CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

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

Medical Review(s)

XELODA® (capecitabine), Ro 09-1978 Efficacy Supplement Clinical Review

NDA Number: 20,896
Submission Date: March 7, 2001
Completion Date: August 29, 2001

Medical Reviewer: Patricia Cortazar, M.D.
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Division of Oncology Drug Products

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Clinical Review for NDA 20896

. *Executive Summary*

This multidisciplinary medical-statistical review addresses an efficacy supplement to NDA 20-896 for use of Xeloda® (capecitabine) in combination with Taxotere® (docetaxel) for the treatment of patients with metastatic breast cancer progressing after treatment with an anthracycline-containing regimen. The original NDA for Xeloda, submitted in 1998, received accelerated approval under Subpart H of 21 CFR 314.500 on the basis of a surrogate endpoint, response rate, in a single phase 2 trial conducted in patients considered to have refractory breast cancer. The current supplement presents the results of a randomized, controlled clinical trial (S014999) in a similar patient population to satisfy a commitment required by the accelerated approval regulations

I. Recommendations

A. Recommendation on Approvability

The Division of Oncology Drug Products recommends approval of the combination of Xeloda and docetaxel for the proposed indication: *treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing chemotherapy.*

The efficacy claims in support of this application are based on the results of the clinical trial S014999 entitled, "An open-label randomized Phase III study of capecitabine in combination with docetaxel versus docetaxel monotherapy in patients with advanced and/or metastatic breast cancer." A total of 511 patients were randomized to either combination treatment or monotherapy. The protocol-specified primary endpoint was time-to-progression; secondary endpoints were response rate and survival. The combination arm demonstrated statistically significant and clinically relevant superiority in the three traditional oncology endpoints including survival as measured against an accepted control arm. Survival is considered the primary endpoint of interest in the treatment of first-line metastatic breast cancer, as discussed at the Oncology Drugs Advisory Committee meeting of June 7, 1999.

The safety profile of Xeloda in combination with docetaxel is consistent with the known toxicities of both agents and typical of antineoplastic therapy. Common toxicities included diarrhea, stomatitis, hand-foot syndrome, hyperbilirubinemia and neutropenia, which are currently identified in the Xeloda label. The incidence of grade 3 and 4 adverse events was higher in the combination arm as were dose modifications and treatment discontinuations. The A total of four patients on the combination arm and one on the monotherapy arm died of treatment-related events. Xeloda label identifies hepatic failure as a rare event; one in 255 patients died of hepatic failure in S014999.

Although the trial demonstrated a clear survival benefit to combination therapy, it is not known whether the survival benefit could be preserved with less toxicity by a regimen employing the sequential treatment of Xeloda and docetaxel. A head to head comparison to answer this question has been suggested to the sponsor.

Labeling supplement #011 was submitted on July 27, 2001 reporting the results of a drug interaction study of Xeloda and warfarin (study BP15966). This trial had been designed on the basis of signals from post-marketing surveillance suggesting an interaction.. This supplement has been reviewed in detail by Clinical Pharmacology/Biopharmaceutics. In summary, the results demonstrated that coadministration of Xeloda with a single dose of warfarin 20 mg increased the mean AUC of S-warfarin by 57% and decreased its clearance by 37%. Baseline corrected AUC of INR in 4/4 patients in the trial increased by 2.8 fold and the maximum observed mean INR value was increased by 91%. The study was closed prematurely after 4 patients since the objective of the study was reached. Information on this drug-drug interaction should be featured more prominently in the current label.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

The Division recommends the following phase 4 studies:

- An open-label, randomized phase 2 study of standard dose intermittent oral capecitabine (Q3W) versus "low" dose intermittent oral capecitabine versus alternate dose and schedule intermittent oral capecitabine (Q4W) in patients with metastatic breast cancer.

Rationale: Safety data from S014999 indicate 79% of patients required treatment interruptions and 65% of patients required dose modifications due to adverse events in the combination arm. The sponsor is encouraged to systematically explore through clinical trials whether alternative doses and schedules of Xeloda can preserve activity and/or efficacy while reducing toxicity.

- A clinical pharmacology study to determine if long-term coadministration of capecitabine and docetaxel alters the pharmacokinetics of the parent compounds and/or their metabolites.

Rationale: Limited pharmacokinetic data of the combination has been submitted with this sNDA and reviewed by Clinical Pharmacology/Biopharmaceutics. The sponsor is encouraged to examine whether pharmacokinetics are altered with chronic administration of the combination and whether this might correlate with clinical toxicity. Data may suggest more favorable dosing regimens.

The Division asks for a risk management plan, to include revised labeling with a boxed warning, communicating potential health risks and increased frequency of monitoring when Xeloda is co-administered with coumarin-like anticoagulants.

Rationale: The results of clinical trial BP15966, submitted July 27, 2001, unequivocally confirm the drug-drug interaction suggested by post-marketing reports. The magnitude of the risk is considered high since laboratory evidence of a coagulopathy can occur after a single dose or at doses as low as 1 mg. Furthermore, deaths have been reported. Since this adverse event is preventable, an improved risk management program should be considered.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Xeloda is an orally administered prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR), a metabolite enzymatically converted in many tissues throughout the body to the active drug, 5-fluorouracil. The original NDA for Xeloda received accelerated approval under Subpart H of 21 CFR 314.500 in 1998 on the basis of response rates in a phase 2 trial of patients with refractory breast cancer. The indication reads: "treatment of patients with breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy may be contraindicated, e.g., patients who have received cumulative doses of 400 mg/m^2 of doxorubicin or doxorubicin equivalents." Study S014999, the subject of this review, was submitted March 7, 2001 to satisfy the accelerated approval requirement for further trials to demonstrate clinical benefit..

Xeloda has also been approved for the treatment of metastatic colorectal cancer (approval letter dated April 30, 2001).

