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**APPLICATION NUMBER: NDA 20571/S9**

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**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20,571/SE1-009

Submission Date: October 19, 1999  
December 15, 1999

Drug Name: Camptosar® (CPT-11, Irinotecan HCl)

Formulation: Injectable

Sponsor: Pharmacia & Upjohn Company  
Kalamazoo, MI 49001

Reviewer: Z. John Duan, Ph.D.

Type of Submission: New Drug Application, Supplement

This is a review of the Clinical Pharmacology and Biopharmaceutics (CPB) studies submitted in sNDA 20-571 in support of Camptosar as a component of first-line therapy for patients with metastatic colorectal cancer.

### I. SYNOPSIS

Irinotecan is a topoisomerase I inhibitor and a derivative of camptothecin. The applicant has submitted this efficacy supplemental NDA to seek an approval for irinotecan as a component of first-line therapy for patients with metastatic colorectal cancer. In the current sNDA, the applicant submitted four studies, including two clinical pharmacokinetic studies, an in vitro metabolism study, and a protein binding study. In addition, seven literature references were provided.

This review is completed by using the Question Based Review approach, which focuses on the drug interaction issues when utilizing combination regimens of irinotecan, Fluorouracil (5-FU), and Leucovorin (LV).

#### *1. What are the proposed dosage regimens for the first-line treatment of Camptosar?*

The DOSAGE AND ADMINISTRATION Section of the proposed package insert includes three dosing regimens which are shown in the following table.

Table. Combination Treatment Regimens

Regimen 1	Camptosar	125 mg/m <sup>2</sup> IV over 90 min, d 1,8,15,22 then 2-wk rest
	LV	20 mg/m <sup>2</sup> IV, d 1,8,15,22 then 2-wk rest
6-wk course	5-FU	500 mg/m <sup>2</sup> IV, d 1,8,15,22 then 2-wk rest

Regimen 2 6-wk course <sup>2</sup>	Camptosar	180 mg/m <sup>2</sup> IV over 90 min, d 1,15,29 then 1-wk rest
	LV	200 mg/m <sup>2</sup> IV over 2 h, d 1,2,15,16,29,30 then 1-wk rest
	5-FU	400 mg/m <sup>2</sup> IV bolus then 1-wk rest 600 mg/m <sup>2</sup> over 22 h, d 1,2,15,16,29,30 then 1-wk rest
Regimen 3 7-wk course <sup>3</sup>	Camptosar	80 mg/m <sup>2</sup> IV over 90 min, d 1,8,15,22,29,36 then 1-wk rest
	LV	500 mg/m <sup>2</sup> IV over 2 h, d 1,8,15,22,29,36 then 1-wk rest
	5-FU	2300 mg/m <sup>2</sup> IV over 24 h, 1,8,15,22,29,36 then 1-wk rest

Note: The applicant decided to withdraw Regimen 3 for the treatment. Therefore, Regimen 3 is not discussed in the review.

**2. Has the pharmacokinetics of CPT-11 and SN-38 been evaluated in the proposed dosage regimens?**

The pharmacokinetics of CPT-11 and SN-38 has been evaluated in two of the three dosage regimens:

- Regimen 1: P&U Protocol M6475/0007
- Regimen 2: RPR Protocol F106

In addition, an in vitro metabolism study and a protein binding study have been conducted.

**3. Is there any effect of 5-FU/LV on the pharmacokinetics of irinotecan for Regimen 1?**

A Phase I, single center, open label, dose escalation trial was conducted and reported.

Forty-two patients were enrolled in the study. Twenty-seven were treated in the dose-escalation phase of the study, and 15 patients were added to the study once the recommended phase II doses of irinotecan, 5-FU and leucovorin were achieved. In the dose-escalation phase, 21 patients were treated with irinotecan at a starting dose of 100 mg/m<sup>2</sup>. The distribution of these patients by 5-FU starting dose was as follows: 210 mg/m<sup>2</sup> (3 patients), 265 mg/m<sup>2</sup> (3 patients), 340 mg/m<sup>2</sup> (3 patients), 425 mg/m<sup>2</sup> (6 patients), and 500 mg/m<sup>2</sup> (6 patients). Six additional patients were treated with the 500 mg/m<sup>2</sup> starting dose of 5-FU (after this dose was found to be tolerable); 3 of these patients were treated with 125 mg/m<sup>2</sup> of irinotecan and 3 were treated with 150 mg/m<sup>2</sup> of irinotecan. Fifteen additional patients were subsequently treated with starting doses of 500 mg/m<sup>2</sup> of 5-FU, 125 mg/m<sup>2</sup> of irinotecan, and 20 mg/m<sup>2</sup> of LV once the MTD doses had been identified.

The starting dose of irinotecan was initially fixed at 100 mg/m<sup>2</sup>. The starting dose of 5-FU was escalated in each successive cohort of 3 patients. Once a dose of 500 mg/m<sup>2</sup> 5-FU was matched, the irinotecan starting dose was escalated to as high as 150 mg/m<sup>2</sup>. A fixed dose of 20 mg/m<sup>2</sup> of LV was given to all patients

A baseline pharmacokinetic assessment of irinotecan alone was performed on week one (Treatment A; Week 1). Pharmacokinetic evaluations were then repeated when irinotecan was given immediately before LV/5-FU (Treatment B; Week 2), and when irinotecan was given immediately following LV/5-FU (Treatment C; Week 7). Thus, each patient served as his or her

own control for irinotecan and SN-38 pharmacokinetic evaluation.

