30 on each*

arm. The disparity between treatment arms is entirely confined to deaths on study. The sponsor states "The majority of deaths during treatment were considered by the investigators to be due to progressive disease and unrelated to treatment in both treatment groups." The majority of deaths on treatment where not to do progressive disease although were coded as unrelated to treatment; the majority of death within 28 days of treatment were due to progressive disease.

Reviewer Table 44:
Deaths on or within 28 Days of Treatment

	Capecitabine N = 596	*5-FU/LV N = 593*
Total	*50 (8.4%)*	*32 (5.4%)*
Death on Study	*19 (3.2%)*	*2 (0.3%)*
CVA	*1*	-
Cerebral Hemorrhage	*1*	-
GI Necrosis, GI Hemorrhage, Cerebral hemorrhage	*3*	-
PE	*2*	-
Sudden Death	*1*	-
MI, Cardiac Failure	*3*	-
Sepsis	*1*	-
Pneumonia/Sepsis	*1*	-
PD	*7*	*2*
Death within 28 Days	*31 (5.2%)*	*30 (5.0%)*
PD	*19*	*14*
Sepsis	*3*	*3*
Respiratory Failure, ARDS, URI	-	*3*
PE	*1*	*3*
MI, CAD, Cardiac Failure	*3*	*2*
CVA	*2*	-
Intestinal Obstruction	*0*	*2*
Enterocolitis, UGI Hemorrhage	*1*	*1*
Electrolyte: Hyperosmolar, Hypokalemia	*1*	*1*
Renal Tubular Necrosis	-	*1*

Appendix I: Listing of Deaths, vol. 36, p.1-3

- **Premature Withdrawals**

The incidence of premature withdrawals due to adverse events of any cause was higher in patients receiving capecitabine (13.3%) vs. patients treated with 5-FU/LV (10.8%). The incidence of premature withdrawals due to adverse events related to treatment was also higher in patients receiving capecitabine (9.6%) vs. 5-FU/LV (6.7%).

Sponsor Table 46:
Summary of Most Frequent (≥ 1%) Adverse Events Leading to Premature Withdrawal

	Capecitabine N = 596		5-FU/LV N = 593	
[redacted]				
Total				
No. of pts with at least one AE	78 (13.1%)		63 (10.6%)	
Total No. of AEs	118		92	
Diarrhea	16	2.7%	10	1.7%
Stomatitis	6	1.0%	13	2.2%
Vomiting	8	1.3%	2	0.3%
Nausea	6	1.0%	1	0.2%
Small Intestinal Obstruction NOS	4	0.7%	2	0.3%
Dehydration	3	0.5%	4	0.7%
Weight Decrease	-	-	6	1.0%
Cachexia	3	0.5%	1	0.2%
CVA	3	0.5%	2	0.3%
DVT (Limbs)	3	0.5%	2	0.3%
Pyrexia	-	-	3	0.5%
Hand-and-Foot Syndrome	10	1.7%	-	-
Angina Pectoris	3	0.5%	1	0.2%
[redacted]				
Total				
No. of pts with at least one AE	57 (9.6%)		40 (6.7%)	
Total No. of AEs	83		64	
Diarrhea	16	2.7%	10	1.7%
Stomatitis	6	1.0%	13	2.2%
Vomiting	7	1.2%	2	0.3%
Nausea	6	1.0%	1	0.2%
Dehydration	2	0.3%	4	0.7%
Hand-and-Foot Syndrome	10	1.7%	-	-
Angina Pectoris	3	0.5%	1	0.2%

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- **Treatment Emergent Adverse Events**

The following table presents treatment emergent adverse events occurring in ≥ 5%, regardless of relationship to treatment, by body system, all grades and grade 3 - 4 events.

Reviewer Table 45:
Percent Incidence of AE Irrespective of Cause in ≥ 5% of Patients

Body System/ Adverse Event	Capecitabine N = 596			5-FU/LV N = 593		
	Total	Gr 3	Gr 4	Total	Gr 3	Gr 4
GI						
Diarrhea	52.9	12.2	1.5	59.5	10.5	1.9
Nausea	42.8	4.0	-	50.6	2.7	0.2
Vomiting	27.2	3.7	0.2	30.4	3.5	0.2
Stomatitis	24.8	2.0	0.2	61.7	14.2	0.5
Abdominal Pain NOS	25.0	6.5	-	21.4	3.4	-
Abdominal Pain Upper	12.1	1.7	-	9.4	1.7	-
Constipation	13.9	1.0	0.2	17.2	0.8	-
Dyspepsia	7.2	0.2	-	7.9	0.5	-
Flatulence	6.2	-	-	4.2	-	-
Dry Mouth	4.7	-	-	4.2	-	-
Skin & Subcutaneous						
Hand-Foot Syndrome	53.7	17.1	-	6.2	0.5	-
Dermatitis NOS	10.9	0.2	-	12.1	-	-
Dry Skin	7.7	0.2	-	5.9	0.3	-
Alopecia	6.0	-	-	21.1	0.2	-
Rash Erythematous	5.5	0.2	-	5.1	0.2	-
General						
Fatigue	26.0	2.0	-	28.7	1.9	-
Weakness	9.7	1.2	-	9.9	1.5	-
Lethargy	4.0	0.3	-	6.4	0.7	-
Asthenia	5.4	0.8	-	5.7	0.5	-
Pyrexia	17.4	1.0	-	20.7	1.7	-
Pain in Limb	8.2	0.3	-	5.2	0.5	-
Neurological						
Headache NOS	9.6	1.0	-	7.4	-	-
Dizziness (exc.vertigo)	8.4	0.3	-	7.6	0.2	-
Insomnia	7.2	-	-	6.9	-	-
Taste Disturbance	4.9	0.3	-	10.1	0.3	-
Metabolism						
Anorexia	12.8	1.0	-	16.4	0.8	-
Appetite Decreased	10.4	1.2	-	11.0	0.8	-
Dehydration	7.0	2.0	0.2	7.9	2.7	0.5
Weight Decrease	6.0	0.2	-	9.3	0.3	-
Eye						
Lacrimation Increased	7.4	-	-	5.6	-	-
Respiratory						
Dyspnea	10.6	1.0	-	7.9	0.3	0.3
Cough	7.2	0.2	-	7.6	-	-
Nasopharyngitis	4.7	-	-	3.7	-	-
Epistaxis	3.0	0.2	-	6.2	-	-
Sore Throat NOS	2.2	-	-	5.6	-	-
Infection						
UTI NOS	5.7	0.3	-	5.4	-	-
URINOS				5.1	0.2	-
Cardiac						
Edema Lower Limb	10.6	0.8	-	6.6	0.7	-
Vascular						
DVT, limb	5.0	2.0	0.3	2.9	1.7	-
Musculoskeletal						
Back Pain	10.1	1.5	-	9.1	0.3	-
Arthralgia	7.2			5.6	0.7	-

Reviewer Comment: It is important to remember that while the safety profiles differ between the two treatment arms, one is not safer than the other (per sponsor's submitted advertising). Fewer dose modifications for capecitabine is an artifact of the protocol-specified guidelines. When one includes treatment interruption along with dose modifications, capecitabine loses any apparent advantage. The data show more deaths on study with capecitabine, more premature withdrawals with capecitabine, greater numbers of patients with adverse events (due to all causes or treatment-related), greater number of patients with grade 3 adverse events (due to all causes or treatment-related) and greater number of patients with grade 4 adverse events (due to all causes but not treatment-related). Reviewer Table 45 above does show a lower incidence of diarrhea, nausea and vomiting (which is maintained when considering only treatment-related events); however, the grade 3 or 4 events are not dissimilar nullifying a claim for greater safety.

- **Laboratory Findings**

Sponsor Table 59 presents the incidence of grade 3-4 laboratory abnormalities (not limited to those reported as adverse events or considered treatment-related). The incidence of grade 3-4 neutropenia is greater on 5-FU/LV (21.08%) than on capecitabine (2.18%). Three patients on 5-FU/LV were coded as being withdrawn prematurely due to neutropenia vs. one on capecitabine. The incidence of grade 3-4 hyperbilirubinemia was greater on capecitabine (19.63%) vs. 5-FU/LV (4.89%). Two patients receiving capecitabine were withdrawn from study for hyperbilirubinemia/jaundice (one coded as unrelated) vs, none on 5-FU/LV. Overall, 5 patients receiving capecitabine were withdrawn prematurely for adverse events which included abnormal laboratory abnormalities vs. 4 on 5-FU/LV.