B. Efficacy

Study S014999 was an open label, multicenter, multinational, randomized, parallel group phase 3 study designed to compare the efficacy and safety of Xeloda with and without docetaxel in patients with metastatic breast cancer progressing after treatment with an anthracycline. A total of 511 patients were randomized from 75 investigational sites in 16 countries.

The treatment arms were well balanced for important baseline characteristics. Most of the patients (65% to 69%) had received previous chemotherapy for metastatic disease. Time to progression was the primary endpoint; survival and overall response rate were the secondary endpoints. The combination of Xeloda and docetaxel resulted in a statistically significant reduction of 35% in the risk of tumor progression for combination therapy patients (hazard ratio 0.65, p= 0.0001) with median time to progression of 186 days for the combination therapy compared to 128 days for the monotherapy patients. The xeloda doxetaxel combination arm resulted in a statistically significant reduction of 22% in the risk of death for combination therapy (hazard ratio 0.78, p=0.013. Overall tumor response was reported by the investigator, peer-reviewed, with disagreements reconciled by the sponsor according to a prespecified

algorithm. The reconciled data demonstrated a response rate of 32% for the combination and 22% for docetaxel alone (p=0.009). Overall, the consistency of outcome across the study endpoints demonstrates the efficacy of xeloda and docetaxel in metastatic breast cancer.

C. Safety

The safety profile of Xeloda given as monotherapy is contained in the current label based on clinical trial data in patients with metastatic breast cancer, metastatic colorectal cancer as well as post-marketing reports.

The safety profile of Xeloda given as a combination therapy is consistent with the toxicities described in the label for the individual study drugs. Gastrointestinal adverse events such as stomatitis and diarrhea were more common in the combination therapy arm. Hand and foot syndrome was presented in 63% of the patients receiving combination of xeloda/docetaxel. Treatment-related neutropenia leading to medical intervention occurred with similar frequency in both treatment arms. The incidence of neutropenic fever was higher in the monotherapy treatment group. Treatment-related mortality was higher in the xeloda/docetaxel arm (4 patients: enterocolitis, sepsis, hepatic coma and pulmonary edema) compared to the docetaxel monotherapy arm (1 patient: sepsis). There was a higher incidence of hyperbilirubinemia grade $\geq$ 3 in the combination therapy arm (11%) compared to the monotherapy arm (5%).

Study results from study BP15966 (supplement #011) indicate there is a significant xeloda-warfarin drug interaction. Altered coagulation parameters and or bleeding, including death, have been reported in patients taking xeloda concomitantly with coumarin derivative anticoagulants. Post-marketing reports have shown increases in PT and INR. These events occurred in patients with and without liver metastases who were stabilized on anticoagulants at the time xeloda was introduced. *Reference: Clinical Pharmacology/Biopharmaceutics Review of Supplement #011.*

D. Dosing

The recommended dose of Xeloda is 1250 mg/m2 administered orally twice daily (total daily dose is 2500 mg/m2) with food for 2 weeks followed by a 1-week rest period given as 3 week cycles for monotherapy as well as in conjunction with docetaxel.

The percentage of patients requiring dose reductions and or treatment interruptions in study S014999 was higher in the combination arm (84%) compared to the monotherapy arm (37%). Since most of patients in the combination arm were dose reduced due to adverse events, uncertainty remains about the optimal dosing. A phase 4 commitment will include a study to explore optimal doses of xeloda to improve the safety profile.

In the current label, Xeloda is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min [Cockroft and Gault]). In patients with moderate renal impairment at baseline (creatinine clearance 30 - 50 mL/min [Cockroft and Gault]), a dose

reduction to 75% of the Xeloda starting dose when used as monotherapy or in combination with docetaxel (from 1250 mg/m^2 to 950 mg/m^2 twice daily) is recommended. No adjustment to the starting dose is recommended in patients with mild renal impairment. *Reference: Medical Officer Review of Amendment SE1-006, submission date October 31, 2000.*

Based on a formal hepatic impairment study, the label currently recommends careful monitoring and does not recommend starting dose adjustment for patients with mild to moderate hepatic dysfunction due to liver metastases. Patients with severe hepatic dysfunction have not been studied.

E. Special Populations

Study S014999 was conducted solely in females since it targeted breast cancer. Colorectal studies previously submitted included males and females. No formal studies have been conducted to examine the effect of age or gender or ethnicity on the pharmacokinetics of capecitabine and its metabolites.

Increased adverse events were suggested in subset analyses of women > 60 year old: stomatitis in both arms, neutropenia in the monotherapy arm and hand and foot syndrome in the combination arm. Deaths during treatment or within 28 days after the last dose of study drug were not increased in patients > 60. Toxicity did not reverse the positive outcome trends in the study endpoints. We strongly encourage the sponsor to pursue the optimal dose of capecitabine in a prospective studies.

The sponsor applied for a waiver for pediatric study requirements. On September 23, 1999, the Agency granted a waiver for pediatric studies for metastatic breast cancer and metastatic colon cancer.

. *Clinical Review*

I Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Drug Name:
Established: Capecitabine (Ro 09-1978)
Trade Name: Xeloda ™
Chemical Name: 5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine

Applicant
Hoffman-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-119

Pharmacologic Category
Fluoropyrimidine carbamate

Sponsor's Proposed Indication
"Xeloda in combination with Docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior anthracycline containing chemotherapy."

Dosage Form and Route of Administration
"The recommended dose of Xeloda™ is 1250 mg/m^2 administered orally twice daily (total daily dose is 2500 mg/m^2) with food for 2 weeks followed by a 1-week rest period given as 3 week cycles. Xeloda™ tablets should be swallowed with water."

How Supplied:
Xeloda™ is supplied as film coated tablets, available in two dose strengths, 150 and 500 mg.