Mean ( $\pm$  SD) pharmacokinetic parameters for irinotecan and SN-38 for the 27 patients treated during the dose-escalation phase of the study were reported. A statistically significant reduction in SN-38  $C_{max}$  ( $p < 0.001$ ) and  $AUC_{0-\infty}$  ( $p < 0.002$ ) values were observed on week 2 (Treatment B: LV/5-FU administered immediately following irinotecan administration). The mean percent decreases in SN-38,  $C_{max}$ , and  $AUC_{0-24}$  values among patients were 13.7% and 8.2%, respectively, when compared to the corresponding values determined when irinotecan was given alone. A comparison of SN-38  $AUC_{0-24}$  when irinotecan was given alone (Treatment A; week 1) versus when irinotecan was given immediately following 5-FU (Treatment C; week 7) showed no statistically significant difference between these values ( $p > 0.9$ ). The comparison of pharmacokinetic parameters is shown in the following table.

**Table. Mean ( $\pm$  SD) Irinotecan and SN-38 Pharmacokinetic Parameters for Patients Treated in the Dose-Escalation Phase of P&U Protocol M/6475/0007 [Saltz 1996]**

Parameter	Treatment A Irinotecan Alone [N=26]*	Treatment B Irinotecan Followed by 5-FU/LV [N=26]*	Treatment C 5-FU/LV Followed by Irinotecan [N=22]**	ANOVA p Value
		Irinotecan		
$t_{max}$ (h)	1.44 $\pm$ 0.254	1.46 $\pm$ 0.162	1.42 $\pm$ 0.198	0.6180
$C_{max}$ (ng/mL)	1148 $\pm$ 294	1122 $\pm$ 264	1084 $\pm$ 231	0.7758
$NC_{max}$ (ng/mL) †	1087 $\pm$ 293	1055 $\pm$ 227	1028 $\pm$ 193	0.9043
$AUC_{0-24}$ (ng $\cdot$ h/mL) ¶	6396 $\pm$ 2237	6191 $\pm$ 2006	6002 $\pm$ 1271	0.3536
$NAUC_{0-24}$ (ng $\cdot$ h/mL) §	5996 $\pm$ 1984	5827 $\pm$ 1859	5685 $\pm$ 1005	0.5824
CL (L/h/m <sup>2</sup> )	16.6 $\pm$ 12.3	15.2 $\pm$ 3.72	14.9 $\pm$ 2.77	0.9987
$V_z$ (L/m <sup>2</sup> )	153 $\pm$ 150	137 $\pm$ 37.1	138 $\pm$ 32.7	0.9507
$t_{1/2}$ (h)	6.13 $\pm$ 0.71	6.24 $\pm$ 0.607	6.51 $\pm$ 1.59	0.5293
	6.1	6.2	6.3	
		SN-38		
$t_{max}$ (h)	2.00 $\pm$ 0.684	2.16 $\pm$ 1.05	2.04 $\pm$ 0.418	0.5775
$C_{max}$ (ng/mL)	20.6 $\pm$ 7.61	17.0 $\pm$ 8.41	20.5 $\pm$ 7.59	0.0009
				A>B p=0.0002
				A=C p=0.2587
$NC_{max}$ (ng/mL) †	19.4 $\pm$ 7.05	16.3 $\pm$ 8.64	19.7 $\pm$ 7.78	0.0136
				A>B p=0.0040
				A=C p=0.4171
$AUC_{0-24}$ (ng $\cdot$ h/mL) ¶	166 $\pm$ 67.2	146 $\pm$ 58.1	167 $\pm$ 47.5	0.0018
				A>B p=0.0012
				A=C p=0.9486
$NAUC_{0-24}$ (ng $\cdot$ h/mL) §	156 $\pm$ 56.2	140 $\pm$ 59.3	160 $\pm$ 50.3	0.0179
				A>B p=0.0111
				A=C p=0.9100

$t_{1/2}$ (h)	14.8±6.74	14.2±4.41	16.1±7.70	0.3370
	12.7	13.0	13.7	

\* Patient 125 only had a pharmacokinetic assessment performed during week 2 (Treatment B) and was not included in the statistical analyses

\*\* Patients 102, 110, 118, 125, and 127 did not have a pharmacokinetic assessment performed on Week 7 (Treatment C)  
Irinotecan concentrations expressed in free base units

‡ Observed maximum plasma concentration normalized to a 100 mg/m<sup>2</sup> dose

¶ Area under the plasma concentration-time curve from start of infusion to last collection time (i.e., -24 hours after the end of the infusion)

§ Area under the plasma concentration-time curve from start of infusion to last collection time (i.e., -24 hours after the end of the infusion);  
normalized to a irinotecan dose of 100 mg/m<sup>2</sup>

Harmonic mean

Following completion of the dose-escalation phase of the study, 15 additional patients were evaluated once the recommended phase II doses had been achieved. The irinotecan and SN-38 pharmacokinetic and statistical results are similar to those obtained in the patients treated during the dose-escalation phase.

