

**CAMPTOSAR + 5-FU/LV FOR
FIRST-LINE TREATMENT
OF METASTATIC COLORECTAL CANCER:
A POST-MARKETING REEVALUATION OF SAFETY**

NDA 20-571

PREPARED BY:

ISAGANI M. CHICO, MD
MEDICAL OFFICER

November 2001

TABLE OF CONTENTS

<u>Section</u>	<u>Page</u>
1 Regulatory History	3
2 Review of Approval: Camptosar for First-Line Treatment of Metastatic Colorectal Cancer	4
3 Post-Marketing Events: Clinical Hold of Two Cooperative Group Trials and Results of the “Independent” Panel Review of Deaths in N 9741 AND CALGB 89803	6
4 Outline of the FDA Review	8
5 FDA Review of Deaths in N9741 AND CALGB 89803	9
6 FDA Analysis of Early Deaths in the Licensing Trials 0038 and v303.....	14
7 Reanalysis of Camptosar Licensing Trials	18
8 FDA POST-Marketing Data.....	35
9 Proposed Labeling Changes.....	35
10 FDA Reviewer Conclusions	36

LIST OF ABBREVIATIONS

5FU	5-fluorouracil
CEA	carcinoembryonic antigen
CIVI	continuous intravenous infusion
CPT-11	Irinotecan Hydrochloride
CR	complete response
CRF	case report form/s
CVA	Cerebrovascular Accident
G-CSF	Granulocyte Colony Stimulating Factor
GM-CSF	Granulocyte-Macrophage Colony Stimulating Factor
IFL	Irinotecan/5-fluorouracil/Leucovorin
IV	intravenous
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
LV	leucovorin
MCRC	metastatic colorectal cancer
NI	non-inferiority
NF/I	neutropenic fever/ infection
PD	progressive disease
PK	pharmacokinetics
PR	partial response
P&U	Pharmacia and Upjohn
SGOT	serum glutamate-oxalate transferase
TTF	time to treatment failure
TTP	time to tumor progression
UNL	upper limit of normal
WBC	white blood count

1 REGULATORY HISTORY

The following is a summary of the regulatory history of CPT-11:

DATE

June 1996	Accelerated Approval for treatment of recurrent disease or progression of colorectal CA following 5-FU based therapy.
September 1998	Full approval for treatment of recurrent disease or progression of colorectal CA following 5-FU granted based on two phase 3 trials (V301 and V302) that showed a significant survival advantage in the CPT-11 treatment group
April 2000	Full approval for first line therapy of MCRC based on two phase 3 trials (Studies 0038 and V303).

POSTMARKETING EVENTS

April 2001	The FDA was informed by the NCCTG of the unexpected number of deaths occurring within 60 days of study entry in Study N9741.
May 2001	P&U proposes and funds an "Independent" Review Committee to review patient records of deaths in the cooperative group trials. The FDA requested the same records for review. Findings of this committee were published in JCO, Sept 2001.
July 2001	Patient records sent to the FDA for review.
August 2001	FDA requested that Pharmacia (1) perform retrospective safety reviews of pivotal trials and other trials that incorporated the CPT-11+5FU/LV combination, (2) propose a clinical trial to address safety and efficacy of "modified" versions of the "Saltz" Regimen, (3) propose labeling changes to address safety concerns. FDA informed Pharmacia of the intent to hold an Advisory Committee meeting to discuss the issues.
Sept-Oct 2001	Pharmacia submitted results of retrospective review and outline of proposed clinical trial. The FDA informed Pharmacia that the safety issues would be presented at the December ODAC

2 REVIEW OF APPROVAL: CAMPTOSAR FOR FIRST-LINE TREATMENT OF METASTATIC COLORECTAL CANCER

Two randomized, prospective, multicenter clinical trials that enrolled more than 400 patients examined CPT-11 in combination with 5-fluorouracil/leucovorin (5FU/LV) for first-line treatment of colorectal cancer. Study 0038 (U.S.) was a three-arm trial comparing CPT-11+ 5FU/LV weekly x 4 (Saltz Regimen), 5FU/LV daily x 5 (Mayo Clinic Regimen), and CPT-11 alone. Study V303 compared two infusional regimens of 5FU/LV, each in combination with CPT-11, to the same infusional regimens without CPT-11. Statistically significant differences in survival, time to tumor progression and response rates favoring the CPT-11 arms were observed in both studies.

Table 1. Summary of Efficacy in Licensing Trials (Study 0038 and V303)

EFFICACY	Study 0038 (U.S.)			Study V303 (Europe)	
	Arm B Saltz CPT-11+ 5FU/LV N=231	Arm C 5FU/LV N=226	Arm A CPT-11 N=226	Arm A CPT-11+ 5FU/LV N=198	Arm B 5FU/LV N=187
Median Survival (months)	14.5	12.6	12.0	16.8	14.0
Original Analysis	p=0.097			p= 0.028	
Updated Analysis	14.8	12.6	12.0	17.4	14.1
	p=0.042			p=0.032	
Median TTP (months)	7.0	4.3	4.2	6.7	4.4
	p=0.004			p=0.001	
Response Rate	39%	21%	18%	35%	22%
	p<0.001			p<0.005	

Measurement of survival was not the primary endpoint in both studies. The primary endpoint in Study 0038 was time to tumor progression (TTP) and tumor response rate in Study v303. In the initial protocol-specified survival analysis of Study 0038 (US trial), the Saltz regimen (Arm B) showed a trend toward increased survival compared to the Mayo 5-FU/LV regimen (Arm C). An updated analysis showed a statistically significant survival benefit. Analyses of time to progression and response also showed significant differences favoring the Saltz regimen. In study V303 (European trial), both the original and updated survival analyses demonstrated significantly superior survival associated with the infusional (Douillard + AIO) regimens (Arm A).

Cholinergic symptoms, diarrhea, nausea, vomiting and asthenia were more frequent and more severe in the CPT-11+5-FU/LV arms of both studies. Severe neutropenia and fever with neutropenia were more frequent on the CPT-11+5-FU/LV arm of Study V303 relative to the control, but less frequent compared to the 5-FU/LV arm of Study 0038. There were more frequent hospitalizations in the CPT-11+5-FU/LV arms. Treatment related deaths occurred in less than 2% in both studies.

Table 2. Summary of Safety (Licensing Studies 0038 and V303)

	Study 0038 (U.S.)			Study V303 (Europe)	
SAFETY (%)	Arm B Saltz	Arm C	Arm A	Arm A	Arm B
Gr 3 /4 Adverse Events	CPT-11+ 5FU/LV N=231 (%)	5FU/LV N=226 (%)	CPT-11 N=226 (%)	CPT-11+ 5FU/LV N=198 (%)	5FU/LV N=187 (%)
Neutropenia	54	67	31	42	11
Fever w/ Neutropenia	7	15	6	5	1
Late Diarrhea	23	13	31	23	11
Nausea	15	8	16	4	4
Vomiting	10	4	12	6	3
Asthenia	20	12	14	10	3
Mucositis	2	17	2	3	3
Alopecia (Gr 1-4)	43	27	46	51	17
TREATMENT DISCONTINUED DUE TO TOXICITY	7	6	11	8	3
Hospitalization for Any Cause	50	39	44	43	26

Data from these two clinical trials constituted compelling evidence that CPT-11 administered in combination with 5FU and leucovorin is efficacious in the first-line treatment of metastatic colorectal cancer. The Oncologic Drug Advisory Committee voted unanimously for its approval, and the FDA approved the use of CPT-11 in two regimens (the Saltz/bolus regimen and the Douillard/continuous IV infusion regimen) for this indication in April 2000.

**3 POST-MARKETING EVENT:
CLINICAL HOLD OF TWO COOPERATIVE GROUP TRIALS FOR SAFETY ISSUES
ASSOCIATED WITH THE SALTZ (BOLUS) REGIMEN AND
RESULTS OF THE “INDEPENDENT” PANEL REVIEW OF DEATHS
IN N9741 AND CALGB 89803**

The North Central Cancer Treatment Group (NCCTG) study, N9741, was originally a six-arm, phase III Intergroup trial designed to compare several investigational combination chemotherapy regimens to 5-FU/LV in patients with metastatic colorectal cancer. The study was revised into a 3-arm study using the Saltz regimen as the new control arm after Camptosar was approved in combination with 5FU/LV for first line treatment of metastatic colorectal cancer. The original control arm of 5FU/LV was dropped and high death rates in two other treatment arms prompted their closure. The Cancer and Leukemia Group B (CALGB) study C89803, is a phase III Intergroup adjuvant trial comparing the Saltz regimen to the weekly 5FU/LV Roswell Park regimen in patients with Dukes' Stage C (TNM Stage III) colon cancer.

Pre-specified interim analysis of N9741 in April 2001 showed an unexpected number of early deaths within the first 60 days of starting treatment in patients randomized to the Saltz regimen. This finding led to an unplanned interim safety analysis of CALGB 89803, where a higher death rate associated with the Saltz regimen was also observed. Accrual to the NCCTG trial was temporarily suspended until the trial was redesigned. CALGB 89803 was permanently closed to new accrual.