B. State of Armamentarium for Indication(s)

As discussed at the June 1999 ODAC meeting, overall survival is the primary endpoint of interest in the metastatic setting of breast cancer. The standard of care for first-line cytotoxic therapy of metastatic breast cancer is anthracycline-based therapy. Doxorubicin has a modest but real survival advantage in the first-line setting, estimated at about 6 months (Craig Henderson's presentation at ODAC meeting June 1989). Current practice routinely includes anthracyclines in the adjuvant setting for most patients. Therefore, current practice includes other therapies for metastatic breast cancer. Existing therapies that convey a survival advantage include: Herceptin in combination with chemotherapy (paclitaxel) for HER2/neu overexpressors and taxotere which is approved after failure of prior chemotherapy. Overall, few chemotherapy agents have shown survival superiority in metastatic breast cancer. The combination of xeloda with docetaxel in the current application, showed survival superiority in addition to the baseline docetaxel survival advantage.

C. Important Milestones in Product Development

- May 20, 1994: The initial IND [ ] application was filed.

- May 23, 1997: Protocol SO14999 entitled, "An open-label Phase III study of capecitabine in combination with docetaxel (Taxotere) versus docetaxel monotherapy in patients with advanced and/or metastatic breast cancer", was submitted to the IND.

- April 30, 1998: Xeloda was granted accelerated approval for the treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated, e.g., patients who have received cumulative doses of 400 mg/m2 of doxorubicin or doxorubicin equivalents. Resistance was defined as progressive disease while on treatment, with or without an initial response, or relapse within 6 months of completing treatment with an anthracycline-containing adjuvant regimen. This indication was approved based on response rate (25.6%) in a single arm trial. No results were available from controlled trials that demonstrated a clinical benefit such as improvement in disease-related symptoms, disease progression or survival.

- To satisfy the requirements of the accelerated approval regulations (21 CFR 314.510), the following Phase 4 commitment was specified:

  Commitment 1: study SO 14999B entitled, "An open-label Phase III study of capecitabine in combination with docetaxel versus docetaxel monotherapy in patients with advanced and/or metastatic breast cancer". FDA agreed, at the time of accelerated approval, that clinical benefit could be demonstrated in this study if patients randomized to the capecitabine and docetaxel combination arm had a clinically significant improvement in time to progression compared to patients randomized to docetaxel monotherapy.

Other Phase 4 commitments were:
Commitment 2: alternative studies were to be submitted. The sponsor stated there were no alternative studies and agreed to submit and discuss with FDA any major amendments to the Phase 4 protocol.
Commitment 3: the submission of the ongoing study [redacted] entitled, "A Phase II study of capecitabine in patients who have received previous treatment with paclitaxel or docetaxel for locally advanced and/or metastatic breast cancer". The sponsor agreed to submit the results of the study when completed.

- August 31, 1999: The sponsor found on a preliminary review of the study data, that patients were receiving other anticancer treatments prior to documentation of disease progression. This constituted a protocol violation and the sponsor was concerned that the primary endpoint (TTP) may be biased. Therefore, the sponsor proposed to augment the sample size and change the analysis of time to progressive disease by censoring patients at the time they initiated new therapy before PD was documented. FDA consulted with the ODAC statistical member, Dr. Richard Simon, and the following joint response was communicated to the sponsor:

  The proposal to augment the sample size for the newly proposed censoring analysis is flawed. There was an overwhelming concern in the bias introduced by changing the sample size based on an unplanned comparative look at the data. It might be justifiable to increase the sample size for a survival analysis but the type I error level would need to be adjusted to a level of 0.03.

- The Division conveyed ODAC's recommendation at the June 7, 1999 meeting, to consider survival as a primary endpoint in treatment of first line metastatic breast cancer. FDA recommended increasing the sample size to detect an improvement in survival. The sponsor stated that they planned to maintain the predefined primary endpoint as TTP. FDA affirmed that the Division would recognize the commitment made in the April 30, 1999 approval regarding the use of TTP as the primary endpoint of trial SO 14999. However, the acceptability of the endpoint would likely depend on the magnitude of benefit. In addition, any clinical benefit would be weighed against toxicity in decisions of approval.

D. Other Relevant Information

Capecitabine has been approved in more than 50 countries, including the US, Canada and Switzerland, for the treatment of patients with metastatic breast cancer that is resistant to paclitaxel and an anthracycline-containing regimen or for whom further anthracycline treatment is not indicated. Xeloda is also approved for use as first-line treatment of patients with colorectal cancer in over 20 countries, including the U.S., European Union, Canada, Switzerland and Australia. The current application is the Phase-4 commitment to satisfy the requirements for accelerated approval.

E. Important Issues with Pharmacologically Related Agents

Capecitabine is a pro-drug of 5-fluorouracil (5-FU), an antimetabolite that has been used for decades in the treatment of many types of cancer. Safety profile of 5-FU is well described. Main adverse events described for 5-FU are gastrointestinal, mucositis and on the continuous infusion schedule, hand-foot-syndrome.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Xeloda is a marketed drug; the chemistry and manufacturing controls have been previously reviewed and approved. On May 18, 2001, a categorical exclusion from environmental assessment was granted. No new information with regard to chemistry, pharmacology, toxicology and microbiology was submitted with this NDA. This review is a combined medical and statistical review.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Xeloda is a marketed drug; the clinical pharmacology and mechanisms of action have been previously reviewed and described in the label. See current pharmacokinetics reviews by Gene Williams and Safaa Ibrahim.

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

No effect of capecitabine and docetaxel on each other's pharmacokinetics ocurred with acute administration (Study 15304). However, the effect of chronic administration (Study SO14999) was inconclusive because of the small number of patients studied (n = 5). Nonetheless, the mean behavior shows a 120%, 50% and 43% increase in Cmax for capecitabine, 5'-DFCR (a capecitabine metabolite) and 5'-DFUR (another capecitabine metabolite), respectively. Correspondingly there are 53%, 27% and 16% increases in the AUCs for these moieties. It should be noted that the protocol for Study SO14999 had the objective of measuring pharmacokinetics in 16 patients. We recommend that the Applicant acquire data to determine if pharmacokinetics are altered with chronic administration of capecitabine and docetaxel.