Sponsor Table 59:
Incidence of Laboratory Events Representing a Grade 3-4 or Grade 4 Value

Lab Parameter	Capecitabine				5-FU/LV			
	Grade 3-4 N (%)		Grade 4 N (%)		Grade 3-4 N (%)		Grade 4 N (%)	
ALAT (SGPT	3	0.50	0	-	4	0.67	0	-
ASAT (SGOT)	4	0.67	0	-	7	1.18	0	-
Alk Phos	20	3.36	1	0.17	24	4.05	0	-
Calcium (Hyper)	4	0.67	3	0.50	1	0.17	1	0.17
Calcium (Hypo)	4	0,67	1	0.17	1	0.17	0	-
Glucose (Hyper)	38	6.38	2	0.34	23	3.88	1	0.17
Glucose (Hypo)	2	0.34	2	0.34	1	0.17	0	-
Granulocytes	1	0.17	1	0.17	12	2.02	5	0.84
Hemoglobin	12	2.01	1	0.17	10	1.69	2	0.34
Lymphocytes	219	36.74	45	7.55	223	37.61	47	7.93
Neutrophils	13	2.18	9	1.51	125	21.08	76	12.82
Platelets	6	1.01	3	0.50	2	0.34	1	0.17
Potassium	6	1.01	1	0.17	2	0.34	0	-
S. Creatinine	5	0.84	2	0.34	0	-	0	-
Sodium	6	1.01	0	-	2	0.34	1	0.17
Total Bilirubin	136	22.82	27	4.53	35	5.90	15	2.53
WBC	8	1.34	2	0.34	69	11.64	20	3.37

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- **Analysis by Age**

A total of 236 patients receiving capecitabine experienced a grade 3 or 4 adverse event. These patients are catagorized by age and type of toxicity in Sponsor Table 49. The incidence rose for patients $\geq$ 70 years a age, a phenomenon also seen with 5-FU. Laboratory adverse events of hyperbilirubinemia and neutropenia did not increase with age.

Sponsor Table 49:
Incidence of Treatment-Related Grade 3 or 4 Adverse Events by Age: Capecitabine

Rx-Related Grade 3 & 4 Adverse Events	All	Age-Range (years) <40 N=20	40 to < 60 N=203	60 to < 70 N = 209	70 to < 80 N=151	≥80 N=13
All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea	[redacted]	1 (5.0)	25 (12.3)	28 (13.2)	20 (13.2)	4 (30.8)
Hand-Foot	[redacted]	4 (20.0)	29 (14.3)	29 (13.9)	38 (25.2)	2 (15.4)
Stomatitis	[redacted]	1 (5.0)	1 (0.5)	7 (3.3)	3 (2.0)	1 (7.7)
Vomiting	[redacted]	0 -	7 (3.4)	4 (1.9)	4 (2.6)	2 (15.4)
Nausea	[redacted]	1 (5.0)	7 (3.4)	3 (1.4)	3 (2.0)	1 (7.7)

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11.3 Post-Marketing Safety Report

The latest PSUR submitted with the NDA covered the period November 1998 to April 1999 and provided rough estimates of global sales (based on factory sales data/kg of capecitabine sold). It is estimated that approximately ___ patients received capecitabine during this 6 month period. Because the post-marketing patient exposure is so much greater than the safety data included for the single indication requested by this sNDA and in light of medical literature criticizing the approved dose as too high, OPDRA was consulted to review potentially underestimated serious or life-threatening toxicities. Based on signals derived from all types of submissions to the Agency as well as the literature, the following terms were searched: cerebrovascular events, cardiac events, serious hepatotoxicities (hepatitis, cirrhosis, fibrosis, necrosis and hepatic failure) and ileus (possibly related typhlitis).

See Appendix III for the complete post-marketing safety report.

11.4 Dose

The approved dose of capecitabine has been criticized in the medical literature as "too high." O'Shaughnessy and Blum recently published an abstract (Proc ASCO 19:#400, 2000) of a retrospective evaluation of dose modifications and efficacy in the four phase 2 trials conducted in women with metastatic breast cancer. Published phase 2 trials in other disease sites such as colorectal cancer were not reviewed; phase 3 trials in breast or colorectal cancer have not yet been published. A total of 321 patients were identified; 131 had at least a 25% dose reduction; 29 patients had a further reduction to 50%. Efficacy outcomes in patients who had dose response and those who did not are shown below. Twenty eight of 131 patients required a second dose reduction. The overall response rate was 21%. The conclusion was that there was no signal that dose reduction compromised efficacy.

Reviewer Table 46[1]
Efficacy Outcomes in Patients with and without Dose Reduction

	Dose Reduction (DR) N = 131 Median time to 1st DR = 49d[2] Median time to 2nd DR = 105d		No Dose Reduction N = 190	
	Nonresponder	Responder	Nonresponder	Responder
N	89	42 (32%)	162	28 (15%)
# responding before DR		26		
# responding after DR		16		
Age (yrs)	56	59	57	58
Duration of response (d)		222		211
TTF (d)	107	234	48	218
Survival (d)	255	350	192	243

[1]Data in table updated by Dr. O'Shaugnessy, personal communication, from submitted paper.
[2]Treatment cycle is 21 days.

Reviewer Comment: *The Xeloda label is noteworthy for containing explicit directions for when and how to dose modify on the basis of toxicity, as provided in the protocols for the clinical trials.*

11.5 Drug-Drug Interactions

Warfarin. A potential drug interaction between capecitabine and warfarin was detected during post-marketing surveillance by both the Agency and the sponsor (ref. OPDRA consult dated March 26, 1999 and Dear Health Professional Letter dated Marcy 1999). Abnormalities in coagulation measurements as well as associated clinical events such as GI or cerebral bleeding were noted. Protocol _____ entitled "Effect of capecitabine on the PK and PD of warfarin," is ongoing. The mechanism of the interaction is not yet known. Frequent monitoring of coagulation parameters is advised in the label. Data submitted from the randomized trials did not contribute further information.

Phenytoin. A potential interaction between capecitabine and phenytoin was detected by review of post-marketing spontaneous reports. The clinical events were consistent with phenytoin toxicity. Labeling has been submitted to recommend more frequent monitoring of phenytoin levels in patients who are also taking capecitabine. Data submitted from the randomized trials did not contribute further information.

11.6 Renal Impairment

Reviewer Comment: *The sNDA did not include information from WP15811, entitled "Effect of renal impairment on the PK of capecitabine in cancer patients." The Agency asked for a summary when it was noted in a submission to the IND that the last patient was entered December 1999. The Agency had also received a report of a death on study in a patient with comorbid conditions. On September 5, 2000 (correspondence date), the sponsor submitted a "brief summary" of the trial. There were 4 deaths on study or within 28 days of receiving study drug, one of which was coded as due to capecitabine. The sponsor concludes in their cover letter that "preliminary safety results indicate that capecitabine treatment should be contraindicated in patients with severe renal impairment. The recommended starting dose of capecitabine for patients with moderate renal impairment should be 75% of the normal dose. Please note that we intend to propose labeling revisions based on the final outcome of the study WP15811."*

Whether there is sufficient information to include a warning in the label at this time in part depends on advice from Clinical Pharmacology/Biopharmaceutics. This reviewer's opinion is that a primary launch should not proceed without appropriate warnings about high risk subgroups whose risk includes life-threatening toxicity. It is not expected that these patients will comprise a large population of colorectal cancer patients; however, until proven otherwise, this warning would extend to breast cancer patients

which is an active area of development. Arguments are as follows: (1) The Agency has been made aware of deaths in this subgroup; (2) Important information should be included in the launch when practitioners are processing the overall information; and (3) Submitted material from the launch indicates that capecitabine's safety profile is safer (not different) than 5-FU/LV. Such advertising may place subgroups at higher risk at greater risk.

12. Four Month Safety Update

No new patients have been added to the safety database (N = 1189). Additional follow-up is provided from the two phase 3 trials in colorectal cancer. Although enrollment had been completed, 36 patients continued to receive treatment (in cycles 9 through 18). The median duration on treatment remains unchanged. Six patients remain on study.

The additional information is as follows:

- Three additional grade 3 AEs occurred on capecitabine and three on 5-FU/LV. Of these, one was considered treatment-related in the capecitabine group
- One premature withdrawal due to an AE (gall bladder obstruction thought to be unrelated to treatment) in the capecitabine group

There were no further incidences of grade 4 AEs, serious AEs, or deaths.