Reviewer's comment: *The analysis of safety by the NCCTG External Data Monitoring Committee and the CALGB internal review of C8903 identified and focused on deaths that occurred within the first 60 days of start of treatment. Describing deaths that occur in the first 60 days on study limits the dataset to a relatively small window, but does give a perspective on the degree of acute toxicity associated with a treatment. The safety data from the trials that were the basis of Camptosar's first line treatment approval were not presented in this fashion in the product label. In contrast, study deaths are usually presented and reviewed within the context of NDA's for oncology drugs as deaths that occur within 30 days of drug administration throughout the entire study. This method is viewed as the most reliable way to make comparisons across study arms because the temporal relationship to last treatment implies the potential role of treatment in the death, and removes the bias that would invariably be inserted by allowing investigator/sponsor to judge causality. This approach not only minimizes bias, but it is more comprehensive than an "early death on study" analysis since it includes data from all treatment cycles.*

A special panel brought together by Theradex to review the clinical data in the two cooperative group trials was charged with assigning attribution of death, reviewing the management of the patients on study, and identifying patient characteristics that put them at high risk for death on treatment. The committee indicated that there was a disproportionately high number of deaths on the Saltz control arms of these studies compared to the controls, and that the deaths were earlier in onset on the Saltz

arms. The median time to death 29 days (n=29) vs. -47 days (n=5) on the Roswell Park control arm of the adjuvant trial. Not surprisingly, they found that the primary cause of drug-related death was a combination of chemotherapy-induced diarrhea, neutropenia, fever, and consequent dehydration and electrolyte abnormalities. In addition, a number of patients were found to have had fatal vascular events (both arterial and venous). These vascular events were considered by the committee to be potentially treatment-related, although a specific pharmacological basis for the causality was not put forward. The committee concluded that close patient monitoring was important, that supportive care measures (particularly use of antibiotics) could be improved, and that dose modification criteria were not sufficiently aggressive. The committee recommended that oncologists be advised of the possibility of fatal gastrointestinal and vascular events associated with the CPT-11 + 5FU/LV regimen and that the need for careful first-cycle patient monitoring should be emphasized. It recommended that “more stringent guidelines for monitoring patients” should be developed, that early support with antibiotics for diarrhea and/or neutropenia (including use of an oral fluoroquinolone, as is common in Europe [Jacques 1997a, Jacques 1997b, Gruia 1999] should be encouraged, and that more aggressive irinotecan and 5-FU dose modifications should be instituted.

The committee noted its review was necessarily limited in scope since it was limited to clinical information for patients who died within 60 days of initiating protocol treatment. Because the committee’s analysis did not include patients who experienced severe, but non-lethal toxicities or those who developed moderate, mild, or no toxicities, they could not develop a risk profile for those patients most likely to encounter varying degrees of toxicity or die while receiving treatment. In addition, the committee was not able to review the balance of prognostic factors (e.g., performance status or organ dysfunction) across the arms of the 2 studies or relative to other studies to more fully assess the risk.ⁱ

Reviewer’s comment: *There are limitations associated with subset analyses and interim looks at ongoing studies. At the time of analysis, only about 275 of the projected 375 patients (73%) have been enrolled in each arm of study N9741. However, the higher number of deaths on the CPT-11 + 5FU/LV arms of these two cooperative group studies relative to their control arms and the fact that these deaths occurred early raised concern that the toxicity associated with the Saltz combination regimen had not been fully described and appreciated. Concerns arising from the observations have led to recommendations to modify the dose or schedule of administration of the Saltz regimen. Such unstudied modifications have the potential to adversely affect the therapeutic index of this regimen if they are associated with a decrement in efficacy. These issues constitute the foundation of this review.*

4 OUTLINE OF THE FDA REVIEW

The FDA worked with the sponsor in examining the issues raised by the interim safety analyses of the two cooperative group trials. All available data from the randomized controlled trials that were the basis for the approval of the CPT-11 + 5FU/LV combination for first-line treatment of metastatic colorectal carcinoma and any additional available post-marketing data were requested by the FDA. The FDA review is divided into the following sections:

1. FDA Review of Early Deaths from the NCCTG and CALGB studies
2. FDA Review of Early Deaths from the Pivotal Trials 0038 and v303
3. Reanalysis of Safety in the Pivotal Trials 0038 and v303
4. FDA Review of Post-Marketing Data

The safety issues that prompted this review, the Theradex panel's recommendations, and the dose modifications that have been proposed by different parties must be examined as potential changes to the product's label. Unanswered questions that remain after a comprehensive review of the data would warrant conducting new studies to resolve those issues.

The objectives of this review are to describe the patients identified as having died on the cooperative group studies within 60 days of study entry and attempt to identify risk characteristics for early death. Patient management on study with respect to adherence to protocol eligibility criteria, chemotherapy administration, and adherence to dose modification guidelines was evaluated. Inpatient and outpatient records of patients who died within 60 days of starting treatment with the Saltz regimen were reviewed in detail. Specific information abstracted from these records included: (1) Patient Demographics and Eligibility; (2) Treatment Administration; (3) Adverse Events Prior to Death; (4) Clinical Management and Supportive Care; (5) Overall Assessment and Comments.

5.1 RESULTS

5.1.1 PATIENT CHARACTERISTICS

The FDA received a total of 44 records, 29 of which were from patients treated with the Saltz regimen. Of the 29, 13 patients were from study NCCTG 9741 and 16 were from CALGB 89803. The median age of the patients treated with the Saltz regimen was 69, with a slight preponderance of patients greater than 65 years old. There was a slight predominance of females and most of the patients had a Karnofsky performance status 0 to 1 at baseline. None of the patients had had prior radiation therapy.

Eleven of the 29 had a history of cardiovascular problems that were controlled at study entry. These 11 patients had prior histories of hypertension, coronary artery disease, coronary artery bypass grafts, myocardial infarction, or deep venous thrombosis, etc. There were four potential protocol violations at entry. One patient started chemotherapy only three weeks from surgery. Another patient had an unresolved gastrointestinal infection. There was a patient with baseline creatinine of 1.6 and one patient who possibly had a performance status of 3. The characteristics of patients who died early while on treatment with the Saltz regimen in the two studies are summarized in the following table:

Table 4. Patient Demographics: Early Deaths on the Saltz Arms of NCCTG 9741 and CALGB 89803

	DEMOGRAPHICS (n=29)	
AGE	Median	69
	<65	12
	>65	17
GENDER	M	12
	F	17
KPS	0-1	26
	2	2
	unknown	1
LIVER INVOLVEMENT (NCCTG ONLY)	11 of 13	
MEDICAL HISTORY	Cardiovascular	11
	Renal	2
	Endocrine	3
WEEKS FROM SURGERY	3	1
	4-8	21
	10	1
ENTRY VIOLATIONS	3 weeks from surgery (1) Unresolved GI Infection (1) Baseline Creatinine 1.6 (1) Performance Status 3 (1)	

The panel recommended after its review that “older individuals” should be followed “especially closely”. The patient distribution broken down by age cut-off of 65 years suggests that patients who are >65 years old might be at increased risk of early death when treated with the Saltz regimen. However, the distribution of risk by sex is similar to that broken down by age 65, and could lead to a similar conclusion that females should be more closely monitored. Surprisingly the preponderance of patient deaths did not occur in patients with performance status 2 relative to PS 0-1. Note that there were protocol violations in 4 of the 29 patients (13.7%) that involved underlying conditions that could have increased the risk of administration of this therapy. Meaningful assessment of this data is limited by the lack of knowledge of the total number of patients.

5.2 TREATMENT ADMINISTRATION

Most deaths occurred within 4 weeks of starting treatment with the Saltz regimen. Most patients had received two full doses of treatment before subsequent chemotherapy was either terminated or modified. Fourteen of the 29 patients (48%) received full doses until the time of their death. Five patients whose doses of chemotherapy should have been reduced were not and one patient received an inappropriately low dose of chemotherapy.

The fact that so many were treated at full dose on a weekly regimen up to the time of death suggests that the downhill course from onset of adverse events to death is rapid; and supports the proposal for reducing the starting dose. It also raises questions about what monitoring should or could be on a schedule of weekly drug administration. It has to be recognized that this dataset is limited only to patients who died within the first 60 days of treatment, and recommendations for close follow up should be considered for all cycles of therapy and not limited to the first cycle.