The sponsor also submitted study No. BP15966 conducted to assess the potential for drug-drug interaction between Xeloda (capecitabine) and warfarin. The pharmacokinetic results show that the co-administration of capecitabine with warfarin in four patients resulted in an increase in $AUC_{0-\infty}$ and $t_{1/2}$ of S-warfarin by 57% and 51%, respectively. The 90% confidence interval for the ratio of Log-transformed AUC was 1.317 to 1.879. The increase in the $AUC_{0-\infty}$ and $t_{1/2}$ of R-warfarin was 13% and 15%, respectively. Plasma concentrations of capecitabine and its metabolites on Days 20 (without warfarin) and 61 (with warfarin) at times 0, 2, 4 and 8 hours do not appear to be different.

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

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

B. Pharmacodynamics

Xeloda is a marketed drug; the clinical pharmacology has been previously reviewed by Safra Ibrahim, Ph. D. and described in the label. See previous section for review of study BP15966.

IV. Description of Clinical Data and Sources

A. Overall Data

The sNDA consisted of paper volumes for sections 1,2,3,6,8 and 10 and 5 CD-ROMs for sections 11 and 12. The NDA submission consisted of the primary clinical data from one principal study.

The principal study is:

- Study Protocol SO14999: an open label, multinational, randomized Phase III study of capecitabine in combination with docetaxel versus docetaxel monotherapy in patients with advanced and or metastatic breast cancer. A total of 511 patients with locally advanced or metastatic breast cancer resistant to, or recurring after an anthracycline-containing chemotherapy , or relapsing during or recurring within two years of completing an anthracycline-containing adjuvant therapy were randomized to either combination (255) or monotherapy (256) treatment group.

Key Volumes

NDA report item	**VOLUME**
Detailed index to the application	1
Labeling	2
Application Summary:	3
Human Pharmacokinetic and Bioavailability	4-11
Clinical and Statistical	12-70
Case Report Tabulations and Datasets	CDs 1&2
Patient Case Report Forms	CDs 2-5

B. Tables Listing the Clinical Trials

The only trial submitted with this NDA is Phase III trial (Study Protocol SO14999):

- Combination Arm: Xeloda 1250 mg/m^2 twice daily for 14 days followed by one week without treatment and docetaxel 75 mg/m^2 as a one-hour infusion in three-week cycles
- Monotherapy Arm: Docetaxel 100 mg/m^2 as a one-hour infusion in three-week cycles

C. Postmarketing Experience

Xeloda was approved in April 30, 1998 for the treatment of patients with metastatic breast cancer. Postmarking experience incorporated in the labeling includes drug-drug interactions with phenytoin and coumarin:

"*Phenytoin:* Postmarketing reports indicate that some patients receiving XELODA and phenytoin had toxicity associated with elevated phenytoin levels. The level of phenytoin should be carefully monitored in patients taking XELODA and phenytoin dose may need to be reduced"

"*Coumarin Anticoagulants:* Altered coagulation parameters and/or bleeding have been reported in patients taking XELODA concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. Patients taking coumarin-derivative anticoagulants concomitantly with XELODA should be monitored regularly for alterations in their coagulation parameters (PT or INR)".

D. Literature Review

The efficacy and safety data of the xeloda plus docetaxel combination is derived from this randomized study. The sponsor selected the dose of capecitabine used in combination with docetaxel based on a phase I study where a range of doses of docetaxel given every 3 weeks in combination with an intermittent regimen (14 days treatment, 7 days rest) of standard dose capecitabine were studied (Pronk et al.:*Br J Cancer* 83:22-29, 2000). The combination of 1250 mg/m^2 twice-daily capecitabine and 75 mg/sqm/3wks docetaxel was well tolerated and five of 33

patients had a response. The currently approved dose of 100 mg/m^2 for single agent docetaxel administered every 3weeks is the control arm of the phase III study

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V. Clinical Review Methods

A. How the Review was Conducted

There was only one trial, Protocol SO14999 submitted with this sNDA. The medical review of sNDA 20896 included:

- Regulatory history of the application.
- Initial submission of Protocol SO14999 to IND[ ]
- Protocol SO14999 amendments.
- Annual report for IND[ ]
- The following volumes from the NDA submission:

1	Index
2	Labeling
3	Application Summary
4	Pharmacokinetics Summary
12-70	Clinical and Statistical

- Case report forms (electronic) from Protocol SO14999.
- Patients listings (electronic) which were subject of queries in and

- Safety update.
- Statistical review included analyses on the SAS datasets.

B. Overview of Materials Consulted in Review

The review of sNDA 20896 included NDA #20896, regulatory history of the application, labeling, correspondence and meeting minutes from Phase 4 commitments.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

There are two reasons why DSI audit was not conducted:

1. This application is a supplement.
2. Survival is the primary endpoint of interest.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The study was conducted under US IND[ ]in full compliance with the principles of the Declaration of Helsinki, including all current amendments, or with the laws and regulations of the country in which the study was conducted. Prior to initiation of the study, the protocol, and the patient informed consent were reviewed and approved by the ethics committees or institutional review boards of the centers involved in the study. Subsequent protocol amendments were also submitted, reviewed and approved before implementation.

E. Evaluation of Financial Disclosure

Requirements for Financial Disclosure were discussed with the applicant during the pre-NDA meeting on 12/21/00. The study was completed after 2/2/99 and therefore was subject to the financial disclosure requirements.

Disclosures

Form 3454 was submitted with the application.