13. Foreign Marketing Experience

Xeloda was approved first in the U.S. Subsequently, Xeloda has been approved for the same indication in 23 additional countries (vol. 3, p. 44) or "at least 18 other countries" (vol.3, p. 84).

[redacted] however, specifics are not provided. The application for registration for first-line treatment of colorectal has been submitted first in the U.S.

14. Financial Disclosure

The vice president of drug regulatory affairs, Dr. Don Maclean, signed the *Certification: Financial Interests and Arrangements of Clinical Investigators*. No investigator had a proprietary interest in the study drug or a significant equity in the sponsor as defined in 21 CFR 54.2(b).

15. Summary

The efficacy claims of this sNDA are based on the results of two open-label, comparative trials randomizing a total of 1207 patients with metastatic colorectal cancer to capecitabine or 5-FU/LV. Study SO14695 randomized 605 patients from 61 sites in the U.S., Canada, Brazil and Mexico. Study SO14796 randomized 602 patients from 59 sites in Italy, England, Scotland, Spain, Germany, Belgium, Russia, Australia, New Zealand and Taiwan. Both protocols are identical in objectives, patient population, design and control arm (the Mayo Clinic regimen of 5-FU/LV approved by the FDA on the basis of a survival advantage in this population).

The protocol-specified primary endpoint of *response rate* showed a statistically significant advantage for patients treated with capecitabine in both trials (21% vs 11% and 21% vs 14%). The robustness of the response rate is strengthened by eligibility criteria requiring bidimensionally measurable disease, review by a blinded panel with subsequent reconciliation of disagreements in data, as well as the similarity in results between the two large randomized trials. Furthermore, the predominant toxicity of capecitabine, the hand-foot syndrome, is the toxicity characteristic of continuous infusion 5-FU (CIV 5-FU) and not bolus 5-FU +/- LV. A body of literature exists supporting the contention that CIV 5-FU has a greater response rate than does bolus 5-FU (Meta-Analysis Group in Cancer. J Clin Oncol 16:301-308, 1998). The meta-analysis of CIV 5-FU vs. 5-FU (not 5-FU/LV) gave response rates of 22% vs. 14%.

It should be noted that response rates in colorectal cancer have been well described as an endpoint that does not correlate to survival. The Advanced Colorectal Cancer Meta-analysis Project analyzed nine randomized trials of 5-FU/LV vs. 5-FU for the treatment of colorectal cancer (J Clin Oncol 10:896-903, 1992). Response rate was 22% vs. 11% ($p = 0.045$); the odds ratio for survival was only 0.97 ($p = 0.57$). This article has been criticized for not including the Mayo Clinic/NCCTG trial that resulted in the approval of leucovorin in conjunction with 5-FU; however, the authors argue that patients with nonmeasurable disease were entered into the Mayo Clinic trial and therefore their data would not contribute significantly to the analysis of correlation between response rate and survival. At the ODAC convened March 2000, both CPT-11 and oxaliplatin were presented for first-line treatment of colorectal cancer. Response rates for CPT-11 plus 5-FU/LV vs. 5-FU/LV were 35% vs. 21% and 39% vs. 22%, respectively, in the two randomized trials. The response rate for oxaliplatin plus 5-FU/LV vs. 5-FU/LV was 51% vs. 23%, respectively. A significant survival advantage only seen in the two CPT-11 trials.

Although response rate was the primary endpoint of the phase 3 protocols, survival has been the traditional endpoint of interest to the Agency in this population, since the Mayo Clinic regimen of 5-FU/LV was approved for a survival benefit. The two phase 3 protocols did include demonstration of non-inferiority in survival as a secondary endpoint. Non-inferiority was defined quantitatively by the upper bound of the 95% C.I. of the hazard ratio of capecitabine to 5-FU/LV, but did not address whether this preserved a clinically relevant fraction of the survival benefit conferred by the addition of leucovorin to 5-FU.

The Agency's analysis of non-inferiority is described in detail in Appendix II. Based on a 10-paper meta-analysis to determine the hazard ratio and confidence intervals for survival of 5-FU to 5-FU/LV, an analysis of non-inferiority based on maintaining an approximate one-sided 2.5% type I error rate was conducted. The definition of non-inferiority was retention of $\geq$ 50% of the effect of adding leucovorin to 5-FU. The studies were vastly underpowered to demonstrate non-inferiority: 4460 events would be required to allow 80% power with the one-sided 0.025 type I error rate methodology. The number of events increases to 15,840 for 80% power using the "CBER Method."

On the basis of the updated survival data from May 15, 2000 (941 events) and without a multiple analysis type I error adjustment, a claim of > 50% retention of the historical survival effect due to adding leucovorin to 5-FU can be made for S014796 and the pooled analysis (but not for #S014695) and of greater than 0% (i.e., better than 5-FU alone) for trial S014695.

Criticisms of the application include (1) the retrospectively determined definition of non-inferiority and type of analysis to be performed; and (2) lack of adjustment for multiple analyses. In this reviewer's opinion, the first is primarily a casualty of an evolving field both within and outside the Agency. The lack of adjustment for multiple analyses resulted from survival being a secondary endpoint -- a cutoff date and/or number of events was not specified in the protocol. Nevertheless, these are weaknesses that the package as a whole must overcome.

In its favor, the definition of non-inferiority as retention of the magnitude of 50% of the historical survival effect when the trial has 40% power, is conservative. For a historical survival benefit of 3-4 months, it could be argued that demonstration of an effect greater than placebo or 5-FU should be sufficient, which the second trial achieves. Secondly, sensitivity analyses included performing the one-sided 0.025 type I error rate methodology using an 8-paper meta-analysis, the prospectively defined "standard" or "per protocol population" and a Bayesian analysis (Simon's method) – all were supportive of the results. Thirdly, the degree of conservatism of methodology ought to be appropriate to the clinical setting. For instance, in the adjuvant setting were treatment is curative, retention of even 50% of a historical effect may be inappropriate. Treatment in metastatic colorectal cancer at best extends life on the order of months and is never curative. Lastly, capecitabine is a prodrug of an antimetabolite that is known to be effective in this disease. It has demonstrated biologic activity in other supportive endpoints, such as superiority in response rate to 5-FU/LV in two randomized trials.

The randomized phase 2 trial #S014797, although supportive in terms of response rate, is most informative in providing a concurrent comparison of capecitabine alone or with leucovorin. Increased toxicity but no advantage in response rate was observed, suggesting biochemical modulation with leucovorin is not

necessary with the to-be-marketed dose and schedule of capecitabine. This is consistent with data with continuous infusion 5-FU. SWOG randomized 88 patients with metastatic colorectal cancer to 5-FU at a dose of 300 mg/m^2/day as a continuous infusion for 28 days or to 5-FU at a lower dose of 200 mg/m^2/day as a continuous infusion for 28 days plus leucovorin 20 mg/m2 IV for 7 days. Response rates were 18% and 17% and median survivals 15 and 14 months, respectively (Rubiales AS, del Valle ML. Cancer. 85: 1866-7, 1999). The value of leucovorin has been clearly established only with the bolus infusion regimens of 5-FU.

The *safety profile* of capecitabine in colorectal cancer at the to-be-marketed dose and schedule consists of 596 patients from the two phase 3 trials and 34 from the randomized phase 2 trial. The randomized design of the phase 3 trials allows the use of adverse events of all causes to define the safety profile. The most frequent adverse events in patients receiving capecitabine were hand-foot syndrome (54%) and GI symptoms: diarrhea (53%), nausea (43%), vomiting (23%) and stomatitis (25%). Hand-foot syndrome occurred in only 7% of patients receiving 5-FU. The most frequent adverse events with 5-FU/LV were GI: stomatitis (62%), diarrhea (60%), nausea (51%) and vomiting (30%). The trends in overall incidences of GI events with 5-FU/LV were not associated with an increase in grade 3-4 GI events except in the case of stomatitis (capecitabine 2% vs 5-FU/LV 15%). The primary laboratory abnormality of clinical importance associated with 5-FU/LV is neutropenia (21% grade 3-4 events vs. 13% with capecitabine). The primary laboratory abnormality associated with capecitabine is hyperbilirubinemia (23% grade 3-4 events vs. 6% with 5-FU). The clinical relevance of the hyperbilirubinemia is not known and furthermore not characteristic of the CIV 5-FU regimens. Hepatic failure and necrosis have been reported as rare events with capecitabine.