Table 3. Treatment Administration, Patterns of Dose Modification and Timing of Death in Patients Treated with the Saltz Regimen in Studies NCCTG 9741 and CALGB 89803

	# of Patients (n=29)
Doses Before Death	
1	1
2	5
3	10
4	8
5	2
>5	3
Number of Full Doses Before Modification, Hold or Termination	
1	8
2	10
3	9
4	2
5	0
Dose Modification	
No Dose Modification	14
Dose Modification Appropriate	9
Doses Should have been reduced	5
Dose Inappropriately Reduced	1

ADVERSE EVENTS PROFILE

The panel recommended after their review of the data that there should be increased awareness among health care providers regarding the gastrointestinal and vascular “syndromes” associated with the Saltz regimen. Adverse events that individually constitute the gastrointestinal and hematologic “syndromes” are well known toxicities of the regimen. They have been grouped as “syndromes” in the following table:

Table 6. Adverse Event Syndromes Preceding Death in Patients Treated with the Saltz Regimen in Studies NCCTG 9741 and CALGB 89803

Syndromes	NCCTG n=(13)	CALGB (n=16)	TOTAL (n=29)
Gastrointestinal ^a	1	0	1
Hematologic/Infections ^b	2	1	3
GI + Heme/Infections	7(54%)	11(69%)	18(62%)
Vascular ^c			
Vascular + GI	3	4	7
Vascular Only	2	3	5
Median Time to Gr. 3	12 days	20 days	15 days
Median Time to Death	26 days	29 days	28 days

^a defined as a constellation of gastrointestinal symptoms including diarrhea, nausea, vomiting, anorexia, and abdominal cramping^b defined as a constellation of hematologic findings such as neutropenia, leukopenia with or without fever, with or without documentation of infections

^c defined as a constellation of acute myocardial infarction, pulmonary embolus, or cerebrovascular accident

A small number of patients experienced the GI or hematologic/infection syndromes alone but most experienced both in concert. This finding points out that the combination of these two syndromes may be very risky; but such a conclusion should be supported by the distribution of toxicity from the rest of the patients in the study. Management of these toxicities, especially when they occur in combination, should be aggressive, incorporating drugs for both prophylaxis and symptom management. This will be discussed further in the section on proposed labeling changes.

Fatal vascular events were also identified in both trials; but, as shown in the table above, a number of these patients also experienced symptoms of the gastrointestinal syndrome. It is possible that dehydration and immobility from dehydration could have triggered or aggravated these vascular events. For patients in the CALGB study who received adjuvant treatment, prior and relatively recent abdominal surgery could have been an added risk factor for a vascular event. The interrelationships of these events might better be evaluated with complete safety data from these trials.

The median time to grade 3 event in the patients who experienced early deaths on these trials was about two weeks, confirming the observation that most patients received two weekly full doses before dose reduction or termination of treatment. This rapid onset of toxicity has prompted suggestions for lowering the starting dose by 20% (i.e., 100 mg/m²) and a treatment administration schedule change to add one week of rest after every two weeks of treatment. These changes should be considered, but their impact on either safety or efficacy can only be a matter for speculation with no supportive data.

Currently the product label states under the Precautions section, in a subsection titled “Information for Patients,” that “each patient should be instructed to have loperamide readily available and to begin treatment for late diarrhea...at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient.’ This is followed by instructions for administration of loperamide. This same section includes a list of conditions that patients should be told to call their physicians about, including vomiting, fever, evidence of infection, and symptoms of infection. The Warnings section of the label refers the reader to the same Information for Patients subsection of Precautions after a statement that “Late diarrhea should be treated promptly with loperamide”. The label does not include instructions on making antibiotics available to the patient. The panel recommended a more aggressive approach to the treatment of diarrhea where patients are given both prescriptions for loperamide and antibiotics prior to treatment with explicit instructions on when each should be started and under what circumstances the patient should go to the hospital.

Reviewer’s comment: *An appropriate label change might be to include in the Warnings section the recommendations for providing loperamide and antibiotic prescriptions with instructions for their use to the patient. In addition, these recommendations could be included in a Patient Package Insert.*

The panel also recommended that before retreatment, patients should be diarrhea-free for at least 24 hours without the use of antidiarrheals. This recommendation differs from what is currently in the label. The label includes a table of recommended dose modifications for the CPT-11 + 5FU/LV combination schedules that reflects the dose modification utilized in the licensing trial (Table 11). The table states that “a new course of therapy should not begin until treatment related diarrhea is fully resolved.” Under the table’s column, “During a Course of Therapy,” the dose modifications for weekly dosing state that the Camptosar dose should be continued at a reduced dose (one dose level) for grade 2 diarrhea, but should return to the initial starting dose of the cycle at the subsequent cycle if no intervening grade ¾ toxicity occurs. Grade ¾ diarrhea weekly dosing is held until resolution to grade 2 when the dose is reduced 1 dose level for grade 3 and 2 dose levels for grade 4 diarrhea. Weekly dosing is allowed to continue in the face of grade 2 diarrhea.

Reviewer’s comment: *More detailed algorithms incorporating intake of prophylactic medications such as antidiarrheals, antibiotics and G-CSF, and timing of follow-up and hospital admission should be proposed, discussed and, if warranted, clearly included in the label.*

6 FDA ANALYSIS OF EARLY DEATHS IN THE LICENSING TRIALS 0038 AND V303

It is important to first place the deaths from the cooperative group trials NCCTG 9741 and CALGB 89803 in perspective with the deaths in the randomized controlled trials that were the basis for the approval of Camptosar for the treatment on colorectal carcinoma, Studies 0038 and V303. The following table summarizes the deaths in all 4 trials, according to method of analysis.

Table 7. Deaths from Cooperative Group and Licensing Trials

DEATH ALL CAUSES	NCCTG 9741			CALGB 89803		0038		V303	
	Saltz (289)	Ox-FL (277)	Ox-I (275)	Saltz (635)	RP-FL (628)	Saltz (231)	MayoFL (226)	Douillard (145)	DeGramont (143)
60 Days from Start of Therapy	4.8%	1.8%	1.8%	2.2%	0.8%	6.4%	7.0%	2.0%	2.1%
30 Days from Last Treatment	NA	NA	NA	NA	NA	9%	7%	4%	3%

Saltz = bolus Irinotecan + 5-FU/LV
Ox-FL = oxaliplatin + 5FU/LV
Ox- I = Oxaliplatin + Irinotecan

MayoFL = Mayo Clinic bolus 5FU/LV
Douillard = Irinotecan + CIV 5FU/LV
deGramoont = CIV 5FU/LV

The 60-day death rates from the Saltz regimen arms of the NCCTG and CALGB studies were at least twice those of their corresponding control arms. However, these differences were not statistically significant. In the licensing trials, the rates of death within 60 days of starting treatment in the Saltz regimen arm (bolus IFL) of 0038 and the Douillard arm (CIV IFL) of Study V303 were similar to their corresponding control arms. The rate of death within 60 days of starting therapy in the Saltz regimen arm of licensing trial 0038 is higher than observed on the Saltz regimen arms of the cooperative group trials.

An analysis of deaths within 60 days of treatment is not presented in the Camptosar label. The rate of deaths within 30 days of last treatment is included in the label, and was 9% in the Saltz regimen arm of Study 0038 and 4% in the Douillard arm of Study V303. These percentages are slightly higher than they would have been if presented as deaths within 60 days of starting treatment on study. If this type of analysis of “early deaths” on study had been included in the product labeling, it has been argued that the cooperative group interim analysis could have been anticipated. The concern over “disproportionate” number of deaths on the Saltz arm relative to the controls, however, would not necessarily have been averted with this information since the proportions of deaths between arms on the licensing trial were similar.

The following table shows selected baseline characteristics of patients who died within 60 days of starting treatment in both of the Camptosar licensing studies.

Table 8. Baseline Characteristics of Patients who Died Within 60 Days of Start of Treatment in the Licensing Studies

Patient Characteristic	Study 0038			Study V303	
	Irinotecan 5-FU/LV	5-FU/LV	Irinotecan	Irinotecan 5-FU/LV	5-FU/LV
	SALTZ N = 231	Arm A N = 226	Arm C N = 226	N = 198	N = 187
No. of Patients who Died within 60 Days (%)	15 (6.4%)	16 (7%)	15(6.6%)	6 (3%)	4 (2.1%)
Age					
Median (years, range)	61 (35-81)	63 (45-79)	63 (45-79)	60 (43-70)	64 (52-70)
>65	6	4	7	2	2
<65	9	12	8	4	2
Gender					
Male	11	8	9	4	1
Female	4	8	6	2	3
Performance Status					
0				1	1
1	12	15	10	3	3
2	3	1	5	2	0
No. of lesions					
>2	3	7	4	---	---
y2	12	9	11	---	---
Liver Involvement	12	13	13	4	2
Total Bili >UNL	3	3	2	---	---
LDH >UNL	12	10	10	---	---
Prior Radiation Therapy				0	0

Unlike the cooperative group trial deaths, where the median age of patients was 69, the majority of the patients who died within 60 days in the licensing trials were less than 65 years old. In particular, the median age of patients who died in the Saltz regimen arm was 61. Like the cooperative trial deaths, the performance status of patients at study entry was usually 1 or better and there was involvement of tumor by the liver in most of the patients. Most of the patients who died within 60 days of starting treatment with the Saltz regimen on Study 0038 had normal bilirubin levels, but the majority had LDH levels above the upper limit of normal. Radiation was not allowed in Study 0038; but in study V303, where prior radiotherapy was permitted, none of the patients who died had a history of prior radiotherapy.

The following table shows that the median number of days to death was similar between the 5FU/LV and CPT-11+5FU/LV arms in both licensing studies in this group of patients. The median time to death in the Saltz regimen arm of the cooperative group studies was similar to the median time to death in the Saltz regimen arm of Study 0038 (28 days). The median time from last day of treatment to death in the Saltz regimen arm of Study 0038 was 18 days, similar to the other arms of the study.