- Compensation affected by the outcome of the clinical studies
  None stated or apparent
- Proprietary interest in the tested product (patent, trademark, copyright, licensing agreement)
  None stated or apparent

Reviewer's assessment

- Analysis and publication of the results and submission of an application are based on the completion date of May 11,2000. Although follow-up continues, patient accrual is complete and the majority of events have occurred.
- The submitted information seems to be adequate and the reviewer believes it to be in compliance with financial disclosure requirements.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Protocol SO 14999 was a prospective randomized controlled trial of Xeloda in combination with docetaxel compared to docetaxel monotherapy for metastatic breast cancer. The populations were well balanced. Most of the patients (65% to 69%) had received previous chemotherapy for metastatic disease. Time to progression was the primary endpoint; survival and overall response rate were the secondary endpoints. The combination of xeloda and docetaxel resulted in a statistically significant reduction of 35% in the risk of tumor progression for combination therapy patients (hazard ratio 0.65, p= 0.0001) with median time to progression of 186 days for the combination therapy compared to 128 days for the monotherapy patients. The xeloda

doxetaxel combination arm resulted in a statistically significant reduction of 22% in the risk of death for combination therapy (hazard ratio 0.78, p=0.013). These differences are clinically significant. Overall tumor response as assessed by the reconciled tumor response data was statistically superior with the combination of xeloda docetaxel therapy (p=0.009). Overall, this study demonstrates the efficacy of xeloda and docetaxel in metastatic breast cancer.

B. General Approach to Review of the Efficacy of the Drug

The review of the Xeloda supplement consisted of a single randomized well controlled trial, Protocol S0 14999. Detailed efficacy review is described in the next section.

C. Detailed Review of Protocol SO14999

"An open label randomized Phase III study of capecitabine in combination with docetaxel (Taxotere) versus docetaxel monotherapy in patients with advanced and/or metastatic breast cancer"

Principal Investigators

E. Mickiewicz	(Argentina)
S. Ackland	(Australia)
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B Colwell	
D Goss	
R Wong	
T Vandenberg	
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L Yelle	
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T Bachelot	
R Mertelsmann	(Germany)
K Possinger	
D Miles	(Great Britain)
C Twelves	
D Talbot	
J Mansi	
S O'Reilly	
K O'Byrne	
A Makris	
R Leonard	
M Inbar	(Israel)
S Rizel	
R Catane	
D Geffen	
B Uzieli	
G Fried	
B-S Menachem	
R Rosso	(Italy)
PF Conte	
E Villa	
G Comella	
M Tonato	
A Santoro	
G Cervantes	(Mexico)
F Gonzalez	
A Silva	
G Morgan-Villela	
M Findlay	(New Zealand)
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Protocol Milestones:

Milestone	Dates	# Patients Entered
Protocol Version A Submission	May 23, 1997	25
Protocol Version B Submission	June 18, 1998	486
Protocol Version C Submission	February 4, 2000	511
Data Cutoff	May 11, 2000	511
NDA Submission	March 7, 2001	511

Objectives:

Primary: "To demonstrate superiority in the time to progression in favor of the capecitabine-docetaxel combination arm."

Secondary:

- To demonstrate superiority of the capecitabine-docetaxel combination arm over docetaxel monotherapy in terms of overall response rate (complete and partial responses).
- To observe at least equivalent survival curves for the two treatment groups.
- To evaluate and compare the safety profile of each treatment arm.
- To evaluate and compare changes from baseline in the Quality of Life of the two treatment groups (in selected centers).
- To collect data on medical care utilization in the two treatment groups.
- To demonstrate the pharmacokinetics of capecitabine in 16 patients randomized to the combination arm.

A protocol amendment submitted on February 4, 2000 reflects the following change:

- To demonstrate superiority in survival of the capecitabine-docetaxel combination arm over docetaxel monotherapy in case at least equivalence was established.

Overall Study Design:

The protocol design was a Phase III, multicenter, multinational, randomized, parallel, open-label study comparing the safety and efficacy of intermittent therapy (3 week schedule) with capecitabine in combination with docetaxel versus docetaxel monotherapy, in patients with locally advanced and/or metastatic breast cancer. Patients were to be resistant to or recurring after an anthracycline-containing therapy, or relapsing during or recurring within two years of completing an anthracycline-containing adjuvant therapy. Target accrual was approximately 454 patients (227 patients per treatment arm), who were to be enrolled at approximately 80 participating sites in Europe, Australasia and the Americas. Patients were to be stratified by previous paclitaxel treatment or not. Patients were to be assessed for tumor response every six weeks until week 48 and then every 12 weeks until disease progression. Patients responding (complete, partial response or stable disease) at the end of 6 cycles treatment continue to receive treatment until disease progression. No other anticancer treatment was to be given until disease progression in patients who stopped study treatment for other reasons. The study was to end 28 days (for follow-up) after the last patient stopped study medication. Clinical cut-off for the study analysis was to be 9 months after the last patient was enrolled.

Reviewers Comments:

Post therapy treatment in patients that do not have disease progression may confound the primary endpoint of TTP and secondary endpoint of survival.

Protocol Amendments:

The protocol was amended twice, on June 9, 1998 and February 4, 2000. The first amendment was a change to the inclusion criteria. The second amendment included administrative changes in study personnel, clarified and/or modified specifications related to the conduct of the study, and made changes to the statistical analysis plan.

First amendment: submitted June 18, 1998, included the following:

- A modification allowing the inclusion of patients relapsing during or within 2 years of completing an anthracycline-containing adjuvant chemotherapy. The Division accepted this modification.
- Clarification of statistical design and methods. The protocol amendment incorporated suggestions made by FDA with respect to (a) potential prognostic factors and selection procedure methods for the Cox proportional hazard model for the statistical analysis of time to disease progression were specified in the protocol and (b) the same clarification regarding the Cox proportional hazard model for the time to death analysis was also included in the protocol. The protocol was also amended to include a longitudinal analysis of quality of life.
- Clarification of the study policy when docetaxel treatment delay alone or capecitabine treatment delay alone was indicated in the combination arm: At the beginning of a treatment cycle if docetaxel treatment delay alone or capecitabine treatment delay alone was indicated in the combination arm, both docetaxel and capecitabine treatment were to be delayed and treatment restarted according to dose modification schemes.
- The protocol was modified to clarify study procedures in case of capecitabine treatment-related increases in bilirubin as well as management of study drugs when cutaneous reactions (i.e., rash, erythema) and hand-foot syndrome occur.