Substantial differences in mean irinotecan pharmacokinetic parameters were not observed when irinotecan was administered with and without LV/5-FU. There was a statistically significant reduction in SN-38 C<sub>max</sub> (13.7%) and AUC<sub>0-24</sub> (8.2%) during the week when irinotecan was followed by 5-FU and LV; however, this reduction was not evident 5 weeks later when pharmacokinetic sampling was performed with irinotecan administered immediately following 5-FU. Such differences in C<sub>max</sub> or AUC are unlikely to be of clinical importance; thus, 5-FU does not substantially alter the pharmacokinetics of irinotecan or its active metabolite SN-38.

#### *4. Is there any effect of 5-FU/LV on the pharmacokinetics of irinotecan for Regimen 2?*

The applicant provided a full report of a European Phase I study to address this question.

In this study, Irinotecan was administered as a 90-min infusion every 2 weeks at escalating dose levels ranging from 100 to 300 mg/m<sup>2</sup>. On days 1 and 2, LV was administered as a 2-h IV infusion, followed by 5-FU (400 mg/m<sup>2</sup>) as a 10-min IV bolus, followed by 5-FU (600 mg/m<sup>2</sup>) as a continuous 22-h infusion. LV/5-FU was started 1 h after the end of the irinotecan infusion. All three drugs were given every 2 weeks.

Pharmacokinetic parameters were determined in 21 patients (median age 61 years; range 41 to 38 years) during the first cycle of chemotherapy.

The pharmacokinetic results of this trial were compared with previous data from studies of irinotecan administered as a single agent at similar dose levels to 168 cancer patients [Chabot 1995]. The mean clearance value observed in patients treated with irinotecan, 5-FU, and LV in this trial (14.7 L/h/m<sup>2</sup>) was comparable to that observed in single-agent studies (14.8 L/h/m<sup>2</sup>). The terminal half-life for irinotecan was longer in the current trial than in studies utilizing irinotecan monotherapy (22.5 ± 14.6 h vs. 12.0 ± 7.8 h). SN-38 half-life values were comparable to those determined in patients treated with irinotecan alone (12.0 vs. 10.6 h). SN-38 C<sub>max</sub> and AUC values were also in the same range as those observed with single-agent therapy. SN-38/irinotecan AUC ratios were approximately stable over the tested dose range and were close to

those observed with irinotecan single-agent therapy (4.1% vs. 3.1%). Therefore, it is concluded that 5-FU/LV had no significant effect on the pharmacokinetics of irinotecan and SN-38 comparing with historical data for irinotecan monotherapy.

**5. Are there any other evidence to support that 5-FU does not have significant influences on the pharmacokinetics of irinotecan?**

The results of in vitro studies demonstrated that 5-FU (25  $\mu$ M) does not markedly alter carboxylesterase-mediated conversion of irinotecan to SN-38 in human hepatic microsomes using standardized in vitro conditions.

In a protein binding study, it was shown that 5-FU did not alter the binding of SN-38 to human plasma proteins.

These two in vitro studies support that 5-FU does not have significant influences on the pharmacokinetics of irinotecan.

**6. Are the pharmacokinetics of 5-FU and LV affected by coadministration with CPT-11?**

The influence of CPT-11 on the pharmacokinetics of 5-FU and LV was not evaluated by the applicant. However, under the request of the reviewer, a publication was provided, which reported that steady-state plasma concentrations of 5-FU were not influenced by combination therapy with CPT-11 (Sasaki 1994). In the study, steady-state concentrations of 5-FU determined 24-164 hours after starting a 400 mg/m<sup>2</sup>/day 5-FU continuous infusion averaged 0.165  $\mu$ g/mL, among 12 patients receiving irinotecan doses ranging from 100 to 150 mg/m<sup>2</sup>. This steady-state concentration was comparable to those reported by other investigators when 5-FU was infused as a single agent (Yoshida 1990).

An ASCO abstract reported the results of a phase I study which determined the influence of the order of administration on the pharmacokinetics of both CPT-11 and 5-FU [Bastian 1998]. In cycle 1, CPT-11 (200-350 mg/m<sup>2</sup>) was administered as a 30-minute infusion on Day 1 and 5-FU (375 mg/m<sup>2</sup>) was given by IV bolus on Day 2 through Day 6. In the second 6-day cycle, 5-FU was given on Day 1 through Day 5 and CPT-11 was given on Day 6. The pharmacokinetic parameters were determined on both cycles as shown in the following table.

Parameters	Cycle 1	Cycle 2
CPT-11 CL (L/h)	25.9 $\pm$ 2.2	27.04 $\pm$ 2.98
SN-38 AUC ( $\mu$ g $\cdot$ h/mL)	0.53 $\pm$ 0.33	0.53 $\pm$ 0.4
5-FU AUC ( $\mu$ g $\cdot$ h/mL)	11.6 $\pm$ 6.85	12.11 $\pm$ 6.55

This study suggested that irinotecan did not result in a clinically relevant alteration in the pharmacokinetics of 5-FU.