Table 9. Timing of Deaths in Licensing Studies 0038 and V303 Among Patients Who Died Within Sixty Days of Starting Treatment on Study

	Study 0038			Study V303	
	Irinotecan 5-FU/LV	5-FU/LV	Irinotecan	Irinotecan 5-FU/LV Douillard N = 6	5-FU/LV N = 4
	SALTZ N = 15	Arm A N = 16	Arm C N = 15		
Median Days from Start of Treatment to Death	28	28	40	24	24
Range (days)	12-54	9-55	5-53	7-30	13-53
Median Days from Last Day of Treatment to Death	18	17	22	9	21
Range (days)	5-37	2-48	5-50	1-20	13-30

A combination of events observed prior to death were grouped into one of three main syndromes: (1) GI syndrome, which may include diarrhea, nausea, vomiting, cramps, dehydration, increased BUN, IVF fluid use, syncopal episodes, hypotension; (2) Hematologic/Infectious syndromes include neutropenia, fever with or without documentation of infections; (3) a combination of 1 and 2; and (4) Cardiovascular syndromes such as acute MI, PE, or strokes.

Table 10. Toxicity Syndromes Preceding Early Death in Study 0038 and V303

SYNDROMES	Study 0038			Study V303	
	Irinotecan 5-FU/LV	5-FU/LV	Irinotecan	Irinotecan 5-FU/LV N = 6	5-FU/LV N = 4
	SALTZ N = 15	Arm A N = 16	Arm C N = 15		
Gastrointestinal	3	2	4	3	2
Hematologic/Infectious	3	2	3	--	--
GI + Heme/Infectious	9	9	5	2	--
Cardiovascular	--	--	3	1	1
Other	--	2	--	--	1

A combination of GI and hematologic syndromes was observed in most patients treated with the Saltz regimen and the 5-FU/LV control arm of Study 0038. The predominance of GI+Heme/Infectious syndromes (60% for Saltz in Study 0038 above) is similar to that observed in the cooperative group trials (Table 6 of this review). This trend across studies supports the need for heightened awareness of the risk associated with the simultaneous occurrence of GI and hematologic syndromes.

Over half (8/15) of the patients who died within 60 days of starting treatment with the Saltz regimen in Study 0038 presented initially with a Grade 2 event. The Theradex panel has suggested that a more aggressive approach to dose modification with this regimen should be considered. One modification that has been recommended is to hold treatment at the first sign of a Grade 2 toxicity related to these syndromes. If the Study 0038 protocol had required that treatment be held at the occurrence of Grade 2 toxicity, how would the patients who died within 60 days in the Saltz arm of Study 0038 have been

impacted? Among the patients treated with the Saltz regimen in Study 0038, the timing of occurrence of the first Grade 2 and Grade 3 gastrointestinal and or hematologic events was tabulated below.

Table 11. Timing of Grade 2 and Grade 3 Toxicities in the Fifteen Patients Who Died Within Sixty Days of Starting Treatment on the Saltz Regimen Arm of Study 0038

Cycle 1 Week	Study 0038 Saltz Regimen (n=15)	
	Onset of Gr 2 AE ^a	Onset of Gr 3/4 AE
1	1	
2	2	1
3	3	7
4	2	2
5		
6		1
End of Treatment	1	
No GI or Hematologic Events	6	4

^a Only AE's contained in the GI and hematologic syndromes were considered in this analysis since these adverse events are being considered for more aggressive dose reductions

Of the fifteen patients who died within 60 days of starting treatment with the Saltz regimen in Study 0038, Grade 2 adverse events were experienced by eight between Week 1 and Week 4, while six patients were not reported to have experienced a Grade 2 event at all. Eleven of the 15 patients experienced a Grade 3 event initially or developed a Grade 3 event within the first cycle of treatment. This argues that merely altering therapy at first sign of Grade 2 toxicity would have been inadequate to forestall toxicity that led to subsequent death.

7 REANALYSIS OF CAMPTOSAR LICENSING TRIALS FOR FIRST-LINE TREATMENT OF METASTATIC COLORECTAL CANCER

In response to the findings of the interim safety analyses of the two cooperative group trials, the FDA asked Pharmacia to perform an additional retrospective review of the licensing trials that were the basis for Camptosar's approval for first line treatment of metastatic colorectal cancer because:

1. These large, randomized trials have complete and mature safety databases that permit re-analysis of safety by a variety of approaches, including those utilized by the data monitoring committees of the cooperative group trials. Such a reanalysis provides an opportunity to assess the early findings from the cooperative group trials in the context of a mature dataset.
2. The safety database could be reanalyzed to explore signals or questions raised from the review of early deaths in the cooperative group trials.
3. The Saltz regimen was not the only CPT-11 + 5FU/LV regimen approved for the first-line treatment of colorectal carcinoma. The safety profile of the approved infusional combination (Douillard) could be reassessed in light of the findings from the cooperative group trials.

The sponsor was asked to focus their analysis of the licensing trials on the following areas:

1. Patient characteristics/risks for severe toxicities, etc.
2. Patterns of dose modification
3. Use of concomitant medications to manage diarrhea, fever and neutropenia
4. Review of toxicities and deaths

Reviewer's comment: *Approval of Camptosar for first-line treatment of CRC was granted on the basis of a favorable overall risk benefit assessment of trials 0038 and V303. Since the primary issue of concern now is safety of the Saltz regimen, it became necessary to critically evaluate the relative safety profiles of the two approved regimens, despite the limitations of cross study comparisons. In the following section, the sponsor's findings will be presented in addition to results from queries made by the FDA reviewer of the original electronic NDA database submitted to the agency in December 1999 to further explore the safety issues raised.*

7.1 PATIENT POPULATION

Inclusion and exclusion criteria were generally similar in both trials. Prior radiation therapy was allowed only in Study V303 (European trial). Prior adjuvant therapy was allowed in both studies; however, the diagnosis of metastatic disease would have to be at least 12 months after adjuvant treatment in the U.S. study. Baseline patient characteristics are presented in Table 12:

Table 12. Baseline Patient Characteristics by Study and Therapy in Licensing Studies 0038 and V303

Patient Characteristic	Study 0038			Study V303	
	Irinotecan 5-FU/LV	5-FU/LV	Irinotecan	Irinotecan 5-FU/LV	5-FU/LV
	Arm B N = 231	Arm C N = 226	Arm A N = 226	Arm A N = 198	Arm B N = 187
Age					
Median (years, range)	62 (25-85)	61 (19-85)	61 (30-87)	62 (27-75)	59 (24-75)
Gender					
Male	151 (65.4%)	123 (54.4%)	145 (64.2%)	132 (66.7%)	99 (52.9%)
Female	79 (34.2%)	101 (44.7%)	80 (35.4%)	66 (33.3%)	88 (47.1%)
Not available*	1 (0.4%)	2 (0.9%)	1 (0.4%)	-- --	-- --
Performance Status					
0	89 (38.5%)	93 (41.2%)	104 (46.0%)	102 (51.5%)	96 (51.3%)
1	106 (45.9%)	102 (45.1%)	103 (45.6%)	83 (41.9%)	77 (41.2%)
2	35 (15.2%)	29 (12.8%)	18 (8.0%)	13 (6.6%)	14 (7.5%)
Not available*	1 (0.4%)	2 (0.9%)	1 (0.4%)	-- --	-- --
Site of Primary Tumor					
Colon	188 (81.4%)	192 (85.0%)	189 (83.6%)	108 (54.5%)	121 (64.8%)
Rectum	38 (16.5%)	31 (13.7%)	33 (14.6%)	90 (45.5%)	66 (35.5%)
Not available*	5 (2.2%)	3 (1.3%)	4 (1.8%)	-- --	-- --
Number of Involved Organ Sites					
1	147 (63.6%)	149 (65.9%)	140 (61.9%)	123 (62.1%)	117 (62.6%)
2	59 (25.5%)	52 (23.0%)	64 (28.3%)	46 (23.2%)	53 (28.3%)
>2	24 (10.4%)	23 (10.2%)	21 (9.3%)	29 (14.6%)	17 (9.1%)
Not available*	1 (0.4%)	2 (0.9%)	1 (0.4%)	-- --	-- --
Time from Initial Diagnosis to Randomization					
Median (months, range)	1.9 (.1-161)	1.7 (.1-203)	1.8 (.1-185)	4.5 (.1-88)	2.7 (0-104)
Time From Diagnosis of Metastatic Disease to Randomization					
Median (months, range)	1.1 (0-4 3)	1.3 (0-49.9)	1.2 (.1-30)	1.4 (0-67)	1.6 (0-92)
Prior Adjuvant 5-FU					
No	206 (89.2%)	208 (92.0%)	203 (89.8%)	147 (74.2%)	143 (76.4%)
Yes	25 (10.8%)	18 (8.0%)	23 (10.2%)	51 (25.8%)	44 (23.5%)
Prior Radiotherapy					
Any Radiotherapy	7 (3.0%)	5 (2.2%)	3 (1.3%)	40 (20.2%)	29 (15.5%)
Pelvis/Abdomen	4 (1.7%)	2 (0.9%)	3 (1.3%)	-- --	-- --
Other Sites	3 (1.3%)	3 (1.3%)	0 (0.0%)	-- --	-- --
Baseline Laboratory Abnormalities					
CEA ≥100 ng/mL	89/224 (39.7%)	82/213 (38.5%)	81/219 (37.0%)	67/192 (34.9%)	59/182 (32.4%)
LDH >UNL	126/210 (60.0%)	112/201 (55.7%)	104/195 (53.3%)	68/158 (43.0%)	70/156 (44.9%)
SGOT >UNL	64/223 (28.7%)	55/217 (25.4%)	67/218 (30.7%)	42/191 (22.0%)	38/180 (21.1%)
Total Bilirubin >UNL	15/226 (6.6%)	9/218 (4.1%)	22/220 (10.0%)	13/196 (6.6%)	13/186 (7.0%)
WBC ≥8 x 10 ³ /mm ³	119/227 (52.4%)	115/217 (53.0%)	113/221 (51.1%)	93/197 (47.2%)	71/187 (38.0%)
Hemoglobin <11 g/dL	58/227 (25.6%)	55/217 (25.3%)	57/221 (25.8%)	32/198 (16.2%)	40/187 (21.4%)
Creatinine >UNL	16/227 (7.1%)	8/218 (3.7%)	12/222 (5.4%)	10/198 (5.1%)	11/184 (6.0%)