The prominence of hand-foot syndrome is consistent with the profile of 5-FU given as a continuous infusion. In the 1,219 patients pooled in The Meta-analysis Group in Cancer, hand-foot syndrome was reported in 13% of patients receiving bolus 5-FU and in 34% of patients receiving CIV 5-FU. Grade 3 or 4 hematologic toxicity was reported in 31% of patients randomized to bolus 5-FU and but only in 4% CIV 5-FU. Other toxicities, such as mucositis, nausea, vomiting and diarrhea were similar between the schedules. The majority of exposure to capecitabine comes from post-marketing use. Consultation from OPDRA suggests that the label accurately reflects the discovered drug-drug interactions with warfarin and phenytoin and rare but serious adverse events such as cardiac and hepatic toxicities.

Finally, although the results of the PK study in renal impaired patients was submitted late and is still under review, the occurrence of 4 deaths (one considered related to treatment) in 27 patients is of concern. The sponsor suggests that severe renal impairment may be a contraindication to treatment with capecitabine and that moderate impairment warrants a 75% dose reduction. Although this data is only available in summary form, the known potential for life-threatening consequences would be important to include in a launch.

16. Recommended Regulatory Action

Approval for the requested indication: first-line treatment of colorectal cancer.

Reviewer Comment: *If we cannot reach agreement about labeling for renal impairment by September 20, 2000, I would recommend an approvable letter.*

17. Phase IV Commitments

- Update of survival analysis after a total of 1180 deaths have occurred in the two phase 3 trials.

Rationale: When the FDA requested a survival update, the cutoff date chosen by the sponsor was May 15, 2000. The reason for choosing this date is not known. Since the last update of survival (September 15, 1999 cutoff) submitted with the 4-month safety update, 34 of the 64 patients on the 5-FU/LV arm and 15 of the 57 in the Xeloda arm died. If Xeloda and 5-FU/LV have the same survival distribution, such a disparity would be rather unlikely. At the time of September 15, 2000, the probability that among the next 49 deaths, 15 or fewer would belong to either treatment arm if the survival distributions are equal is roughly 0.0023.

- Submission of data from the trials of capecitabine being conducted under non-US INDs with irinotecan (_____: Phase 1 study of irinotecan in combination with capecitabine as first line chemotherapy in metastatic colorectal cancer; _____: A randomized phase 2 trial comparing two schedules of irinotecan (CPT11) in combination with capecitabine (Ro 09-1978) as first line chemotherapy in patients with metastatic colorectal cancer).

Rationale: The addition of irinotecan to 5-FU/LV was approved in March 2000 on the basis of superiority in RR, TTP and survival from two randomized, multicenter phase 3 trials. Although capecitabine is may be approved as an oral equivalent of 5-FU/LV, the field has moved forward. The sponsor should anticipate that the use of capecitabine will be similar to the use of 5-FU/LV, i.e., as a component of combination therapy. The sponsor should therefore provide safety and efficacy data of capecitabine in combination with irinotecan in anticipation of its use in general practice.

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/S/ 9-12-00

Alison Martin, M.D. (date)
Medical Reviewer

/S/ 9-12-00

Ning Li, M.D., Ph.D. (date)
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/S/ 9-13-00

Mark Rothmann, Ph.D. (date)
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/S/ MD 9-12-00

John Johnson, M.D. (date)
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See also my Clinical Team Leader Review

/S/ 9/13/00

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George Chi, Ph.D. (date)
Director, Division of Biometrics 1

Cc: Original File
HFD-150 Div File
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APPENDIX I: Completed Trials of Capecitabine with or without Leucovorin (LV) in Patients with Colorectal Cancer

STUDY	US IND	DESCRIPTION	PT #	DOSE mg/m^2/d	COMMENTS
Phase 1					
SO14798	No (Europe)	Phase I study of capecitabine in combination with oral LV in patients with metastatic solid tumors	31	LV 60 mg/d 1004 (continuous) 1004-2510 (intermittent[1])	DLT: GI and HFS LV had no effect on PK
[redacted]	No	Phase I of capecitabine + irinotecan in metastatic colorectal cancer	?	?	Ongoing[3]
[redacted]	No	Phase I of capecitabine + XRT in pts with rectal cancer	?	?	Ongoing[3].
Phase 2					
[redacted]	Yes	Open label study of capecitabine in metastatic colorectal carcinoma progressing on 5-FU	?	2510 intermittent[2]	Ongoing[4] -- 21 pts enrolled as of 11/30/99.
[redacted]	No	A randomized phase 2 trial comparing two schedules of irinotecan in combination with capecitabine as first line chemotherapy in patients with metastatic colorectal cancer	?	?	Ongoing
SO14797	Yes	An open-label randomized phase 2 study comparing the efficacy and safety of continuous therapy with capecitabine, intermittent therapy with capecitabine and intermittent therapy with capecitabine in combination with oral LV as first-line therapy in patients with advanced and/or metastatic colorectal carcinoma	109	Arm 1: 1331 continuous Arm 2: 2510 intermittent[2] Arm 3: 1657 intermittent + LV 60 mg/d	Arm 1: RR 22%; TTP 127d Arm 2: RR 25%; TTP 230d Arm 3: RR 24%TTP 165d *Arm 3 selected for phase 3 trials based on similar longest TTP, highest dose intensity.*
Phase 3					
SO14695	Yes	An open-label randomized phase 3 study comparing capecitabine with 5-fluorouracil in combination with leucovorin as first-line chemotherapy in patients with advanced and/or metastatic colorectal carcinoma	605	Vs 5-FU 425 + LV 20 D1-5 (Mayo Clinic Regimen)	See Section 7.3
SO14796	No Europe, Israel, Taiwan, Australasia	An open-label randomized phase iii study comparing capecitabine with 5-fluorouracil in combination with leucovorin as first-line chemotherapy in patients with advanced and/or metastatic colorectal carcinoma	602	Vs 5-FU 425 + LV 20 D1-5 (Mayo Clinic Regimen)	See section 8.3
[redacted]	Yes	Capecitabine vs. 5-FU/LV as adjuvant therapy in Dukes C colorectal cancer	?	Vs 5-FU 425 + LV 20 D1-5 (Mayo Clinic Regimen)	Ongoing[4] – 732 of planned 1956 pts enrolled as of 3/25/00.

[1]Intermittent schedule refers to two weeks of BID Xeloda followed by one week off, comprising a three week cycle. This is the schedule labeled for refractory breast cancer patients.
[2]Dose and schedule labeled for refractory breast cancer patients.
[3]Ongoing as of June 1999 when data was censored for the last annual report to the IND dated August 27, 1999.
[4]Ongoing as of annual report to the NDA dated May 30, 2000.

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pages of trade secret and/or confidential commercial information

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Appendix II: Xeloda Survival Analysis
By Mark Rothmann & Ning Li
August 30,2000

TESTED HYPOTHESIS

The hypothesis being tested is that Xeloda retains at least 50% effect on survival with respect to hazard ratios due to adding LV to 5-FU (i.e., HR(Xeloda/5-FU) < (1+HR(5-FU+LV/5-FU))/2). Since there is no treatment arm of 5-FU alone, historical data are used to make statistical inferences about the 5-FU/5-FU+LV hazard ratio. If the HR(5-FU/5-FU+LV) is constant then the above hypothesis is equivalent to HR(Xeloda/5-FU+LV) < (1+HR(5-FU/5-FU+LV))/2 . It is this hypothesis that is formally tested using data from historical trials and those active-controlled Xeloda trials.

THE NON-INFERIORITY MARGIN

The non-inferiority margin (value for (1+HR(5-FU/5-FU+LV))/2) will be determined from a meta-analysis involving 10 papers. If the 97.5% confidence upper bound for the HR(Xeloda/5-FU+LV) lies below the non-inferiority margin, non-inferiority will be claimed.

FACTORS AFFECTING TYPE I ERROR RATE

The type I error rate depends largely on these factors: the validity of historical data, the change in the historical effect on survival due to adding LV, the value from historical data for the 5-FU vs. 5-FU/LV hazard ratio used to define the margin, the desired percent of effect to maintain, and a ratio of variances/information between the meta-analysis and these active controlled Xeloda trials.