## II. COMMENTS:

### General

1. The two clinical studies, an in vitro metabolism study, and a protein binding study indicated that 5-FU/LV had no significant effect on the pharmacokinetics of CPT-11 and SN-38. However, the following points should be noted.
  - There was a statistically significant reduction in SN-38  $C_{max}$  (13.7%) and  $AUC_{0-24}$  (8.2%) during the week when irinotecan was followed by 5-FU and LV compared with when irinotecan was given alone.
  - The comparison between combination therapy and monotherapy for Regimen 2 was based on historical data.
2. The effects of other components (irinotecan and LV) in the dosage regimens on the pharmacokinetics of 5-FU have not been evaluated, which may have clinical significance.
3. In future pharmacokinetic study of irinotecan, the sample collection time should be long enough (at least three half-lives) to allow for the terminal phase to be accurately estimated. The half-life of irinotecan is about 6-12 hours. However, the sampling time was only up to 24 hours in the US study,

4.

### Labeling

1. The labeling in the "Clinical Pharmacology" section that reads:

Should be changed to:

### Drug-Drug Interactions

In a phase 1 clinical study involving irinotecan, 5-FU, and leucovorin (LV) in 26 patients with solid tumors the disposition of irinotecan was not substantially altered when the drugs were co-administered. However, SN-38  $C_{max}$  and  $AUC_{0-24}$  were reduced (by 14% and 8% respectively) when irinotecan was followed by 5FU and LV administration compared with irinotecan given alone. Formal in vivo or in vitro drug interaction studies to evaluate the influence of irinotecan on the disposition of 5-FU and LV have not been conducted.

2. The following section should be added to the "Precautions" section.



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Proposed Labeling Change

## VI. APPENDIX II. INDIVIDUAL STUDY SYNOPSIS

### 1. U.S. Phase I Clinical and Pharmacokinetic Study.

**Study title:** A Phase I Clinical and Pharmacological Study of Irinotecan (CPT-11) Plus 5-Fluorouracil (5-FU), and Leucovorin (LV) in Patients with Advanced Solid Tumor Malignancies (P&U Study M/6475/0007) [Saltz 1996]

**Investigator & location:**

**Study period:** Information not available.

**Study formulation:** Sterile solution 20 mg/mL, lot # 27122, 27123, 27227, 27231, 27253, 27254, 27230, 27283, 27362, PM7965; 100mg/5mL vial, lot # PM8019a, PM8121A; 40mg/2mL vial, lot # PM8019b, PM8121B;

**Objectives:** (1) to define the maximum tolerated dose (MTD) of 5-FU when given with fixed doses of irinotecan and LV, (2) to define the dose-limiting toxicities (DLTs) of this combination regimen, (3) to determine, through pharmacokinetic analyses, the effect of 5-FU/LV on the pharmacokinetics of irinotecan and its active metabolite SN-38, and (4) to determine the effect of the order of administration of irinotecan and 5-FU/LV on irinotecan pharmacokinetics and toxicity when given on the weekly schedule.

**Subjects:** Forty-two patients (25 men and 17 women) of median age 52 years (range, 34-73 years) with various solid tumor types were enrolled to the study. Of the 42 patients, 27 were treated in the dose-escalation phase of the study, and 15 patients were added to the study once the recommended phase II doses had been achieved.

#### **Study Design:**

This was a Phase I, single center, open label, dose escalation trial.

Forty-two patients were enrolled to the study. Twenty-seven were treated in the dose-escalation phase of the study, and 15 patients were added to the study once the recommended phase II doses had been achieved. In the dose-escalation phase, 21 patients were treated with irinotecan at a starting dose of 100 mg/m<sup>2</sup>. The distribution of these patients by 5-FU starting dose was as follows: 210 mg/m<sup>2</sup> (3 patients), 265 mg/m<sup>2</sup> (3 patients), 340 mg/m<sup>2</sup> (3 patients), 425 mg/m<sup>2</sup> (6 patients), and 500 mg/m<sup>2</sup> (6 patients). Six additional patients were treated with the 500-mg/m<sup>2</sup> starting dose of 5-FU (after this dose was found to be tolerable); 3 of these patients were treated with 125 mg/m<sup>2</sup> of irinotecan and 3 were treated with 150 mg/m<sup>2</sup> of irinotecan. Fifteen additional patients were subsequently treated with starting doses of 500 mg/m<sup>2</sup> of 5-FU, 125 mg/m<sup>2</sup> of irinotecan, and 20 mg/m<sup>2</sup> of LV once the MTD doses had been identified.

The starting dose of irinotecan was initially fixed at 100 mg/m<sup>2</sup>. The starting dose of 5-FU was escalated in each successive cohort of 3 patients. Once a dose of 500 mg/m<sup>2</sup> 5-FU was matched

the irinotecan starting dose was escalated to as high as 150 mg/m<sup>2</sup>. A fixed dose of 20 mg/m<sup>2</sup> of LV was given to all patients.

A previously reported study suggested that 5-FU reduced the metabolism of irinotecan to SN-38, presumably by interference with the function of in vivo carboxylesterases involved in this conversion [Sasaki 1994]. Therefore, in the study, a baseline pharmacokinetic assessment of irinotecan alone was performed on week one (denoted as Treatment A; Week 1).