* Data not available for some patients who were randomized but not treated

Abbreviations: 5-FU = 5-fluorouracil, CEA = carcinoembryonic antigen, LDH = lactate dehydrogenase, LV = leucovorin, SGOT = serum glutamate-oxalate transferase, UNL = upper normal limit, WBC = white blood count

(Table 3 from Therapy of Colorectal Cancer with Combination Regimens of Camptosar, 5-FU and Leucovorin, submitted by P&U to the FDA on September 28,2001)

Reviewer’s comment: *Although patient characteristics are generally balanced between treatment arms of each study, there are some differences across studies (highlighted) that should be considered when making comparisons of safety across studies.*

According to the sponsor, patients who received the Saltz regimen in study 0038 were more likely to have characteristics consistent with baseline compromise than in Study V303 since the upper end of the age range included on study was higher; there were fewer patients with performance 0; the proportion of patients with performance status 2 was doubled; and the frequencies of abnormal LDH, SGOT, hemoglobin, and creatinine were higher. Whether these differences in characteristics translate to a relative difference in clinical outcomes between studies is uncertain.

Efficacy Results by Performance Status

Patients with poor performance status may represent a population that is particularly susceptible to treatment-related toxicities. Given this concern, it is important to also understand the prospects for tumor control and survival benefit in this group. The table below represents a meta-analysis of efficacy variables for the combined datasets of the two licensing trials by performance status. Patients with a performance status of 2 are compared to those with performance status of 0 or 1.

Table 13. Efficacy Results by Therapy and Performance Status in Patients Randomized to Licensing Studies 0038 and V303

7.1.1.1.1.1.1.1	Efficacy Endpoint	Performance Status = 0/1	Performance Status = 2
	Irinotecan/5-FU/LV	N = 195* + 185† = 380	N = 35* + 13† = 48
	Confirmed Response Rate (%)	40.5	12.5
	Median TTP (months)	7.1	2.5
	Median Survival (months)	17.4	4.1
	5-FU/LV	N = 195* + 173† = 368	N = 29* + 14† = 43
	Confirmed Response Rate (%)	23.4	7.0
	Median TTP (months)	4.4	2.6
	Median Survival (months)	14.9	6.0

* As-randomized patients from Study 0038

† As-randomized patients from Study V303

Abbreviations: 5-FU = 5-fluorouracil, LV = leucovorin, TTP = time to tumor progression

(Table 7 from Therapy of Colorectal Cancer with Combination Regimens of Camptosar, 5-FU and Leucovorin, submitted by P&U to the FDA on September 28, 2001)

According to the sponsor, these data emphasize the general futility of chemotherapy for patients with poor performance status. Response rates were low in this subgroup, over half of the patients had

progressed within 2 cycles of therapy, and most had died within 6 months of randomization. In the combined small population of patients with PS 2 from these trials, despite the fact that the response rate appeared higher in those treated with the CPT-11 + 5FU/LV combination, the median survival is numerically higher in those treated on the 5FU/LV control arms.

Reviewer’s comment: *The table below represents an analysis of efficacy variables only in Study 0038 for patients with a performance status of 2 compared to those with performance status of 0 or 1. The results are consistent with the findings of the meta-analysis by the sponsor, in that patients with poor baseline performance status (PS=2) had numerically lower median TTP and survival in both treatment arms. Also consistent with their observation from the meta-analysis, is the worse results for patients with PS=2 at baseline treated with the IFL regimen compared to 5-FU/LV alone.*

Efficacy Results by Therapy and Performance Status in Patients
Randomized to Study 0038

Study 0038 Arm	Baseline PS	N	Median TTP (Months)	Median Survival (Months)
5-FU/LV	0	88	4.3	14
	1	102	4.2	12
	2	29	1.9	6.1
Saltz	0	87	7.3	17
	1	105	5.4	12
	2	33	1.6	3.9

7.2 TREATMENT ADMINISTRATION

In Study 0038, patients were allocated to receive 1 of 3 regimens:

Table 14. Treatment Regimens in Study 0038

Arm (Regimen)	Drugs*	Starting Doses	Cycle Schedule
A	Irinotecan	125 mg/m ² IV over 90 minutes	Weekly for 4 weeks every 6 weeks
B (Saltz)	Irinotecan LV 5-FU	125 mg/m ² IV over 90 minutes 20 mg/m ² IV bolus 500 mg/m ² IV bolus	Weekly for 4 weeks every 6 weeks
C (Mayo Clinic)	LV 5-FU	20 mg/m ² IV bolus 425 mg/m ² IV bolus	Daily for 5 days (Days 1-5) every 4 weeks

*For each regimen, agents are listed in the order in which administered.

Abbreviations: 5-FU = 5-fluorouracil, IV = intravenous, LV = leucovorin

(Table 1 from Therapy of Colorectal Cancer with Combination Regimens of Camptosar, 5-FU and Leucovorin, submitted by P&U to the FDA on September 28,2001)

In Study V303, patients were allocated to receive 1 of the following treatment regimens:

Table 15 Treatment Regimens in Study V303

Arm (Regimen)	Drugs*	Starting Doses	Cycle Schedule	
A	A1 (AIO)	Irinotecan LV 5-FU	80 mg/m ² IV over 90 minutes 500 mg/m ² IV over 2 hours 2,300 mg/m ² IV over 24 hours	Weekly for 6 weeks every 7 weeks
	A2 (Douillard)	Irinotecan LV 5-FU	180 mg/m ² IV over 90 minutes 200 mg/m ² IV over 2 hours 400 mg/m ² IV bolus, then 600 mg/m ² IV over 22 hours	Day 1 every 2 weeks Day 1, 2 Day 1, 2
B	B1 (AIO)	LV 5-FU	500 mg/m ² IV over 2 hours 2,600 mg/m ² IV over 24 hours	Weekly for 6 weeks every 7 weeks
	B2 (de Gramont)	LV 5-FU	200 mg/m ² IV over 2 hours 400 mg/m ² IV bolus, then 600 mg/m ² IV over 22 hours	Day 1, 2 every 2 weeks Day 1, 2

*For each regimen, agents are listed in the order in which administered.

Abbreviations: 5-FU = 5-fluorouracil, AIO = Association of Medical Oncology of the German Cancer Society, IV = intravenous, LV = leucovorin

(Table 2 from Therapy of Colorectal Cancer with Combination Regimens of Camptosar, 5-FU and Leucovorin, submitted by P&U to the FDA on September 28,2001)

The dose modification rules followed in the two studies differed. In Study 0038, treatment during a cycle was reduced by 20% for grade 2 toxicity and omitted for grade 3 or 4 toxicity. Treatment could be resumed once toxicity was resolved to \leq grade 2 but with a reduction by 20% for grade 3 toxicities (including hematologic toxicity) or by 40% for grade 4 toxicities or neutropenic fever. When treatment was resumed in a new cycle of therapy, patients who had experienced a maximum of grade 2 toxicity in the prior cycle, could start treatment at the original dose level in the subsequent cycle, despite the earlier interim 20% dose reduction. In Study V303, patients who experienced Grade 4 myelosuppression, neutropenic fever, or Grade 3 or 4 nonhematologic toxicity were to undergo a 20% dose reduction.

Reviewer’s Comment: *The dose modification criteria currently provided in the product label for CPT-11 + 5FU/LV combination therapy for first line treatment of colorectal carcinoma are the same for all CPT-11+ 5-FU/LV combinations regardless of schedule (i.e. bolus or infusional) and are those utilized in Study 0038 and v303. Specific dose adjustments for each schedule are also included in the label.*

The following table provides information regarding the proportion of patients in Study 0038 who were treated with full-dose chemotherapy, presented by cycle and week. The following cutoff values for total full-dose therapy were employed: Saltz – irinotecan ≥ 120 mg/m²/treatment and 5-FU ≥ 475 mg/m²/treatment; Mayo Clinic – 5-FU ≥ 2050 mg/m²/treatment cycle.