Effect of Selection Bias among Historical Studies

If there is selection bias among all studies - for example, only favorable studies are included for the meta-analysis - then the relationship between survival and adding LV to 5-FU will be misrepresented and the chance of a false final conclusion may be increased.

The Effect of the Active Control over Time

If the current effect on survival due to adding LV to 5-FU is different from the historical effect, the survival comparison between Xeloda and 5-FU alone will be bias.

Effect of the Meta-Analysis Characteristic Used to Define the Margin

When these are not concerns and the point estimate of the HR(5-FU/5-FU+LV) from meta-analysis is used to determine the non inferiority margin, then the (one-sided) type I error rate can be shown to be greater than 0.025. If the lower bound of the 95% two-sided confidence interval (C.I.) for the HR(5-FU/5-FU+LV) is used, the (one-sided) type I error rate can be shown to be less than 0.025.

Ratio of Variances

The ratio of variances (a ratio of uncertainties) represents (inverted) the ratio of information from the meta-analysis and an active-controlled trial.

Percent Effect Retained

When 100% retention of the survival effect due to adding LV is desired, we have a superiority trial and thus, historical data are ignored. When 0% retention of the historical survival effect due to adding LV is desired, results from the meta-analysis and an active-controlled trial are given closer to equal weights - each bit of information from the meta-analysis is given the same weight as each bit of information from the active-controlled trial. The smaller the percent retention of the survival effect due to adding LV that is desired, the more weight that is given to the meta-analysis.

LACK OF ANY CAUSE-AND-EFFECT CONCLUSION

In a double-blind randomized two-arm trial, external factors and baseline characteristics are essentially balanced. Thus, any concluded survival difference between those two arms can be attributed to the difference in treatment. A cause-and-effect relationship between treatment and survival can be established.

When comparing survival between two single-arm trials with different treatments, the same statistical

In the above case, when the upper 97.5% confidence bound is compared to the calculated margin, one-sided type I error rates - at 0% of the survival effect retained using the lower bound of a 48% confidence interval to calculate the margin - range from _____ The percent confidence coefficients whose 100 % two-sided C.I. for HR(5-FU/5-FU+LV) have approximate 2.5% type I error range from 47.6% to 48.0%.

SURVIVAL ANALYSES

Survival analyses are given for both intent-to-treat (ITT; patients as randomized) and standard populations. Table 2 below lists those vital survival descriptive statistics for these two Xeloda trials for cutoff dates of January 1999 and May 15, 2000.

Reviewer Table 2: Summary of Relevant Survival Descriptive Statistics

Study	HR(Xeloda/5-FU+LV)	log HR	SE(logHR)
ITT Population			
SO14695 January 1999 cutoff	1.13	0.1220	0.1031
SO14796 January 1999 cutoff	0.98	-0.0195	0.1019
POOLED January 1999 cutoff	1.05	0.0497	0.0724
SO14695 May 15, 2000 cutoff	1.00	-0.0036	0.0868
SO14796 May 15, 2000 cutoff	0.92	-0.0844	0.0867
POOLED May 15, 2000 cutoff	0.96	-0.0432	0.0613
Standard Population			
SO14695 May 15, 2000 cutoff	0.98	-0.0218	0.0926
SO14796 May 15, 2000 cutoff	0.91	-0.0966	0.0921
POOLED May 15, 2000 cutoff	0.94	-0.0590	0.0652

Table 3 below gives lower limits of various confidence intervals for the hazard ratio of 5-FU to 5-FU+LV. These limits will be used to define non-inferiority margins for analyses given in tables 4 and 5.

Reviewer Table 3: Lower Limits of C.Ls for HR(5-FU/5-FU+LV)

Lower Limits of 100γ% C.I. for HR(5-FU/5-FU+LV)	
100γ%	**10 paper Meta-Analysis**
0%[1]	1.264
30%	1.228
32%	1.225
34%	1.223
39%	1.216
43%	1.211
45%	1.208
48%	1.204
52%	1.199
54%	1.196
60%	1.186
63%	1.182
65%	1.178
95%	1.091

[1] This row gives the point estimate of HR(5-FU/5-FU+LV).

Table 4 below gives results of 0.025 one-sided type I error rate survival analyses (January 1999 cutoff) for the ITT population using the 10-paper meta-analysis. Results are also given for a pooled (Xeloda trials) analysis.

Reviewer Table 4: Non-inferiority Survival Analysis (January 1999 Cutoff) using the 10-paper Meta-Analysis and a 0.025 One-Sided Type I Error Rate (Margins and Results are Given)

Study	50% retained	0% retained
ITT Population		
SO14695		
97.5% confidence	1.114[1]	1.204[2]
upper bound = 1.38	NO	NO
SO14796		
97.5% confidence	1.114[1]	1.204[2]
upper bound = 1.20	NO	YES
POOLED		
97.5% confidence	1.108[3]	1.186[4]
upper bound = 1.21	NO	NO

[1] Margin is computed using the lower limit of the 30% C.I. for HR(5-FU/5-FU+LV).
[2] Margin is computed using the lower limit of the 48% C.I. for HR(5-FU/5-FU+LV).
[3] Margin is computed using the lower limit of the 39% C.I. for HR(5-FU/5-FU+LV).
[4] Margin is computed using the lower limit of the 60% C.I. for HR(5-FU/5-FU+LV).

A greater than 0% retention of the survival effect due to adding LV to 5-FU for the SO14796 trial was the sole statistically significant result at a 0.025 one-sided significance level.

For the standard population, the SO14695 trial, the 97.5% lower bound for the percent of historical survival effect maintained is 16% (46.7% CI lower bound of 1.206; cutoff =1.173). For the SO14796 trial (standard population), the 97.5% lower bound for the percent of historical survival effect maintained is 62% (26.9% CI lower bound of 1.232; cutoff =1.088). For the pooled survival analysis (standard population), the 97.5% lower bound for the percent of historical survival effect maintained is 68.5% (31.9% CI lower bound of 1.225; cutoff =1.071).

Table 6 below gives results of the CBER survival analyses method (January 1999 cutoff) for the ITT population using the 10-paper meta-analysis. The CBER Method uses the 95% C.I. lower limit from the meta-analysis to define the non-inferiority margin. Results are also given for a pooled (Xeloda trials) analysis.

Reviewer Table 6: Non-inferiority Survival Analysis (January 1999 Cutoff) using the 10-paper Meta-Analysis and the CBER survival analysis method

Study	*50% retained*	*0% retained*
ITT Population		
SO14695		
97.5% confidence	1.045	1.091
upper bound = 1.38	NO	NO
SO14796		
97.5% confidence	1.045	1.091
upper bound = 1.20	NO	NO
POOLED		
97.5% confidence	1.045	1.091
upper bound = 1.21	NO	NO

Using this method led to no claim of non-inferiority.

Table 7 below gives results of the CBER method survival analyses using the 10-paper meta-analysis and the most recent updated survival analyses. Results are also given for a pooled (Xeloda trials) analysis.

Reviewer Table 7. Non-inferiority Updated (May 15, 2000 Cutoff) Survival Analysis using the 10-paper Meta-Analysis and the CBER survival analysis method

Study	50% retained	0% retained
ITT Population		
SO14695		
97.5% confidence	1.045	1.091
upper bound = 1.18	NO	NO
SO14796		
97.5% confidence	1.045	1.091
upper bound = 1.089	NO	YES
POOLED		
97.5% confidence	1.045	1.091
upper bound = 1.08	NO	YES
Standard Population		
SO14695		
97.5% confidence	1.045	1.091
upper bound = 1.17	NO	NO
SO14796		
97.5% confidence	1.045	1.091
upper bound = 1.088	NO	YES
POOLED		
97.5% confidence	1.045	1.091
upper bound = 1.07	NO	YES

A greater than 0% retention of the historical survival effect due to adding LV to 5-FU for the SO14796 trial and the pooled analysis are those (association) claims that can be made.

For the ITT population, the SO14695 trial, the largest percent of historical survival effect maintained that can be claimed using the CBER Method is -98% (i.e., the 5-FU is better than Xeloda with respect to survival by about as much as 5-FU+LV is better than 5-FU with respect to survival). For the SO14796 trial (ITT population), the largest percent of historical survival effect maintained that can be claimed using the CBER Method is 2.2%. For the pooled survival analysis (ITT population) , the largest percent of historical survival effect maintained that can be claimed using the CBER Method is 12.1%.