Pharmacokinetic evaluations were then repeated when irinotecan was given immediately before LV/5-FU (denoted as Treatment B; Week 2), and when irinotecan was given immediately following LV/5-FU (denoted as Treatment C; Week 7). Thus, each patient served as his or her own control for irinotecan and SN-38 pharmacokinetic evaluation.

During each pharmacokinetic assessment, whole blood specimens (7 mL) were drawn via venipuncture or indwelling intravenous cannula into heparin-containing tubes at the following times: prior to beginning the 90-min irinotecan infusion; at 45 min following the start of infusion and at the end of the infusion; as well as at 5, 10, 15, and 30 min, and 1, 2, 4, 6, and 24 h after the completion of the infusion. The actual time of blood sampling was recorded and this time, relative to the start of irinotecan infusion, was used in pharmacokinetic analyses.

Total (lactone + hydroxy acid) plasma concentrations of irinotecan and SN-38 were determined using a validated, reverse-phase HPLC-fluorescence method.

## Results:

### Assay performance:

Species	Range (ng/mL)	Cal. Standard		QC standard	
		Precision (%)	Accuracy (%)	Precision (%)	Accuracy (%)
Irinotecan	1.39-3460	2.5-9	91-104	4-6	92-102
SN-38	0.40-1280	1.9-8	-92-100	4-6	98-100

### Pharmacokinetics:

Irinotecan and SN-38 plasma concentration data for the 27 patients in the dose escalation phase of this study were analyzed by non-compartmental methods. Irinotecan concentrations were expressed as hydrochloride trihydrate equivalents.

Peak plasma concentrations ( $C_{max}$ ) and the time ( $t_{max}$ ) at which they occurred, the apparent terminal elimination rate constants ( $\lambda_z$ ), the apparent elimination half-life ( $t_{1/2}$ ), area under the plasma concentration-time curves ( $AUC_{0-24}$ ), area under the irinotecan plasma concentration-time curves through infinite time ( $AUC_{0-\infty}$ ), the systemic clearance (CL) and apparent volume of distribution ( $V_z$ ) of irinotecan were determined. Since irinotecan was administered at three different dose levels (100, 125, and 150 mg/m<sup>2</sup>) in this trial,  $C_{max}$  and  $AUC_{0-24}$  were also normalized to a dose of 100 mg/m<sup>2</sup>. Pharmacokinetic parameters obtained on each of the three pharmacokinetic assessment days were compared using a univariate repeated measures analysis of variance. The statistical model included the effects of interest, dose (between-subject effect)

and treatment (within subject effect), as well as a dose-by-treatment interaction term. Statistical analyses were performed using the General Linear Models (GLM) procedure of the Statistical Analysis System (SAS) (SAS Institute, Inc, Cary, NC) Least squares means analysis was used for pairwise comparisons if a significant treatment effect was detected. For all evaluations, statistical significance was defined by  $p < 0.05$ .

Mean ( $\pm$  SD) pharmacokinetic parameters for irinotecan and SN-38 for the 27 patients treated during the dose-escalation phase of the study and reported in the published manuscript are shown in the following Table.

**Table. Mean ( $\pm$  SD) Irinotecan and SN-38 Pharmacokinetic Parameters for Patients Treated in the Dose-Escalation Phase of P&U Protocol M/6475/0007 [Saltz 1996]**

Parameter	Treatment A Irinotecan Alone [N=26]*	Treatment B Irinotecan Followed by 5-FU/LV [N=26]*	Treatment C 5-FU/LV Followed by Irinotecan [N=22]**	ANOVA p Value
	<b>Irinotecan</b>			
$t_{max}$ (h)	1.44 $\pm$ 0.254	1.46 $\pm$ 0.162	1.42 $\pm$ 0.198	0.6180
$C_{max}$ (ng/mL)	1148 $\pm$ 294	1122 $\pm$ 264	1084 $\pm$ 231	0.7758
$NC_{max}$ (ng/mL) †	1087 $\pm$ 293	1055 $\pm$ 227	1028 $\pm$ 193	0.9043
$AUC_{0-24}$ (ng $\cdot$ h/mL) ¶	6396 $\pm$ 2237	6191 $\pm$ 2006	6002 $\pm$ 1271	0.3536
$NAUC_{0-24}$ (ng $\cdot$ h/mL) §	5996 $\pm$ 1984	5827 $\pm$ 1859	5685 $\pm$ 1005	0.5824
CL (L/h/m <sup>2</sup> )	16.6 $\pm$ 12.3	15.2 $\pm$ 3.72	14.9 $\pm$ 2.77	0.9987
$V_z$ (L/m <sup>2</sup> )	153 $\pm$ 150	137 $\pm$ 37.1	138 $\pm$ 32.7	0.9507
$t_{1/2}$ (h)	6.13 $\pm$ 0.71 6.1	6.24 $\pm$ 0.607 6.2	6.51 $\pm$ 1.59 6.3	0.5293
	<b>SN-38</b>			
$t_{max}$ (h)	2.00 $\pm$ 0.684	2.16 $\pm$ 1.05	2.04 $\pm$ 0.418	0.5775
$C_{max}$ (ng/mL)	20.6 $\pm$ 7.61	17.0 $\pm$ 8.41	20.5 $\pm$ 7.59	0.0009
				A>B p=0.0002
				A=C p=0.2587
$NC_{max}$ (ng/mL) †	19.4 $\pm$ 7.05	16.3 $\pm$ 8.64	19.7 $\pm$ 7.78	0.0136
				A>B p=0.0040
				A=C p=0.4171
$AUC_{0-24}$ (ng $\cdot$ h/mL) ¶	166 $\pm$ 67.2	146 $\pm$ 58.1	167 $\pm$ 47.5	0.0018
				A>B p=0.0012
				A=C p=0.9486
$NAUC_{0-24}$ (ng $\cdot$ h/mL) §	156 $\pm$ 56.2	140 $\pm$ 59.3	160 $\pm$ 50.3	0.0179
				A>B p=0.0111
				A=C p=0.9100
$t_{1/2}$ (h)	14.8 $\pm$ 6.74 12.7	14.2 $\pm$ 4.41 13.0	16.1 $\pm$ 7.70 13.7	0.3370