Table 16. Proportion of Patients Receiving Full-Dose Therapy by Cycle and Week in Licensing Study 0038

Arm B (Saltz)*								
Cycle (C)/Week (W)	C1W1	C1W2	C1W3	C1W4		C2W1		C3W1
Patients at Risk (N)	225	223	209	200		184		156
Irinotecan (%)	99	87	60	42		46		42
5-FU (%)	99	86	60	42		47		40
Arm C (Mayo Clinic)†								
Cycle (C)/Week (W)	C1W1				C2W1		C3W1	C4W1
Patients at Risk (N)	219				194		154	131
5-FU (%)	95				57		49	46

* 6-week cycle length. Proportions are based on planned total doses per treatment of 125 mg/m² of irinotecan and 500 mg/m² of 5-FU. Cutoff values for full-dose therapy were ≥ 120 mg/m²/treatment for irinotecan and ≥ 475 mg/m²/treatment for 5-FU.

† 4-week cycle length. Proportions are based on a planned total dose per treatment of 2125 mg/m² (425 mg/m² over 5 consecutive days per cycle). The cutoff value for full-dose therapy was ≥ 2050 mg/m²/treatment cycle for 5-FU.

Abbreviations: 5-FU = 5-fluorouracil, LV = leucovorin

(Table 20 from Therapy of Colorectal Cancer with Combination Regimens of Camptosar, 5-FU and Leucovorin, submitted by P&U to the FDA on September 28,2001

Dose modifications and omissions were most commonly necessary in Weeks 3 and 4, coinciding with the peak frequencies of cytotoxic dose-limiting side effects of diarrhea and neutropenia. The data indicate that the median dose of Camptosar delivered on the third and fourth weeks is 100 mg/m²; however, 26% of patients had their dose omitted.

Reviewer's comment: A majority of the patients require dose reductions in both arms. There is a sharp drop of about 27% in the proportion of patients treated with full doses of the Saltz regimen between the second and third week of the first cycle. Only 47% of the patients received full-dose therapy by the second cycle. Note that the advantage in survival in favor of the Saltz regimen was demonstrated despite drastic reductions in chemotherapy doses in this trial.

Some sponsors of ongoing clinical trials, including the investigators of NCCTG 9741 have adapted a more stringent dose modification criteria than those used in Study 0038. Those criteria are summarized as follows, and the differences are underlined:

- For Grade 2 Diarrhea or Neutropenia = HOLD, Reduce one level
- For Grade 3 Diarrhea or Neutropenia = HOLD, Reduce TWO levels
- No diarrhea for 24 HRS, otherwise hold treatment for one week

The following table shows the distribution of Grade 2 and Grade 3 adverse events (only GI, hematologic, or infection) observed in individual patients treated with the Saltz regimen in the first cycle of Study 0038, according to first appearance of toxicities and whether the toxicities worsened in subsequent cycles. Patients with simultaneous Grade 2 and 3 AE's were listed under Grade 3.

Table 18. Distribution of First Cycle Gastrointestinal or Hematologic Adverse Events in Patients Treated with the Saltz Regimen in Licensing Study 0038 (FDA Analysis)

Cycle 1	Initial Presentation of Adverse Event			
	Grade 3	Grade 2 and worsened*	Grade 2, did not worsen**	Others
Week 1 (n=225)	0	4	0	
Week 2 (n=223)	7	16	8	
Week 3 (n=209)	26	20	7	
Week 4 (n=200)	19	5	20	
Week 5 (n=186)	4	0	8	
Week 6 (n=184)	0	0	4	
TOTAL (n=225)	56(25%)	45 (20%)	47 (21%)	52
Total Grade 2 or Worse Toxicity	148 (66%)			

N=number of patients at risk

*Toxicity worsened to Grade 3 or 4 in subsequent dosing

**Toxicity did not worsen in subsequent dosing

There were 225 patients initially treated in the Saltz regimen arm of this study. Of the 225 patients, 148 (66%) experienced a Grade 2 or worse gastrointestinal and/or hematologic syndrome related adverse event. Of the 148 patients, 56 (25%) presented with a Grade 3 event initially. These

events clustered between the third and fourth weeks of the first cycle. The next dose of chemotherapy would have been held and then reduced by two levels in this group if the more stringent criteria were used. Forty-five (20%) patients initially presented with a Grade 2 event that became worse upon continuous treatment. The next dose of chemotherapy would have been held until resolution in this group. A total of 101 (45%) of patients would have been affected by the more stringent dose modification criteria. Having almost half the population would require within cycle dose alteration with the proposed dose suggests that the starting dose may itself need to be examined for potential modification.

In 47 (21%) patients, the grade 2 adverse events did not deteriorate. In the majority of patients, the grade 2 event did not occur until after the fourth week when a rest from treatment was scheduled anyway. This indicates that a subset of patients can tolerate the current recommended dosing and dose modification scheme. The concern in this group is that a more aggressive dose modification scheme might impact on the dose intensity and eventually the efficacy of the treatment without impacting on its safety. A total of 52 (23%) patients, experienced adverse events other than those that belong to the gastrointestinal or hematologic syndromes or did not experience any adverse event at all in the first cycle of treatment.

Note also that the incidence of these events tend to increase and peak on the second and third cycles (reported on W3 and 4 respectively). This is consistent with the observation of a large increase in the number of patients who were unable to take full doses of chemotherapy on Cycles 3 and 4 (see Table 7) and supports the argument made by some that a week of rest (Week 3) after the second week should be included in new dose modification instructions to allow time to recover from toxicity, potentially avoiding a severe drop in dose intensity.

The following table provides information regarding the proportion of patients in the second licensing study, Study V303 (which utilized infusional schedules), that received full-dose chemotherapy, presented by cycle and week.

Table 19. Proportion of Patients Receiving Full-Dose Therapy by Cycle and Week in Study V303

Arm A2 (Douillard)*					
Cycle (C)/Week (W)	C1W1	C1W3	C1W5	C2W1	C3W1
Patients at Risk (N)	145	140	136	125	105
Irinotecan (%)	96	89	87	86	79
5-FU (%)	93	88	85	83	76
Arm B2 (de Gramont)†					
Cycle (C)/Week (W)	C1W1	C1W3	C1W5	C2W1	C3W1
Patients at Risk (N)	143	136	135	110	83
	95	95	93	91	89

* 6-week cycle length. Proportions are based on planned total doses per treatment of 180 mg/m² of irinotecan and 2000 mg/m² of 5-FU. Cutoff values for full-dose therapy were ≥175 mg/m²/treatment for irinotecan and ≥1933 mg/m²/treatment for 5-FU.

† 6-week cycle length. Proportions are based on planned total doses per treatment of 2000 mg/m² of 5-FU. The cutoff value for full-dose therapy was ≥1933 mg/m²/treatment for 5-FU.

Abbreviations: 5-FU = 5-fluorouracil, LV = leucovorin

(Table 21 from Therapy of Colorectal Cancer with Combination Regimens of Camptosar, 5-FU and Leucovorin, submitted by P&U to the FDA on September 28,2001

Reviewer's comment: *There is a gradual decline in the proportion of patients who received full doses of chemotherapy in both treatment arms of study V303. More than 85% of patients received full doses of chemotherapy on the second cycle and 80% on the third. The much higher proportion of patients who were able to receive full doses of treatment in this study compared to Study 0038 may indicate better patient tolerance of the higher biweekly dose of Camptosar and infusional 5-FU regimen utilized in this study. Again, cross study comparisons must be approached with caution since different patient characteristics or different supportive care measures could have contributed to these apparent differences. Note that the higher proportion of full dose delivery in Study V303 did not translate into a higher proportion of patient deaths in the first 60 days after starting treatment compared to Study 0038. (See Table 7 in this review.)*

7.3 SUPPORTIVE CARE

The following table lists medications that were given concomitantly to patients with treatment related side effects:

Table 20. Concomitant Treatments, (Licensing Study 0038 and V303)

Atropine	0. 25 mg SC for acute cholinergic symptoms
Loperamide	take 2 caps as soon as first liquid stool, 1 cap q 2 hours for at least 12 hours and up to 12 hours after last liquid stool. Oral rehydration
Antiemetics	Dexamethasone, 10 mg IV as pretreatment
G-CSF/GM-CSF	not recommended but may be considered in patients with prior serious neutropenic complications
Fluoroquinolone (V303 ONLY)	Orally for 7 days for (1) Grade 4 diarrhea; (2) diarrhea for > 48 hours despite recommended loperamide treatment; (3) Diarrhea + Grade 3 neutropenic fever

Differences between treatment arms in percentages of patients receiving concomitant antiemetics, anticholinergics, mouth care, and antidiarrheals were consistent with the relative frequencies of the supported adverse events for the treatment regimens. Patients treated with irinotecan/5-FU/LV generally received all of these types of drugs more frequently than did patients treated with 5-FU/LV alone. The following table summarizes the use of supportive therapies in the IFL arms of Studies 0038 and V303:

Table 21. Proportion of Patients Receiving Supportive Care in Licensing Studies 0038 (Saltz Regimen) and V303 (Douillard Regimen)