For the standard population, the SO14695 trial, the largest percent of historical survival effect maintained that can be claimed using the CBER Method is -90% (i.e., the 5-FU is better than Xeloda with respect to survival by about as much as 5-FU+LV is better than 5-FU with respect to survival). For the SO14796 trial (standard population), the largest percent of historical survival effect maintained that can be claimed using the CBER Method is 3.3%. For the pooled survival analysis (standard population), the largest percent of historical survival effect maintained that can be claimed using the CBER Method is 22%.

Table 8 below gives the power at the time of the last death for the ITT population(assuming exponential distributions) when the true hazard ratio of Xeloda vs 5-FU+LV equals 1. Powers were calculated for 602 deaths (study 14796) and 1207 deaths (pooled studies).

Reviewer Table 8. Power at the Time of the Last Death

	One-Sided 0.025 Percent Retained		CBER Method Percent Retained	
Power at	50%	0%	50%	0%
602 deaths	25%	58%	8%	19%
1207 deaths	40%	80%	12%	33%

For each trial there was very low power to conclude at least 50% retention of the survival effect due to adding LV to 5-FU. For each Xeloda trial, at times prior to the death of the last patient, the power to make an association claim of more than 50% effect retained is at most 25% (8%) using the "One-sided 0.025" procedure (CBER method).

Table 9 below gives the number of events (deaths) needed for each method to guarantee 80% power to claim non-inferiority when a drug yields the same survival distribution as 5-FU+LV. Many events are needed.

Reviewer Table 9. Number of Events (Deaths) Required for 80% Power

	One-Sided 0.025 Percent Retained		CBER Method Percent Retained	
	50%	0%	50%	0%
No. of Events	4460	1200	15840	4135

EIGHT-PAPER META-ANALYSIS RESULTS

When a distribution is mound shaped or normal (symmetric with tails that decay many orders quicker than exponential decay) the sample mean is the best estimator of the point of symmetry in the distribution. The sample mean tends to be closer to the true mean than the sample median or any other trimmed mean. When a distribution is symmetric with exponential decaying tails the sample median has many optimal properties (the sample median is arguably the best estimator). For cases of symmetric distributions with tails between exponential decay and normal tails, a trimmed mean will be a better estimator of the point of symmetry.

The variability in the ten-paper meta-analysis tends is largely between study variability (as opposed to within study variability). Because the distribution of log-hazard ratios of 5-FU /5-FU+LV appears fairly symmetric with heavy tails (an outlying value in each tail) the largest and smallest log-hazard ratios were trimmed. An eight-paper meta-analysis was performed for sensitivity purposes (without any adjustment to resulting variance because of trimming). Results of an eight-paper meta-analysis are given in table 10 below. All hazard ratios are 5-FU/5-FU+LV.

Reviewer Table 10. Results of the 8-Paper Meta-Analysis

log HR	SE(log HR)	HR	95% C.I.
0.23979	0.0593	1.271	(1.132, 1.428)

When these meta-analysis results are used for the ITT population non-inferiority survival analyses, the 97.5% lower bound for the percent of historical survival effect maintained is 22% (41.2% CI lower bound of 1.231; cutoff =1.18) for the SO14695 trial, 64% (25.0% CI lower bound of 1.247; cutoff =1.089) for the SO14796 trial, and 67% (29.9% CI lower bound of 1.242; cutoff =1.08) for the pooled survival analysis.

When these meta-analysis results are used for the standard population non-inferiority survival analyses, the 97.5% lower bound for the percent of historical survival effect maintained is 27% (35.2% CI lower bound of 1.237; cutoff =1.173) for the SO14695 trial, 65% (20.7% CI lower bound of 1.251; cutoff =1.088) for the SO14796 trial, and 71% (27.4% CI lower bound of 1.245; cutoff =1.071) for the pooled survival analysis.

For the ITT population, using the CBER Method the largest percent of historical survival effect maintained that can be claimed is -36% (i.e., the 5-FU is better than Xeloda with respect to survival by 36% of the amount 5-FU+LV is better than 5-FU with respect to survival) for the SO14695 trial, 33% for the SO14796 trial, and 39% for the pooled survival analysis.

For the standard population, using the CBER Method the largest percent of historical survival effect maintained that can be claimed is -31% (i.e., the 5-FU is better than Xeloda with respect to survival by 31% of the amount 5-FU+LV is better than 5-FU with respect to survival) for the SO14695 trial, 33% for the SO14796 trial, and 46% for the pooled survival analysis.

CONCLUSIONS AND SUMMARY

From those updated statistical analyses (May 15, 2000 cutoff) with no multiple analysis type I error adjustment, an association claim of a greater than 50% retention of the historical survival effect due to adding LV to 5-FU can be made for the SO14796 trial and pooled analysis (but not for the SO14695 trial) and an association claim of greater than 0% retention of the historical survival effect due to adding LV to 5-FU can be made for the SO14695 trial. These trials were well under-powered to make an association claim of a greater 50% (0%) retention of the historical survival effect due to adding LV to 5-FU.

The reason for choosing May 15, 2000 as a cutoff date is not known. From the time of the sponsor's last survival analysis update (given in an updated safety analysis submission with a September 15, 1999 cutoff) 34 of those 64 in the 5-FU+LV arm that were alive died while 15 of those 57 alive in the Xeloda arm died. If Xeloda and 5-FU+LV have the same survival distribution, such a disparity would be rather unlikely. At the time of September 15, 2000, the probability that among the next 49 deaths 15 or fewer will belong to either treatment arm if the survival distributions are equal is roughly 0.0023.

We would like to see a further sensitivity analyses on survival when a total of 1180 deaths between the two studies have occurred.

APPEARS THIS WAY
ON ORIGINAL

APPENDIX III: OPDRA Post-Marketing Safety Report

DATE: July 18, 2000

FROM: Mary Mease, R.Ph., M.P.H., Safety Evaluator
Division of Drug Risk Evaluation I, HFD-430

THROUGH: Julie Beitz, M.D., Division Director *(Signed 07-18-00)*
Division of Drug Risk Evaluation I, HFD-430

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

SUBJECT: OPDRA Postmarketing Safety Review (consult; PID# D000265)
Drug: Capecitabine (Xeloda); NDA 20-896
Reactions: cerebrovascular ischemia, ileus, cardiac adverse events, and serious hepatotoxicities

EXECUTIVE SUMMARY

We reviewed AERS (Adverse Event Reporting System) cases of cerebrovascular ischemia (5), cardiac ischemia (6), cardiac function (2), ileus (7), and serious hepatotoxicities (11) in response to your consult request dated April 6, 2000 requesting a review of these adverse events for consideration during the review of the pending capecitabine colorectal cancer efficacy supplement. Our literature search did not identify any citations related to capecitabine and the four adverse events of interest. The AERS cases of cerebrovascular ischemia, ileus, cardiac ishemia, and cardiac function identify possible relationships with capecitabine. The three cases of cirrhosis, fibrosis, and necrosis provides limited information for evaluating the relationship between these hepatotoxicites and capecitabine. The laboratory values provided in the one case of hepatitis did not support the diagnosis of hepatitis. Based on our evaluation of the seven cases of liver failure, the contribution of capecitabine to the development of hepatic failure cannot be excluded. Given the number of cases and the potential outcomes of liver failure, we agree with the sponsor that hepatic failure should be included in the label. However, we have seven cases of hepatic failure whereas the sponsor noted in the proposed label that there are three cases. In addition, we recommend that the number of cases of hepatic failure not be included in the capecitabine label as this number will change over time.