- \* Patient 125 only had a pharmacokinetic assessment performed during week 2 (Treatment B) and was not included in the statistical analyses
- \*\* Patients 102, 110, 118, 125, and 127 did not have a pharmacokinetic assessment performed on Week 7 (Treatment C)
- Irinotecan concentrations expressed in free base units
- † Observed maximum plasma concentration normalized to a 100 mg/m<sup>2</sup> dose
- ¶ Area under the plasma concentration-time curve from start of infusion to last collection time (ie, -24 hours after the end of the infusion)
- § Area under the plasma concentration-time curve from start of infusion to last collection time (i.e., -24 hours after the end of the infusion); normalized to a irinotecan dose of 100 mg/m<sup>2</sup>
- Harmonic mean

A statistically significant reduction in SN-38 C<sub>max</sub> (p<0.001) and AUC<sub>0-∞</sub> (p<0.002) values were observed on week 2 (Treatment B: LV/5-FU administered immediately following irinotecan administration). The mean percent decreases in SN-38, C<sub>max</sub>, and AUC<sub>0-24</sub> values among patients were 13.7% and 8.2%, respectively, when compared to the corresponding values determined when irinotecan was given alone. A comparison of SN-38 AUC<sub>0-24</sub> when irinotecan was given alone (Treatment A; week 1) versus when irinotecan was given immediately following 5-FU (Treatment C; week 7) showed no statistically significant difference between these values (p>0.9).

Following completion of the dose-escalation phase of the study, 15 additional patients were evaluated once the recommended phase II doses had been achieved. The protocol was amended to exclude the pharmacokinetic assessment on Week 7 (i.e., Treatment C) in these patients. Only a limited amount of additional pharmacokinetic information was collected in these patients. The irinotecan and SN-38 pharmacokinetic and statistical results for all patients who had pharmacokinetic assessments performed on more than one occasion during the study are shown in the following Table. These results are similar to those obtained in the patients treated during the dose-escalation phase. Slightly higher C<sub>max</sub> and AUC<sub>0-24</sub> values were observed, at least in part, because the additional patients all received the recommended phase II irinotecan dose of 125 mg/m<sup>2</sup>.

**Table. Mean (± SD) Irinotecan and SN-38 pharmacokinetic Parameters for All Patients Treated in P&U Protocol M/6475/0007**

Parameter	Treatment A Irinotecan Alone [N=37]*	Treatment B Irinotecan Followed by 5-FU/LV [N=37]*	Treatment C 5-FU/LV Followed by Irinotecan [N=22]**	ANOVA p Value
		<b>Irinotecan</b>		
t <sub>max</sub> (h)	1.42±0.241	1.46±0.138	1.42±0.198	0.8267
C <sub>max</sub> (ng/mL)	1192±301	1202±341	1084 ± 231	0.6756
NC <sub>max</sub> (ng/mL) †	1072 ± 277	1073 ± 264	1028 ± 193	0.8375
AUC <sub>0-24</sub> (ng·h/mL) ¶	6714 ± 2380	6891 ± 3138	6002 ± 1271	0.7851
NAUC <sub>0-24</sub> (ng·h/mL) §	5989 ± 1994	6127 ± 2524	5685 ± 1005	0.8755
CL (L/h/m <sup>2</sup> )	16.1 ± 10.8	15.0 ± 4.51	14.9 ± 2.77	0.9908
V <sub>z</sub> (L/m <sup>2</sup> )	145 ± 128	135 ± 38.2	138 ± 32.7	0.9497
t <sub>1/2</sub> (h)	6.14 ± 0.879	6.33 ± 0.930	6.51 ± 1.59	0.4407
	6.0	6.2	6.3	

	SN-38				
$t_{max}$ (h)	2.18±0.937	2.05±0.946	2.04±0.418		0.8474
$C_{max}$ (ng/ml)	23.3±9.83	19.1±9.30	20.5 ± 7.59		0.0005
					A>B p=0.0001
					A=C p=0.3520
$NC_{max}$ (ng/mL) †	20.7±7.97	17.1 ± 8.43	19.7 ± 7.78		0.0077
					A>B p=0.0021
					A=C p=0.5048
$AUC_{0-24}$ (ng•h/mL) ¶	188±108	166±90.2	167±47.5		0.0130
					A>B p=0.0067
					A=C p=0.9086
$NAUC_{0-24}$ (ng•h/mL) §	166±84.4	149±75.7	160±50.3		0.0424
					A>B p=0.0221
					A=C p=0.8780
$t_{1/2}$ (h)	15.5±8.69	15.5±8.04	16.1±7.70		0.4806
	12.7	13.0	13.7		

\* Patients 125, 135, 136, 137, and 142 only had PK assessment performed on one occasion and were not included in the statistical analyses.