Second amendment submitted on February 2000 included the following changes:

- Test for difference in survival was added to the secondary analyses: the statistical analysis for survival, as specified in protocol versions A and B, was limited to establishing at least equivalence and did not included the test for difference. The protocol was amended to add the analysis on the difference in survival based on the Cox regression.
- Duration of Response: an exploratory secondary analysis was included based on the calculation of duration of response starting from the date the response was first recorded to the date of disease progression.
- The definition of intent-to-treat (ITT) population was changed. The original definition of ITT population included patients who took at least one dose of study medication. The new ITT population consisted of all randomized patients.

Reviewer's Comments:

These protocol amendments were submitted after most of the patient population had been accrued. Though these changes took place almost at the end of the study, they are not considered to impact the trial results.

- The primary analysis for the primary endpoint (TTP) is 2-sided log rank test. Therefore, Cox regressional hazard model is considered exploratory and supportive.
- FDA agreed with change from tests for non-inferiority to superiority in survival analysis.

Eligibility Criteria

Inclusion Criteria:

- Female $\geq$ 18 years of age.
- Histologically/cytologically confirmed locally advanced and/or metastatic breast cancer.

- At least one bi-dimensionally measurable lesion which had not been irradiated (i.e., newly arising lesions in previously irradiated areas were accepted). Bone lesions, ascites and pleural effusion were not considered measurable.
- Index lesion(s) with the following minimum size in at least one diameter: Liver: at least one diameter ≥ 20 mm, lung (chest X-ray, CT scan): at least one diameter ≥ 10 mm, skin lesions and lymph nodes (measurable photographically or radiographically: at least one diameter ≥ 10 mm.
- Patients presenting with locally advanced and/or metastatic breast cancer who were resistant to or had recurrent disease after an anthracycline-containing therapy, or who had relapsed during or recurred within two years of completing an anthracycline-containing adjuvant therapy.
- Patients should have received no more than one previous chemotherapy for advanced and/or metastatic disease or no chemotherapy for advanced and/or metastatic disease if the patient had previously failed during or within two years of completing an anthracycline-containing adjuvant chemotherapy.
- Be ambulatory and have a Karnofsky Performance Status (KPS) of ≥ 70%
- Have a life expectancy of at least 3 months.

Exclusion Criteria:

- Pregnant or lactating women. Women of childbearing potential, unless using a reliable and appropriate contraceptive method.
- Patients who had previously been treated with a docetaxel (Taxotere®) containing regimen either in the adjuvant or advanced disease setting; previous treatment with paclitaxel (Taxol®) was allowed.
- Patients who had previously been treated by more than two chemotherapy regimens for advanced/metastatic disease.
- Patients with clinically significant cardiac disease, serious uncontrolled intercurrent infections, evidence of CNS metastases, history of central nervous system disorders that would preclude informed consent or adversely affecting compliance to study drugs.
- Prior unanticipated severe reaction to drugs formulated with polysorbate 80, Taxotere® or other taxanes or fluoropyrimidine therapy (with or without documented DPD deficiency) or known hypersensitivity to 5-fluorouracil.
- Patients with a history of another malignancy (except basal cell carcinoma of skin and carcinoma in-situ of the uterine cervix, and contralateral breast cancer) within 5 years of study entry.
- Patients with abnormal hematologic values: ANC $<1.5 \times 10^9$/L, platelet count $<100 \times 10^9$/L, hemoglobin <8.0 g/dL; impaired renal function serum creatinine ≥ 1.5 x Upper Normal Limit (UNL); impaired hepatic function serum bilirubin >UNL in at least two out of three baseline values (except when Gilbert's syndrome is clearly documented and other LFTs are

normal), ALAT and/or ASAT >5 x UNL. Alkaline phosphatase >5 x UNL (except when bone metastases are present in the absence of any liver disorders).

- Patients with hypercalcemia (serum calcium >11.5 mg/dL).
- Patients having received blood transfusions or growth factors to aid hematologic recovery within 2 weeks prior to study treatment start.
- Patients having received radiotherapy to the axial skeleton within 4 weeks of treatment start or prior radiotherapy to the indicator lesion(s) being measured in the study (newly arising marker lesions in previously irradiated areas are accepted).
- Patients who had received hormonal therapy within 10 days preceding treatment start.
- Patients with a lack of physical integrity of the GI tract or those who had malabsorption syndrome.

Study therapy

Formulation

Capecitabine was supplied as film-coated tablets in two dose strengths: 150 mg and 500 mg. The tablets were not scored and were not to be split. Each dose strength was packed in bottles, the 150 mg tablet strength being packed in bottles of 28 tablets, and the 500 mg tablet strength being packed in bottles of 56 tablets.

Docetaxel was obtainable commercially in vials of 80 mg (2.0 mL) and 20 mg (0.5 mL) and supplied with solvent. Once reconstituted with the solvent, the docetaxel premix solution had a concentration of 10 mg/mL. This was to be further diluted with either 0.9% sodium chloride solution or 5% dextrose solution to produce a final concentration of 0.3 to 0.9 mg/mL, prior to administration.

Dosage schedule

Patients were to receive one of the following dosing regimens:

- Capecitabine/Docetaxel combination arm:
  - Capecitabine intermittent schedule: capecitabine was to be administered orally 1250 mg/m^2 twice daily as intermittent therapy (2 weeks of treatment followed by one week without treatment) for at least 6 weeks.
  - Docetaxel was to be administered as a 1 hour intravenous infusion at a dose of 75 mg/ m^2 on the first day of each 3 week cycle for at least 6 weeks with an appropriate premedication (e.g., dexamethasone).
- Docetaxel monotherapy arm:
  - Docetaxel was to be administered as a 1 hour intravenous infusion at a dose of 100 mg/ m^2 on the first day of each 3 week cycle for at least 6 weeks with an appropriate premedication (e.g., dexamethasone).