<u>Cerebrovascular ischemia (8 reports)</u>

We reviewed eight cases potentially related to cerebrovascular ischemia. Three patients experienced events with unlikely relationships to cerebrovascular ischemia or capecitabine:

(Min-the peripheral neuropathy case I excluded was peripheral peroneal neuropathy with left foot drop thought to be due to underlying tumor. Reporter stated no signs and symptoms of a stroke. The case of paraparesis progressing to tetraparesis had brain edema but no mention of anything else. It was a foreign report with no specific timeline of the events other than it happened 2-3 weeks after capecitabine was dc'd. The patient was treated with steroids and immunoglobulins. I think it would be a very far stretch to say that this was even potentially related to ischemia)

- paraparesis one month following discontinuation of capecitabine in combination with oxaliplatin and radiation to the pelvis and acetabulum for bone metastases.
- hypoxic ischemic encephalopathy following cardiac and respiratory arrest secondary to dehydration and aspiration pneumonia and, therefore, the cerebrovascular ischemia was unlikely due to capecitabine
- hemiplegia following a period of atrial fibrillation seven days following the first cycle of capecitabine and docetaxel in a patient with a history of atrial fibrillation

Five cases described potential cerebrovascular ischemic events (one report each of CVA with, hemiparesis, paralysis of right arm and hand, right occipital CVA, cerebral infarcts, and transient ischemic attack) with no identifiable cause. Following are the five case demographics:

Age:	range=33-72 years, mean=58 years, median=65 years
Gender:	male=3, female=1, unknown=1
Daily dose:	4000mg-5300mg-4, unknown-1
Indication:	colorectal-4, unknown-1
Time to onset:	3-9 days after beginning the first cycle-2, 7 days after the first 14-day cycle-2, 2 days after beginning the second cycle-1
Report year:	1998-1, 1999-1, 2000-3
Report source:	domestic-3, foreign-2
Outcome:	life-threatening-1, hospitalization-2, disability-2

Three cases described signs and symptoms of inability to swallow, disorientation, ataxia, and stammering; the remaining two cases did not report any signs or symptoms. No patients were reported to have brain metastases. Three cases reported normal or negative findings on CT scan, NMR, and MRI; one patient also had negative findings on carotid doppler ultrasound with an echocardiogram that showed severe left ventricular hypertrophy. A fourth case reported negative findings on echocardiogram and carotid doppler ultrasound. One patient with minimal dehydration had concurrent increased intracranial pressure due to an unknown cause. One patient had a history of hypertension and smoking and started aspirin for rheumatoid arthritis one year prior to starting capecitabine. The paralysis experienced by one patient continued and the hemiparesis experienced by a second patient improved after capecitabine was discontinued. Two patients continued on capecitabine without further reported episodes of cerebrovascular ischemia-related adverse events three and six months after the reported cerebrovascular ischemia adverse events. One patient died due to an unknown cause six days after the right occipital CVA.

Following are the five brief case descriptions:

- 72 year old male with a history of colon cancer, hypertension, and smoking developed diarrhea and the inability to move one side of his body seven days after the first 14-day cycle; a CT scan showed left parietal and temporal infarcts
- 72 year old male who received capecitabine for an unknown indication experienced left facial weakness and left hemiparesis two days after beginning the second capecitabine cycle; an echocardiogram and carotid studies were negative
- a 50 year old female with colon cancer experienced paralysis of her right arm and hand seven days after the first 14-day cycle; a CT scan was normal
- a 33 year old female with colon cancer experienced minimal dehydration, increased intracranial pressure, stammering, hemiparesis, and dysphagia three days after beginning the first capecitabine cycle; a CT scan and NMR were negative
- a 67 year old male with colorectal cancer experienced disorientation and acute ataxia nine days after beginning the first capecitabine cycle; a carotid doppler study was negative but an echocardiogram showed severe left ventricular hypertrophy

These five cases represent a possible relationship between capecitabine and cerebrovascular ischemic adverse events. Other potential causes (brain metastases, CNS bleeds, blockage of the carotid artery, and decreased heart function) were ruled out in four patients although one of the five patients had a history of hypertension and smoking which are potential risk factors. Although cerebrovascular ischemic events can occur spontaneously, the close temporal relationship between the initiation of capecitabine and the occurrence of the cerebrovascular ischemic events is suggestive of a potential drug association. Cerebrovascular accident is included in the *Adverse Events* section of the current label. Transient ischemic attack is included in the *Adverse Events* section of the proposed label.

Cardiac (21 reports)

We reviewed 21 cases of cardiac adverse events reported in assocation with capecitabine. There was one report of sudden death with no cardiac event reported. Twelve reports described cardiac events (ventricular tachycardia, cardiac arrest, heart attack, asystole, cardiomyopathy, acute myocardial infarction, acute heart failure, congestive heart failure) likely due to other factors:

- secondary to other events-9
  pulmonary edema, disseminated intravascular coagulation, emboli, shock, surgery, gastrointestinal hemorrhage, severe respiratory distress, liver cirrhosis, and severe metabolic acidosis
- potentially due to concomitant doxorubicin-1
- unlikely temporal relationship-1
  acute heart failure seven days after capecitabine was discontinued
- preexisting condition-1
  severe left ventricular hypertrophy 11 days after capecitabine was started (incidental finding during workup of ataxia and disorientation)

Eight cases described cardiac ischemia (6) and cardiac function changes (2) potentially related to capecitabine.

Cardiac ischemia

There were six cases of cardiac ischemic events (myocardial infarction-4, myocardial ischemia-1, and heart attack-1). Following are the case demographics:

Age:	range=54-76 years, unknown=1, mean=65 years, median=67 years
Gender: male=4, female=2	
Daily dose:	2000mg-5000mg-5, unknown-1
Indication:	colorectal-4, breast-1, unknown-1
Time to onset:	1-3 days-3, 14 days-1, 9 days after completing 5 days of capecitabine-1, unknown-1
Report year:	1998-1, 1999-4, 2000-1
Report source:	domestic-4, foreign-2
Outcome:	died-2, life-threatening-1, hospitalization-2, other-1

The case of heart attack occurred in a patient of unknown age and provided no other details. Of the four cases of myocardial infarction, two provided evidence of an infarction (CPK>1000, CPK 539, and extensive anterior infarction). The case of myocardial ischemia ruled out a myocardial infarction by EKG. One patient who experienced a myocardial infarction was diagnosed with cardiomegaly one month after capecitabine was discontinued; the patient received two doses of capecitabine and had an unknown cardiac history. One patient received prior fluorouracil and a second received prior docetaxel. Three patients, two of whom died following myocardial infarctions, had possible risk factors (smoking, sarcoidosis, and a prior myocardial infarction).

The most interesting case was the case of myocardial ischemia in a 54 year old male (smoker) with two positive rechallenges. The patient had normal coronary anatomy by angiography, normal cardiac enzymes, and normal left ventricular function. The patient experienced radiating chest pain with diaphoresis and nausea three days after the capecitabine was started. The patient experienced chest pain after three doses of capecitabine; an EKG showed ST-segment elevation. The patient resumed capecitabine the following day and an EKG showed ST-segment elevation. The chest pain was persisting six months after capecitabine was discontinued.

Cardiac function

There was one case each of congestive heart failure (CHF) and dilated cardiomyopathy. The one reported age was 72 years Both reporting physicians attributed the cardiac events to capecitabine. The case of CHF

provided no details and occurred in a patient with significant heart disease. The case of dilated cardiomyopathy occurred in a patient with breast cancer and lung metastases who received prior docetaxel and radiation therapy. The patient had no history of heart disease. Within two months of starting capecitabine, the patient developed bilateral pedal edema that was treated with furosemide. Shortness of breath increased requiring continuous oxygen. Five months after the onset of the pedal edema (seven months after starting capecitabine) an echocardiogaphy revealed an ejection fraction of 20%. Quinapril and digoxin were started and capecitabine was discontinued. Shortness of breath was persisting two weeks after capecitabine was discontinued.

In summary, five of the six cases of cardiac ischemia, of which the majority described myocardial infarction, have a close temporal relationship to the initiation of capecitabine. The sixth case of cardiac ischemia occurred nine days after five days of capecitabine in a patient with a history of myocardial infarction. The patients were age 54-76 years old. Two of the six patients had cardiac risk factors. The case of myocardial ischemia with two positive rechallenges is interesting; the persisting chest pain six months after capecitabine was discontinued may represent an irreversible process. In addition, the association between congestive heart failure and dilated cardiomyopathy and capecitabine is unclear. However, the case of cardiomyopathy illustrated a progressive decline in cardiac function coinciding with capecitabine therapy. The few reports of CHF and cardiomyopathy relative to the time capecitabine has been marketed may reflect the possibility that congestive heart failure and cardiomyopathy go undiagnosed due to patients' prognoses and the underlying conditions that may confound the clinical picture. The six cases of cardiac ischemia represent a possible association with capecitabine. Angina pectoris and cardiomyopathy are included in the *Adverse Reactions* section of the current capecitabine label. Myocardial infarction is included in the *Adverse Reactions* section of the proposed capecitabine label.