\*\* The Week 7 PK assessment (Treatment C) was only performed in patients treated during the dose escalation phase (first 27 patients); patients 102, 110, 118, 125, and 127 did not have a PK assessment performed on Week 7.

† Irinotecan concentrations expressed in free base units

‡ Observed maximum plasma concentration normalized to a 100 mg/m<sup>2</sup> dose

¶ Area under the plasma concentration-time curve from start of infusion to last collection time (i.e., -24 hours after the end of the infusion)

§ Area under the plasma concentration-time curve from start of infusion to last collection time (i.e., -24 hours after the end of the infusion); normalized to a irinotecan dose of 100 mg/m<sup>2</sup>

Harmonic mean

### Conclusion:

Substantial differences in mean irinotecan pharmacokinetic parameters were not observed when irinotecan was administered with and without LV/5-FU. There was a statistically significant reduction in SN-38  $C_{max}$  (13.7%) and  $AUC_{0-24}$  (8.2%) during the week when irinotecan was followed by 5-FU and LV. Such differences in  $C_{max}$  or AUC are unlikely to be of clinical importance.

### Comments:

1. One of the objectives of this study was to determine the effect of the order of administration of irinotecan and 5-FU/LV on irinotecan pharmacokinetics and toxicity when given on the weekly schedule. However, this has not been assessed through the available data.
2. This study demonstrated that substantial differences in mean pharmacokinetic parameters of irinotecan and its active metabolite SN-38 were not observed when irinotecan was administered with and without LV/5-FU. However, a statistically significant reduction of SN-38  $C_{max}$  and AUC was observed during combination therapy compared to monotherapy.
3. The effects of other components on pharmacokinetics of 5-FU were not assessed.
4. The half-life of irinotecan is about 6-12 hours. However, the sampling time was only up to 24 hours in this study. In general, the sample collection time should be long enough (at least three half-lives) to allow for the terminal phase to be more accurately estimated.



**Results:**

**Assay performance:**

Species	LOQ (ng/mL)	QC standard (ng/mL)							
		100 (20)*		250 (50)*		500 (75)*		1000 (100)*	
		Precis ion (%)	Accur acy (%)	Precis ion (%)	Accur acy (%)	Precis ion (%)	Accur acy (%)	Precis ion (%)	Accur acy (%)
Irinotecan	2.5	13.93	-9.17	4.77	-6.50	6.63	-4.76	13.69	10.50
SN-38	0.5	14.89	-5.00	6.43	-7.25	10.60	-20.40	13.05	-6.33

\* for SN-38

**Pharmacokinetics:**

Mean ± SD irinotecan and SN-38 pharmacokinetic parameters are shown in the following Table.

**Table. Mean (± SD) Irinotecan and SN-38 Pharmacokinetic Parameters when Irinotecan is Administered in Combination with Leucovorin and 5-fluorouracil [Ducreux 1999]**

Dose (mg/m <sup>2</sup> )	N	Irinotecan			SN-38	
		C <sub>max</sub> (µg/mL)	AUC (µg·h/mL)	CL (L/h/m <sup>2</sup> )	C <sub>max</sub> (µg/mL)	AUC (µg·h/mL)
100	4	0.90±0.14	5.36±1.00	19.5±4.5	0.033 ± 0.022	0.223±0.101
120	2	1.43±0.12	9.74±0.61	12.3±0.8	0.024±0.001	0.257±0.129
150	3	2.80 ± 0.28	15.68 ± 2.87	10.0 ± 2.2	0.039± 0.023	0.225 ± 0.058
180	4	2.13 ± 0.12	22.09 ± 16.89	11.9 ± 5.0	0.033 ± 0.01 1	0.344 ± 0.158
200	1	2.70	16.97	11.8	0.038	0.465
220	1	3.60	20.63	10.7	0.066	0.997
260	3	3.10±0.44	17.34±3.01	15.4±2.4	0.082±0.036	0.578±0.018
300	3	2.75±0.56	15.18±1.96	19.8±2.4	0.184±0.038	1.690±0.537
Total	21			14.7 ± 5.0		

The pharmacokinetic results of this trial were compared with previous data from studies of irinotecan administered as a single agent at similar dose levels to 168 patients with cancer [Chabot 1995]. The mean clearance value observed in patients treated with irinotecan, 5-FU, and LV in this trial (14.7 L/h/m<sup>2</sup>) was comparable to that observed in single-agent studies (14.8 L/h/m<sup>2</sup>). The terminal half-life for irinotecan was longer in the current trial than in studies utilizing irinotecan monotherapy (22.5 ± 14.6 h vs. 12.0 ± 7.8 h). SN-38 half-life values were comparable to those determined in patients treated with irinotecan alone (12.0 vs. 10.6 h). SN-38 C<sub>max</sub> and AUC values were also in the same range as those observed with single-agent therapy. SN-38/irinotecan AUC ratios were approximately stable over the tested dose range and were

close to those observed with irinotecan single-agent therapy (4.1% vs. 3.1%).