Guidelines for dose reduction:
The protocol specified treatment interruptions and dose modifications for grades 2 to 4 toxicity using the NCIC (National Cancer Institute of Canada) Common toxicity criteria. See table below.

Table 1: Schema for Capecitabine and/or Docetaxel Dose Modifications (Modified from Sponsor's Table 3 electronic submission)

Toxicity NCIC Criteria *	**Dose Modification**	**Dose Adjustment for next cycle (% of starting dose)**
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1st appearance	Interrupt treatment until resolved to grade 0–1	100%
2nd appearance	Interrupt treatment until resolved to grade 0–1	75% of original capecitabine dose 55 mg/m^2 of docetaxel
3rd appearance	Interrupt treatment until resolved to grade 0–1	50% of original capecitabine dose and discontinue docetaxel
4th appearance	Discontinue treatment	
Grade 3		
1st appearance	Interrupt treatment and delay for a maximum of two weeks until grade 0-1	75% of original capecitabine dose 55 mg/m^2 of docetaxel with prophylaxis when possible
	If no recovery to grade 0-1 within two weeks delay	75% of original capecitabine dose and stop docetaxel
2nd appearance	Interrupt treatment until resolved to grade 0–1	50% of original capecitabine dose and stop docetaxel
3rd appearance	Discontinue treatment	
Grade 4		
1st appearance	Discontinue treatment unless investigator considers it is in the best interest of the patient to continue with capecitabine at 50% of original dose	

* National Cancer Institute of Canada Common Toxicity Criteria

The protocol specified the following dose modifications for *neutropenia*:

Neutropenia NCIC Criteria *	Dose Modification	Dose Adjustment for next cycle (% of starting dose)
Grade 3	Maintain dose level if neutrophil count $\geq 1.5 \times 10^9$/L	Maintain dose level
Grade 4	Dose reduction if febrile neutropenia or neutrophil count < 0.5×10^9/L for more than 1 week	75 mg/m^2 of docetaxel Maintain dose level of capecitabine *
2nd appearance	Dose reduction or discontinue treatment	55 mg/m^2 of docetaxel Maintain dose level of capecitabine *

* Capecitabine was to be interrupted if any diarrhea or stomatitis coincided with the neutropenic episode.

Reviewer's Comment:

- The protocol does not specify dose adjustments for platelet nadir.
- The protocol does not specify criteria for Granulocyte colony-stimulating factor (G-CSF) support.

The protocol specified the following dose modifications for *hypersensitivity reactions*: Patients who developed severe hypersensitivity reactions (hypotension with a decrease of ≥ 20 mm Hg, or bronchospasm, or generalized rash/erythema) were to immediately discontinue study drugs and be given appropriate therapy. They were not to be rechallenged and were to be taken off the study drugs.

Hand-foot syndrome was graded in the protocol according to the following scale:

Table 2 Hand-Foot Syndrome Grading Scale (From Sponsor's Appendix 3 N 212)

	Clinical Domain	Functional Domain
Grade 1	Numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema	Discomfort which does not disrupt normal activities
Grade 2	Painful erythema with swelling	Discomfort which affects daily living activities
Grade 3	Moist desquamation, ulceration, blistering, severe pain	Severe discomfort, unable to work or perform activities of daily living

The protocol specified dose modifications for *neurologic* toxicity were as follows:

Table 3 Neurologic Toxicity Drug Modifications

Toxicity NCIC Criteria *	Dose Modification	Dose Adjustment for next cycle (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2	Dose reduction	75 mg/m^2 of docetaxel
Grade 3	Discontinue docetaxel	

Dose modifications for capecitabine were done following the general schema dose modifications.

The protocol stated that severe Grade 3 or 4 *fluid retention* (pleural effusion, pericardial effusion or ascites) is possibly related to docetaxel, is cumulative and slowly reversible after stopping treatment. Therefore, docetaxel was to be discontinued and capecitabine was to be continued without dose modification.

The protocol required the following modifications for *hepatic impairment*:

- Docetaxel was not to be given to patients with serum bilirubin above the upper limit of normal.
- In the event that abnormal values for ASAT, ALAT, and alkaline phosphatase levels were determined prior to any docetaxel cycle, the following docetaxel dose modifications were to apply at this cycle:

Table 4 Docetaxel Dose Modifications for liver impairment (from sponsor's submission Vol. 12 page 30)

ASAT and/or ALAT values		Alkaline Phosphatase values	Dose Modification
≤ 1.5 x UNL	and	< 5 x UNL	No dose modification
> 1.5 x UNL ≤ 2.5 x UNL	and	≤ 2.5 x UNL	No dose modification
> 2.5 x UNL ≤ 5 x UNL	and	≤ 2.5 x UNL	25% dose reduction
> 1.5 x UNL ≤ 5 x UNL	and	> 2.5 x UNL ≤ 5 x UNL	25% dose reduction
> 5 x UNL	0r	> 5 x UNL (unless bone metastasis are present in the absence of any liver disorder)	Dose delay by 2 weeks. If no recovery, discontinue docetaxel

- In case of recovery of liver function tests after previous reduction of the docetaxel dose, the docetaxel dose was to be re-escalated to the previous dose-level.
- In case of treatment-related increases of bilirubin, dose modifications for capecitabine were to be followed according to general scheme for dose modifications.

The protocol specified the following dose modifications were required for *diarrhea*:

- Capecitabine was to be stopped for grade 2 diarrhea and treated with loperamide up to 16 mg per day.
- If diarrhea was to be controlled within 2 days, capecitabine was to be re-started at 100% of the original dose.
- If control took longer or recurred despite prophylaxis, capecitabine was to be modified according to the general drug modification scheme.