	Saltz Regimen (0038) N = 225		Douillard + AIO Regimen (v303) N =199	
Antiemetics				
Dexamethasone	209	(92.9%)	98	(49.3%)
Ondansetron	118	(52.4%)	91	(45.7%)
Prochlorperazine	105	(46.7%)	2	(1.0%)
Lorazepam	80	(35.6%)	20	(10.1%)
Granisetron	77	(34.2%)	71	(35.7%)
Metoclopramide	71	(31.6%)	109	(54.8%)
Diphenhydramine	40	(17.8%)	0	(0%)
Antiemetics	8	(3.6%)	94	(47.2%)
Anticholinergics				
Atropine	76	(33.8%)	75	(37.7%)
Mouth Care				
Stomatologicals	13	(5.8%)	53	(26.6%)
Antidiarrheals				
Loperamide	172	(76.4%)	127	(63.8%)
Diphenoxylate	40	(17.8%)	2	(1.0%)
Colony-stimulating Factors				
G-CSF/GM-CSF	18	(8.0%)	4	(2.0%)

(from Tables 25 and 26, Therapy of Colorectal Cancer with Combination Regimens of Camptosar, 5-FU and Leucovorin, submitted by P&U to the FDA on September 28,2001)

The use of quinolones as prophylactic treatment once grade 4 or persistent diarrhea was observed was protocol specified in the protocol for Study V303, but not in Study 0038. The use of quinolones in the IFL arms of studies 0038 and v303 are as follows:

Table 22. Antibiotic Use on the Licensing Studies 0038 and V303

	Saltz 0038 N = 225		Douillard +AIO V303 N = 199	
Antibiotics				
All Antibiotics	120	(53%)	167	(84%)
Quinolones	41	(18%)	50	(25%)

Reviewer’s comment: Among 225 patients enrolled in the Saltz regimen arm of Study 0038, 120 (53%) received one or more antibiotics during the course of treatment compared to a higher number, 167 (84%) in Study V303. Whether antibiotics were for prophylactic or therapeutic use was not captured in the database. The use of quinolones was also slightly higher in Study v303. . It is difficult to infer from the pivotal trial database whether use of antibiotics actually prevented more life threatening sepsis or infections. It would be interesting to evaluate the use of antibiotics in the NCCTG and CALGB studies.

7.4 SAFETY

Adverse events were to be assessed weekly in Study 0038 and at each treatment visit in Study V303. Complete blood counts were to be performed weekly during chemotherapy. Safety was summarized by treatment arm with categorization by each patient’s worst severity grade. The severity of adverse events and laboratory changes were graded according to the NCI Common Toxicity Criteria (CTC), Version 1.0.

7.4.1 Gastrointestinal/Hematologic and Cardiovascular Events

Two syndromes identified in most cases of early deaths in the cooperative group studies were GI-hematologic and cardiovascular syndromes. In the licensing studies, the overall incidence of events comprising the GI-hematologic syndrome (diarrhea, neutropenia and neutropenic events) were lower in the Douillard regimen compared to the Saltz regimen. The incidence of cardiovascular syndrome related events were similar. The incidence of thromboembolic events does not seem to be considerably increased in the infusional 5FU regimen, which required central venous access for administration. Data on these events were summarized by the sponsor in the following table:

Table 23. Overall Adverse Events by Study and Regimen in Licensing Studies 0038 and V303

Adverse Event	Study 0038 Saltz (%) (n=225)	Study V303 Douillard (%) (n=145)
Diarrhea (%)		
Grade 3-4	22.7	14.4
Grade 3	15.1	10.3
Grade 4	7.6	4.1
Vomiting (%)		
Grade 3-4	9.7	3.5
Grade 3	5.3	2.8
Grade 4	4.4	0.7
Mucositis (%)		
Grade 3-4	2.2	4.1
Grade 3	1.8	4.1
Grade 4	0.4	0.0
Neutropenia (%)		
Grade 3-4	53.8	46.2
Grade 3	29.8	36.4
Grade 4	24.0	9.8
Neutropenic Complications (%)*		
Neutropenic Fever	7.1	3.4
Neutropenic Infection	1.8	2.1
Thromboembolism (%)		
Any Event	9.3†	10.4
All Venous Events‡	7.1	7.6
Pulmonary Embolism	2.7	1.4
All Arterial Events§	2.7	2.8
Myocardial ischemia	0.9	0.7
Myocardial infarction	1.3	0.0
Cardiac arrest/sudden death	0.0	0.0
Cerebral ischemia/infarction	0.0	0.7
Peripheral arterial	0.4	1.4

* In Study 0038, includes complications occurring simultaneous with grade 4 neutropenia. In Study V303, includes complications occurring simultaneous with grade 3-4 neutropenia.

† Includes 1 patient (#374) who had both venous and arterial events

‡ Includes COSTART terms: deep thrombophlebitis, pulmonary embolus, thrombophlebitis, thrombosis, vascular disorder

§ Includes COSTART terms: angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, embolus lower extremity, heart arrest, myocardial infarct, myocardial ischemia, peripheral vascular disorder, sudden death

Abbreviations : 5-FU = 5-fluorouracil, LV = leucovorin

(from Tables 8, Therapy of Colorectal Cancer with Combination Regimens of Camptosar, 5-FU and Leucovorin, submitted by P&U to the FDA on September 28,2001

Reviewer's comment: The incidence of Grade 3/4 neutropenia, neutropenic fever and infections, Grade 3/4 diarrhea and vomiting are higher on the Saltz regimen compared to the Douillard regimen. Note that in Study 0038, the definition of neutropenic fever/infections include only complications occurring simultaneous with grade 4 neutropenia. In Study V303, the definition includes complications occurring simultaneous with grade 3-4 neutropenia. Therefore the neutropenic complications associated with Grade 4 neutropenia only with the Douillard regimen could only be lower than reported in the study. Grade 3/4 mucositis was less common in the Saltz regimen.

7.4.2 BASELINE PATIENT CHARACTERISTICS AS PREDICTORS OF FIRST-CYCLE DIARRHEA, NEUTROPENIA, AND SIMULTANEOUS NEUTROPENIC FEVER AND INFECTION

The sponsor examined the proportion of patients that experienced Grade 3/4 diarrhea and neutropenia with fever when treated with the CPT-11 + 5FU/LV combination regimens in studies 0038 and V303. The distribution of risk for developing these toxicities by characteristic examined is summarized in the table below.

Table 24. Proportion Developing First-Cycle Grade 3-4 Diarrhea and Grade 4 Neutropenia and Simultaneous Neutropenia Fever and Infection by Baseline Characteristic in Licensing Studies 0038 and V303

Baseline Characteristic	Study 0038				Study V303			
	Irinotecan/5-FU/LV (Saltz)				Irinotecan/5-FU/LV (Douillard)			
	Arm B N=225				Arm A2 N = 145			
	n	Diarrhea (Gr 3-4)	Neut (Gr 4)	NF/I	n	Diarrhea (Gr 3-4)	Neut (Gr 4)	NF/I
Age (%)								
<65 years	137	12.4	16.8	9.5	92	4.4	2.2*	0.0†
≥65 years	88	13.6	22.7	18.2	53	7.6	9.4	9.4
Gender (%)								
M	114	12.1	17.7	12.2	103	9.5	3.07.1	2.9
F	68	14.1	21.8	14.1	42	3.9		4.8
Performance Status (%)								
0	87	9.2	14.9	8.1	68	2.9	5.9	1.5
1	105	14.3	21.0	14.3	65	7.7	4.6	4.6
2	33	18.2	24.2	21.2	12	8.3	0.0	8.3
LDH (%)								
≤UNL	83	14.5	18.1	13.3	64	3.1	6.36.8	3.1
>UNL	126	11.1	19.1	11.1	44	11.4		6.8
SGOT (%)								
≤UNL	158	12.7	19.0	15.2	109	5.5	6.4	4.6
>UNL	63	11.1	20.6	7.9	30	3.3	0.0	0.0
Bilirubin (%)								
≤UNL	210	13.3	17.6†	12.9	134	6.0	5.2	3.7
>UNL	15	6.7	40.0	13.3	11	0.0	0.0	0.0
WBC (%)								
<8 x10 ³ /mm ³	108	14.8	18.5	13.9	75	4.0	8.0	4.0
≥8 x10 ³ /mm ³	117	11.1	19.7	12.0	70	7.1	1.4	2.0
Hemoglobin (%)								
≥11g/dL	167	13.2	17.4	13.2	120	5.8	5.0	2.5
<11g/dL	58	12.2	24.1	12.1	25	4.0	4.0	8.0
Creatinine (%)								
≤UNL	209	13.4	17.2‡	12.9	140	ND	ND	ND
>UNL	16	6.3	43.8	12.5	5	ND	ND	ND
Prior Radiation (%)								
No	219	ND	ND	ND	115	3.5§	5.2	3.5
Yes	6	ND	ND	ND	30	13.3	3.3	3.3
All Patients (%)	225	12.9	19.1	12.9	145	5.5	4.8	3.5

Statistical significance assessed by Chi-square tests. Significant differences are noted in bold.

* p=0.05, † p<0.01, ‡ p<0.01, § p=0.03.