**Comments:**

1. The pharmacokinetic results of this trial were compared with historical data from studies of irinotecan administered as a single agent at similar dose levels. The pharmacokinetic parameters were comparable to those observed in single-agent studies. Therefore, this study could be supportive for the US study.
2. The terminal half-life for irinotecan was longer in the current trial than in studies utilizing irinotecan monotherapy ( $22.5 \pm 14.6$  h vs.  $12.0 \pm 7.8$  h), this was probably due to the fact that blood collection was performed up to 48 h postinfusion. In general, the sample collection time should be long enough (at least three half-lives) to allow for the terminal phase to be more accurately estimated.

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ON ORIGINAL**

### 3. In vitro metabolism study

**Study title:** In vitro studies on the effect of co-therapy on the carboxylesterase-mediated bioactivation of the anticancer agent CPT-11 (U-1014400E) to its active metabolite SN-38 (U0101503). Report #: 7256-95-091

**Investigator & location:**

**Study period:** 1994-1995

**Objectives:** The objective of this study was to assess the relative ability of known carboxylesterase inhibitors and currently important co-administered drugs to inhibit the carboxylesterase-mediated production of SN-38 from CPT-11 in human hepatic microsomes using standardized in vitro conditions..

**Study Design:** Human hepatic microsomes of known CPT-11 hydrolyzing activity were used to determine the direct effects of potential inhibitors on carboxylesterase-mediated SN-38 formation. Compounds tested were chosen base on a known or possible ability to inhibit carboxylesterase (fluroide, probenecid, disulfiram, metoclopramide, physostigmine, prochlorperazine, p-hydroxymerecuribenzoic acid, p-chloromercuribenzoic acid) or were chosen based on possible clinical co-administration (loperamide, 5-fluorouracil, cisplatin, coumarin, dexamethasone, ethanol, aspirin, acetaminophen and caffeine).

Under standard incubation conditions of 15 min, 100  $\mu\text{M}$  CPT-11 and 1 mg/mL of microsomal protein, SN-38 was determined by quantitation. Bis-nitrophenylphosphate (BNPP) and phosphate buffer were used as inhibitor controls.

#### Results:

In control experiments, BNPP at both 25 and 100  $\mu\text{M}$  abolished CPT-11 hydrolysis to 1.3 - 1.6% of control values. Background hydrolysis in the presence of phosphate buffer and boiled microsomes was 9.3% and 9.7% (uncorrected values) of control. Probenecid (25  $\mu\text{M}$ ) showed a significant (13%,  $P < 0.01$ ) inhibition of CPT-11 hydrolysis, while 5-FU (25  $\mu\text{M}$ ) had no significant inhibitory effect (2%,  $P = 0.06$ ). fluroide, a known esterase inhibitor that is formed from 5-FU, inhibited hydrolysis significantly ( $P < 0.01$ ) by 9% at 25  $\mu\text{M}$ , 14% at 100  $\mu\text{M}$ , and 35% at 481  $\mu\text{M}$ . these are relatively high concentrations, but it is possible based on these data that fluroide, which is formed from breakdown of the 5-FU metabolite, fluoro- $\beta$ -alanine, could potentially decrease SN-38 AUC during cotherapy with 5-FU and CPT-11

#### Comments:

This study showed that 5-FU (25  $\mu\text{M}$ ) had no significant inhibitory effect on carboxylesterase-mediated CPT-11 hydrolysis.

#### 4. Protein binding study

**Study title:** Effects of the commonly administered co-medications loperamide, dexamethasone, lorazepam, and 5-fluorouracil on the plasma protein binding of SN-38 (PNU-101503) determined using ultrafiltration. Report #: 7256-97-003

**Investigator & location:**

**Study period:** 1996

**Objectives:** The objective of this study was to determine the effects of commonly administered co-medications on the plasma protein binding of SN-38.

**Study Design::** The effects of commonly administered co-medications on the plasma protein binding of SN-38 were studied using the method of ultrafiltration. HPLC methods were used to determine protein-bound drug levels in these assays. The drugs tested for their abilities to displace SN-38 (25 ng/ml) from plasma proteins were loperamide (34 nM), lorazepam (1 $\mu$ M), 5-fluorouracil (1mM), and dexamethasone (5 $\mu$ M). These drug concentrations were calculated based on maximum plasma levels typically achieved in patients taking the medications.

The concentration tested for SN-38 was 58.3 nM and the duration of the treatment was 15 minutes.

#### **Results:**

The effects of co-medications on the binding of SN-38 to plasma proteins are summarized in the following table.

Co-medications	Average % SN-38 bound
None	96.2%
Loperamide (34 nM)	94.9%
Lorazepam (1 $\mu$ M)	93.4%
5-fluorouracil (1mM)	93.9%
dexamethasone (5 $\mu$ M)	95.9%

#### **Comments:**

These studies indicated that the presence of commonly used co-medications did not result in significant change in the binding of SN-38 to plasma proteins.