Dose escalation for capecitabine:
When capecitabine was to be continued in the combination arm, after discontinuation of docetaxel and in the absence of disease progression, the capecitabine monotherapy was to be continued without dose escalation for at least one more cycle. Thereafter, in the absence of grade 2, 3 or 4 toxicities, capecitabine doses were to be subsequently escalated once per 3 week cycle in a stepwise manner, i.e., 50% to 75% and 75% to 100% of the calculated baseline dose.

Patient Evaluations

Patient monitoring is summarized in the following table.

Table 5 Schedule of assessments (modified from sponsor's table 7 Vol. 12 page 38)

	Screening Baseline		Capecitabine Treatment Period												
Study Week			1	2	4	7	10	13	16	19	3-weekly visits during treatment with study drugs				Off-Study
Study Day	-14 to 1	-7 to 1	1	8	22	43	64	85	106	127					
Informed Consent	x														
Physical Examination	x														
ECG	x														
Chest X-ray	x														
Vital signs and Physical measurements		x	x		x	x	x	x	x	x	x	x	x	x	
hematology		x		x	x	x	x	x	x	x	x	x	x	x	
Blood chemistry		x			x	x	x	x	x	x	x	x	x	x	
Adverse events															
Medical care utilization															
Tumor measurements	x					x		x		x		x		x	x
Quality of life Questionnaire			x			x		x		x		x		x	x
PK sampling					x		x								
Survival census															x

- Survival census was to be performed every 3 months after disease progression.
- When study drugs were to be discontinued in the absence of progressive disease, the patients were to remain in the study until progressive disease and were to be followed at the tumor assessment visits.
- Tumor assessments were to be done on a 6-week basis up to 48 weeks and 12 weekly thereafter until progressive disease.

Reviewer's Comments:

- The protocol states that patients will be followed every 3 months after the last treatment study dose for determining disease progression. What is not clear is the methods that will be used for surveillance and the frequency of the diagnostic tests that will eventually be used.

- Restaging is planned every 3 months which is common in clinical practice. This interval may be the same size or larger than the expected effect size. However, as long as both treatment groups are handled the same in terms of diagnostic modalities and frequency of follow-up, the time to progression can be compared by treatment arm.
- A better defined post-study follow-up is needed to make Time To Progression a more trustable endpoint.

Criteria for Efficacy Assessment

Per protocol the following defines the rules for response evaluation:

Objective Responses

- Objective response of measurable disease was to be based on the criteria described in the WHO Handbook for Reporting Results of Cancer Treatment given in **Appendix 1**
- A ruler or calipers was to be used for all measurements.
- Only bidimensionally measurable lesions, which were not irradiated, were to be used as indicator lesions. These must have been a minimum size in at least one diameter of 20 mm for liver and 10 mm for lung, skin and lymph node lesions.
- Bone lesions, ascites or pleural effusions were not to be acceptable as bidimensionally measurable indicator lesions.
- Response was to be confirmed a minimum of 4 weeks after the first response had been recorded.
- Tumor response assessment and measurement were to be made on each patient within 2 weeks of study completion, withdrawal or discontinuation.
- All the lesions were to be measured by the same method and the same investigator throughout the study.
- In the case that irradiation had been given to some of the marker lesions during the study, these lesions were excluded from the calculation of total tumor size from the date of irradiation (except if the lesion was indicating progressive disease).
- The investigators were to supply copies of all X–rays, and CT–scans from all patients for blinded review of the response assessment by a panel of independent radiologists. The lesions on the films should have been marked with the lesion numbers corresponding to those given in the CRF. A suitable scale was to be included when photographing skin.

Response parameters are defined below:

Complete Response (CR): The disappearance of all clinically detectable disease determined by 2 observations not less than 4 weeks apart.

Partial Response (PR): $\geq$ 50% decrease (for bidimensional lesions) in total tumor size of the lesions (sum of the products of the two greatest perpendicular diameters of all measurable lesions) which have been measured to determine the effect of therapy by 2 observations not less than 4 weeks apart. In addition there can be no appearance of new lesions or progression of any lesion.

No Change (NC) or Stable Disease (SD): A >50% decrease in bidimensional lesions as defined above cannot be established nor has a 25% increase in the size of one or more measurable lesions been demonstrated throughout the period of treatment.

Progressive Disease (PD): A 25% or more increase in the sum of the products of perpendicular diameters of one or more measurable lesions with minimal area >2cm^2, or the appearance of new lesions. For malignant lesions with minimal areas of ≤ 2cm^2 , increase in size of any individual lesion of at least 1cm^2 will be required.

Time to Progression

The protocol states: "Time to progression will be measured as the time from when the patient is randomized to the time the patient is first recorded as having disease progression, or the patient dies due to causes other than disease progression."

Survival

The protocol states: "Time from randomization to the date of death or the last date the patient was known to be alive. Survival data will be collected by the investigator on a quarterly basis after patients go off study."

Reviewer's Comments:

- The protocol does not specify when patients without progression will be censored. The current recommendation for patients without progression, is to censor at the date of last tumor evaluation, not the date of last contact.
- FDA reviewer agrees with the protocol definitions of the efficacy parameters.

Criteria for Safety Assessment

Safety was to be evaluated as adverse event reports defined in the protocol as "any adverse change from the patient's baseline (pre–treatment) condition, including intercurrent illness, which occurred during the course of a clinical study after treatment had started, whether considered related to treatment or not. "Treatment" includes all investigational agents administered during the course of the study." Adverse events were graded according to the NCIC Common Toxicity Criteria grading system.

For protocol definitions of hand-foot syndrome grading toxicity were described in the dose modifications section of this review.

The severity of an adverse event which could not be graded using NCIC CTC grading system were to be graded using the following criteria:

Mild:	Discomfort noticed but no disruption of normal daily activity
Moderate:	Discomfort sufficient to reduce or affect normal daily activity
Severe:	Incapacitating with inability to work or perform normal daily activity
Life–threatening:	Self–explanatory