Abbreviations: 5-FU = 5-fluorouracil, LDH = lactate dehydrogenase, LV = leucovorin, SGOT = serum glutamate-oxalate transferase, UNL = upper normal limit, WBC = white blood count NF/I = neutropenic fever/infection

The following are the sponsor's conclusions from the above data:

- (1) In Study 0038, there is an increase in the likelihood of grade 4 neutropenia with abnormal bilirubin (p<0.01) and abnormal creatinine (p<0.01), not corroborated in Study V303 due to the small number of patients with low initial grade 4 neutropenia.
- (2) In Study V303, older patients experienced an increased frequency of grade 4 neutropenia (p=0.05) and patients with prior radiation had an increased frequency of grade 3-4 diarrhea

(p=0.03). The correlation between older age and neutropenia was not confirmed by Study 0038, and it was not possible to address the correlation between radiation and toxicity in this trial because so few patients with prior irradiation were enrolled .

- (3) There is a significant increase in neutropenic fever or infection with older age (p=0.003) in Study V303. A similar trend was seen in Study 0038 (p=0.06). The other noteworthy trend is a stepwise increase in the frequency of neutropenic fever or infection with worsening performance status; while not statistically significant, this trend was apparent in both Studies 0038 and V303. The same trend is noted for neutropenia in Study 0038 but not in Study V303.
- (4) While not statistically significant, a stepwise increase in grade 3-4 diarrhea with worsening performance status is suggested in both Studies 0038 and V303.

Reviewer's comment: *The overall incidence of Grade 3-4 diarrhea, Grade 4 neutropenia and NF/I was higher in patients treated with the Saltz regimen compared to the Douillard regimen. The risk factors with significant differences within each study may be important considerations (abnormal bilirubin, creatinine, age, prior radiation therapy, worsening performance status) for designing PK/PD studies or for stratification in new trials using either the Saltz or Douillard regimens. Whether use of the Saltz regimen should be limited to a more tightly defined patient population on the basis of the characteristics examined above should be discussed.*

7.4.3 Neutropenic Fever or Infection

The cooperative group study events that prompted reanalysis of the data from the licensing trials reflected early toxicity. We have commented that interpretation of the cooperative group data was limited somewhat by the fact that the data were not mature and did not include safety data for all cycles of treatment on study. The information provided in Table 25 below condenses all known episodes of fever and infection in conjunction with grade 3-4 neutropenia associated with CPT-11 + 5FU/LV combination therapy on study (not limited to first cycle), and is presented for comparison to the frequency of events that were observed in the first cycle of treatment for regimens employed in Studies 0038 and V303. The Douillard infusional regimen was associated with very few neutropenic complications. The table also demonstrates that the majority of events in both combination regimens can be anticipated to manifest in the first cycle.

Table 25. Overview of Neutropenia Fever and/or Infection* Associated with CPT-11 + 5FU/LV Combination Therapy Presented by All Cycles and First Cycle and by Regimen in Licensing Studies 0038 and V303

Timing	Study 0038	Study V303
	Saltz (%) N = 225	Douillard (%) N=145
All Cycles	36 (16.0)	8 (5.5)
First Cycle	29 (12.9)	5 (3.5)

Includes simultaneous occurrence of grade 3-4 neutropenia or leucopenia with grade ≥ 2 fever or
* grade 3-4 bacterial or fungal infections or sepsis.

Abbreviations : 5-FU = 5-fluorouracil, LV = leucovorin

(from Table10 , Therapy of Colorectal Cancer with Combination Regimens of Camptosar, 5-FU and Leucovorin, submitted by P&U to the FDA on September 28,2001

7.4.4 Discontinuations Due to Adverse Events

The following table provides an overview of the incidence of discontinuations due to adverse events of any type and any potential cause (whether disease- or drug-related) associated with CPT-11 + 5FU/LV combination therapy in all cycles of therapy compared to those that occurred in the first cycle of treatment in Studies 0038 and V303.

Table 26. Overview of Discontinuations Due to Any Adverse Events Associated with CPT-11 + 5FU/LV Combination Therapy Presented by All Cycles and First Cycle and by Regimen in Licensing Studies 0038 and V303

Timing	Study 0038	Study V303
	Saltz (%) N = 225	Douillard (%) N=145
All Cycles	17 (7.6)	9 (6.2)
First Cycle	7 (3.1)	4 (2.8)

When evaluating all cycles of therapy, these data indicate relatively similar rates of discontinuations due to adverse events between patients treated with the Saltz and Douillard regimens. The pattern of first-cycle discontinuations was also similar between combination regimens. Nearly half of the discontinuations were early events (first cycle) in both trials.

8 FDA POST-MARKETING DATA

The CDER post marketing adverse event reporting system was queried for deaths that occurred within 60 days of starting treatment. This review will follow.

9 PROPOSED LABELING CHANGES

P&U proposed to modify the package insert consistent with several of the recommendations by the Theradex committee. Changes include additional warnings regarding the possibility of fatal gastrointestinal and vascular events; more detailed descriptions of the potentially fatal combination of diarrhea, colitis/ileus, fever, and neutropenia; emphasis on weekly first-cycle patient monitoring; and increased stress on the importance of early institution of antibiotics (including use of an oral fluoroquinolone).

The proposed changes to the package insert were submitted for FDA review on September 10, 2001 and summarized into the following categories:

1. Improvement of Supportive Care.
 - Patients with severe diarrhea should be given antibiotic support if they develop ileus, fever, or severe neutropenia. Patients with neutropenic sepsis should be hospitalized and managed promptly with antibiotic support.
 - Consider the use of colony stimulating factors in patients experiencing Grade 2 neutropenia.
 - Patients will be instructed to have a prescription for a 7-day supply of oral fluoroquinolone for the management of diarrhea that persists for more than 24 hours despite loperamide, fever accompanying diarrhea, and for prophylaxis if ANC <500/ μ l. Patients should be hospitalized and receive treatment with intravenous antibiotics if they have persistent diarrhea or fever, or if ileus develops despite oral fluoroquinolones.
 - Patients should be assessed at least weekly, especially during the first course of therapy.
 - Careful monitoring of WBC counts; which should be appropriate within 48 hours before the next treatment.
2. Increased awareness of patients at risk and monitoring of the gastrointestinal and vascular syndromes associated with CPT-11+5FU/LV bolus regimen.
 - Treatment with Camptosar is not recommended for patients with performance status of 3 or 4.

- Patients should be free of diarrhea and without the need for anti-diarrheals for at least 24 hours before receiving the next chemotherapy.

3. Dose Modification

Patients experiencing grade 2, 3, or 4 diarrhea, abdominal cramping or neutropenia on the day of treatment administration should have doses delayed until they recover to # Grade 1. Patients who previously experienced Grade 2 AE's will maintain previous dose level, while patients who experience at least Grade 3 AE's will receive two dose level reductions.

While it is essential to retrospectively examine all available information and critically assess the proposed changes to the label, the possible ramifications of any "modifications" of the Saltz regimen on the efficacy and safety of this approved regimen must be considered. Although they may be perceived as enhancing safety, these modifications in dosing or schedule have not been prospectively demonstrated to achieve the goal of heightened safety, and may have the potential of changing the efficacy of the approved regimen.

10 FDA REVIEWER CONCLUSIONS

The data monitoring committees that performed the interim analyses of the cooperative group trials were not evaluating a mature data set, and one of the interim analyses performed was not a prespecified analysis. When the data on early death from these analyses are compared to mortality data from the licensing trials, the absolute death rates and events that preceded deaths on the Saltz arms appear similar to those observed in the licensing trial. There are inherent flaws in performing cross study comparisons, and the within study comparison of the early death rate associated with the Saltz regimen in the licensing trial was similar to its 5FU/LV control arm, whereas the within study comparisons in the cooperative group trials found that early deaths on the Saltz arms occurred at a disproportionately higher rate than the controls (which were different control arms than studied in the licensing trial).

The Douillard regimen (continuous infusion) is also approved in the United States. Review of the adverse events and patterns of dose modification in the licensing study indicate that this regimen might have a more acceptable safety profile compared to the Saltz regimen, but there has been no "head to head" comparison between the two regimens to fully support those perceptions. The GI Intergroup Executive Committee recently recommended that the Douillard regimen be used as the control arm in new phase 3 trials conducted by the group.

The licensing trial's pattern of early dose modification in a substantial portion of the patients treated with the Saltz regimen suggests that its starting dose may be overly aggressive. The changes to the label that the sponsor has proposed attempt to address these safety concerns. Short of reducing the starting dose; however, it is unclear whether the dose modifications that are included in the changes will affect the efficacy of the regimen.

Changes that affect the administration of the regimen should ideally be prospectively studied to evaluate their impact on safety and efficacy. In the meantime, the Agency needs to determine the most appropriate regulatory response to take to address the current safety concerns. If the safety concerns raised by the cooperative group interim analyses are considered valid, the appropriate regulatory response based on the available clinical data must be discussed. The potential actions that could be taken include no action, altering the recommendations for administration of the Saltz regimen in the product label, altering the supportive care recommended in the product label, or removal of the regimen from the product label.

¹ Rothenberg ML, Meropol NJ, Poplin EA et al. Deaths associated with irinotecan + bolus 5-fluorouracil/leucovorin: report of an independent panel, July 25, 2001.⁸