Ileus (7 reports)

We reviewed seven cases of ileus and intestinal obstruction reported in association with capecitabine. Two cases of paralytic ileus were potentially confounded by concomitant disease and chemotherapy:

- paralytic ileus occurred 10 days after the last doses of capecitabine and ironotecan in a patient with colorectal carcinoma
- paralytic ileus occurred four days after the last capecitabine dose in a patient with breast cancer who received concomitant docetaxel

The remaining five cases of ileus (3), paralytic ileus (1), and intestinal obstruction (1) occurred in female patients with breast cancer (2) and squamous cell carcinoma (2); one indication was unknown. One report had no details. Three diagnoses were made four to 17 days after completion of the second capecitabine cycle; the time to diagnosis in two patients was unknown. The diagnoses of ileus was preceded by diarrhea (4) and hand-and-foot syndrome (1). Two patients were also neutropenic. One patient initially had watery stools that later became bloody. One patient had negative blood and stool cultures and stool cultures for clostridium dificile were initially negative in one patient but were positive 16 days after the negative result. One patient had chronic renal failure secondary to cisplatin. One patient received concomitant radiation to the thoracic and lumbar spine. Four of the five patients died. The ileus contributed to the death of one patient. Three of the deaths resulted from an unknown cause but occurred eight to 12 days after (2) and within seven days (1) of the ileus diagnosis; the ileus in two patients improved between diagnosis and death. The outcome of the fifth patient was unknown.

The five cases of ileus (3), paralytic ileus (1), and intestinal obstruction (1) suggest a possible association between capecitabine and ileus. One case was potentially confounded by concomitant radiation to the lumbar spine. It is interesting to note that four patients experienced diarrhea prior to the diagnosis of ileus. Two of the four patients who experienced diarrhea were also neutropenic, suggesting the possibility that these were cases of typhlitis. It is possible the ileus may be the intestines' reflex response to hypermotility although many patients who receive capecitabine and experience severe diarrhea do not develop ileus. Another possibility is that the ileus is neurogenically mediated but may be unrelated to the diarrhea. Necrotizing enterocolitis (typhlitis) is

included in the *Warnings* section of the current label. Ileus is included in the *Adverse Reactions* section of the proposed capecitabine label.

Serious Hepatotoxicites

We reviewed 11 cases of hepatitis (1), cirrhosis (1), fibrosis (1), necrosis (1), and hepatic failure (7) reported in association with capecitabine. The hepatitis case provided a diagnosis of chemical hepatitis; however, the laboratory test results were not consistent with hepatitis (SGPT=51, lipase=420). The patient who developed hepatic cirrhosis had a baseline CT scan that showed hepatic metastases but no cirrhosis; a CT scan 11 weeks after capecitabine started showed marked cirrhosis and varices and a decrease in the size and number of hepatic metastases. The case of hepatic fibrosis occurred after 11 months of capecitabine therapy in a patient with baseline liver metastases; a CT scan and liver showed chronic hepatopathy and hepatic fibrosis, respectively. The case of hepatic necrosis (confirmed by biopsy) occurred after three days of capecitabine given with concomitant gemcitabine in a patient who had blockage of both bile ducts requiring stent insertion.

Of the seven patients who developed hepatic failure, three patients had altered liver function, hepatic metastases, or early hepatic cirrhosis prior to beginning capecitabine therapy; one of these three patients received concomitant docetaxel. One patient had no evidence of liver metastases at the time of hepatic failure diagnosis but received concomitant drug products known to be hepatotoxic. Five of the seven patients received concomitant drug products known to be hepatotoxic. Of the two patients who did not receive concomitant drug products, the onset of hepatic failure was acute (four weeks and two months after capecitabine was started); one had baseline liver metastases. A third case also had an acute onset (10 days) but occurred in a patient with altered baseline liver function and hepatic metastases who received concomitant hepatotoxic drugs. One patient experienced hepatic veno-occlusive disease and hepatic necrosis prior to developing liver failure; a liver biopsy was performed but the results were not provided in the report. Five of the seven patients died following the hepatic failure.

In conclusion, the majority of the 11 cases of serious hepatotoxicities reported in association with capecitabine included other factors that may have contributed to the development of the hepatotoxicities. The three cases of cirrhosis, fibrosis, and necrosis provide limited information for evaluating the relationship between these hepatotoxicites and capecitabine. The laboratory values provided in the one case of hepatitis did not support the diagnosis of hepatitis. On the other hand, the contribution of capecitabine to the development of hepatic failure cannot be excluded. Given the number of cases and the potential outcomes of liver failure, we agree with the sponsor that hepatic failure should be included in the label. Hepatitis, cholestatic hepatitis, hepatic fibrosis, and hyperbilirubinemia are included in the *Adverse Reactions* section of the current label. Hepatic failure is included in the *Postmarketing* section of the proposed label with a notation that there are three cases. We recommend that the number of cases of hepatic failure not be included in the capecitabine label as this number will change over time.

LITERATURE REVIEW

A MedLine search performed on April 5, 2000 did not identify any citations of cerebrovascular ischemia, ileus, cardiac adverse effects, or serious hepatotoxicities associated with capecitabine.

/S/

(Signed 07-13-00)

Mary L. Mease, R.Ph., M.P.H.
Safety Evaluator

Concur:

Consult Request Information

Date requested	April 6, 2000
Date received	April 6, 2000
Reason	To provide information on the adverse events cerebrovascular ischemia, ileus, cardiac adverse events, and serious hepatotoxicities for consideration during the pending colorectal efficacy supplement review.

Relevant Product Labeling

We reviewed the approved capecitabine label, designated as "current," and the proposed label submitted by the sponsor for the pending supplement, designated as "supplement" (only additions to the label are noted), and found the following relevant product labeling. The adverse events appear in the *Adverse Events* section of the labels unless otherwise noted.

Neurological

current	ataxia, encephalopathy
supplement	tremor, abnormal coordination, facial palsy

Vascular

Current	cerebrovascular accident
Supplement	transient ischemic attack

Ileus

current	typhlitis (Warnings)
supplement	intestinal obstruction, ileus, toxic dilation of intestine

Cardiovascular

current	angina, cardiomyopathy The cardiotoxicity of capecitabine, including myocardial infarction, arrythmias, cardiac arrest, and cardiac failure, is similar to that of other fluorinated pyrimidines. Cardiotoxicity may be more common in patients with a prior history of coronary artery disease. (Precautions)
supplement	tachycardia, bradycardia, arrhythmia, cardiac failure, cardiomyopathy, myocardial infarction

Hepatotoxicities

current	interrupt capecitabine if Grade2-4 bilirubin occurs (Precautions), hepatitis, cholestatic hepatitis, hepatic fibrosis
supplement	hepatic failure (Postmarketing), hepatomegaly, jaundice, fatty liver

The following pharmacokinetic information appears in the labels:

current	The AUC and Cmax of capecitabine increased by 60% whereas there was no effect on the AUC and Cmax of 5-FU. Caution should be exercised when capecitabine is administered to patients with mild to moderate hepatic dysfunction due to liver metastases. The effect of severe hepatic dysfunction on capecitabine is not known.
supplement	A population pharmacokinetic analysis showed gender, race, presence or absence of liver metastases at baseline, total bilirubin, serum albumin, ASAT, and ALAT had no statistically-significant effect on the pharmacokinetics of 5'-

DFUR, 5-FU, and FBAL (2nd, 3rd, and urine metabolites of capecitabine, respectively).

AERS Search Information

Issue	Search Date	Search terms	Number of reports
All reports	May 4, 2000	not applicable	420
Cerebrovascular Ischemia	April 11, 2000	Paralysis (HLT) Cerebrovascular and spinal necrosis and vascular insufficiency (HLT) Central nervous system hemorrhages and cerebrovascular accidents (HLT)	13*
Ileus	June 7, 2000	ischemic colitis, gangrenous colon, ileus, Paralytic ileus, intestinal infarction, Intestinal ischemia	10
Cardiovascular ischemia	April 5, 2000	cardiac arrest, cardiac failure congestive, cardiac failure, cardiomyopathy, myocardial infarction, myocardial ischemia, ventricular hypertrophy	21
Serious hepatotoxicities	June 7, 2000	hepatic cirrhosis, hepatic failure, hepatic Fibrosis, hepatic necrosis, hepatitis	11

* Five reports described events unrelated to CNS ischemia (cerebral hemorrhage-2, aggressive behavior and paranoia, peripheral neuropathy, and brain edema with paraparesis progressing to tetraparesis, bulbar palsy, and respiratory failure with increased cerebrospinal fluid protein level).