NDA20-571

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-571

JUN 14 1996

The Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001-0199

Attention: Hendrik J. de Koning Gans, MD
Director, Worldwide Regulatory Liaison

Dear Dr. de Koning Gans:

Please refer to your December 28, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Camptosar (irinotecan hydrochloride) Injection.

We acknowledge receipt of your amendments dated February 13 and 22; March 29; April 3 and 15; May 16, 21, 29, 30; June 4, 7, 10 and 11, 1996.

This new drug application provides for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has progressed following 5-FU-based therapy.

We have completed the review of this application, including the submitted draft labeling, according to the regulations for accelerated approval, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved under 21 CFR 314.510. Approval is effective on the date of this letter.

Products approved under the Accelerated Approval Regulations 21 CFR 314.500 require further adequate and well-controlled studies to verify and describe clinical benefit. We acknowledge your commitment in your letter dated May 30, 1996 to conduct the controlled clinical trial described below and your estimate that the final study report will be submitted to the FDA in approximately two years. We request that you submit the complete findings of this study as soon as possible for our review to satisfy this requirement.

> A controlled, multicenter, post-marketing study; protocol M/6475/0038 entitled, "Irinotecan HCl: A Phase III, Randomized, Controlled Clinical Trial of Irinotecan HCl Alone, Combined Irinotecan HCl and 5-Fluorouracil Plus Leucovorin, and 5-Fluorouracil Plus Leucovorin Alone in Patients with Untreated Metatastic Colorectal Cancer."

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-571. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind your of your Phase 4 commitments specified in your submissions dated June 6 and 14, 1996. These commitments, along with any completion dates agreed upon, are listed below. Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocol, data, and final reports to this NDA as correspondences. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

You have agreed to complete and submit results of the following studies:

As required by 21CFR 314.550, all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval, must be reviewed by the Agency before their use. After 120 days following marketing approval, you must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Division of Oncology Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

In addition, we request a meeting within 3 months following approval to discuss other studies being conducted or planned by you or other companies developing irinotecan hydrochloride.

If you have any questions, please contact Leslie Vaccari, Project Manager, (301) 594-5778.

Sincerely yours,

Robert Temple 6/14/96

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE (Draft Labeling)

cc:
Original NDA 20-571
HFD-150/Div. file
DISTRICT OFFICE
HFD-150/LVaccari
HFD-150/A Murgo
/JJohnson
/CGnecco
/TKoutsoukos
/GeWilliams
/ARahman
/PAndrews
/JDeGeorge
/RBarron
/RWood
HFD-2/MLumpkin
HFD-101/LCarter (with labeling)
HFD-810/CHoiberg
HF-2/Medwatch (with labeling)
HFD-80 (with labeling)
HFD-40/DDMAC/TAcker (with labeling)
HFD-613 (with labeling)
HFD-735/(with labeling)
HFD-021/JTreacy (with labeling)

Drafted: LVaccari/June 6, 1996/
R/D Init. by:DPease/6-6-96
/A Murgo/6-7-96
/JJohnson/6-12-96
/CGnecco/6-10-96
/TKoutsoukos/6-7-96
/GeWilliams/6-7-96
/ARahman/6-11-96
/PAndrews/6-12-96
/JDeGeorge/WDMcGuinn for 6-11-96
/RBarron/6-14-96
/RWood/6-14-96
/RDeLap/6-14-96
final:
APPROVAL [with Phase 4 Commitments]

DPease 6-14-96

CAMPTOSAR™
brand of irinotecan hydrochloride injection

For Intravenous Use Only

WARNINGS

1. CAMPTOSAR Injection should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

2. CAMPTOSAR can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Both forms of diarrhea may be severe. Early diarrhea (occurring during or within 24 hours of administration of CAMPTOSAR) may be preceded by complaints of diaphoresis and abdominal cramping and may be ameliorated by atropine. Late diarrhea (occurring more than 24 hours after administration of CAMPTOSAR) can be prolonged, may lead to dehydration and electrolyte imbalance, and can be life-threatening. Late diarrhea should be treated promptly with loperamide; patients with severe diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated (see WARNINGS section). Administration of CAMPTOSAR should be interrupted if severe diarrhea occurs.

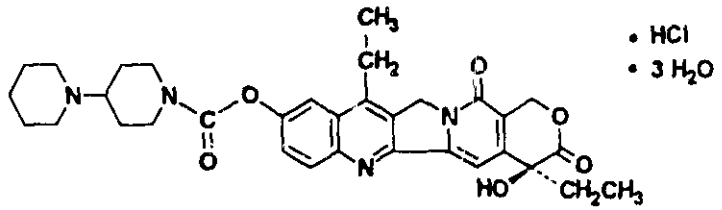
3. Severe myelosuppression may occur (see Warnings Section).

DESCRIPTION

CAMPTOSAR Injection (irinotecan hydrochloride injection) is an antineoplastic agent of the topoisomerase I inhibitor class. Irinotecan hydrochloride was clinically investigated as CPT-11.

CAMPTOSAR is supplied as a sterile, pale yellow, clear, aqueous solution. It is available in 100-mg, single-dose, 5-mL vials. Each milliliter of solution contains 20 mg of irinotecan hydrochloride (on the basis of the trihydrate salt), 45 mg of sorbitol NF powder, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. CAMPTOSAR is intended for dilution with 5% Dextrose Injection, USP (D5W), or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion. The preferred diluent is 5% Dextrose Injection, USP.

Irinotecan hydrochloride is a semisynthetic derivative of camptothecin, an alkaloid extract from plants such as *Camptotheca acuminata*. The chemical name is (4*S*)-4,11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino)carbonyloxy]-1*H*-pyrano[3',4':6,7] indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)dione hydrochloride. Its structural formula is as follows:



Irinotecan Hydrochloride

Irinotecan hydrochloride is a pale yellow to yellow crystalline powder, with the empirical formula $C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$ and a molecular weight of 677.19. It is slightly soluble in water and organic solvents.

CLINICAL PHARMACOLOGY

Irinotecan is a derivative of camptothecin. Camptothecins interact specifically with the enzyme topoisomerase I which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I - DNA complex and prevent religation of these single- strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38. Mammalian cells cannot efficiently repair these double-strand breaks.

Irinotecan serves as a water-soluble precursor of the lipophilic metabolite SN-38. SN-38 is formed from irinotecan by carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and the dipiperidino side chain. SN-38 is approximately 1000 times as potent as irinotecan as an inhibitor of topoisomerase I purified from human and rodent tumor cell lines. In vitro cytotoxicity assays show that the potency of SN-38 relative to irinotecan varies from 2- to 2000-fold. However, the plasma area under the concentration versus time curve (AUC) values for SN-38 are 2% to 8% of irinotecan and SN-38 is 95% bound to plasma proteins compared to approximately 50% bound to plasma proteins for irinotecan (see Pharmacokinetics). The precise contribution of SN-38 to the activity of CAMPTOSAR is thus unknown. Both irinotecan and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. A pH-dependent equilibrium exists between the two forms such that an acidic pH promotes the formation of the lactone, while a more basic pH favors the hydroxy acid anion form.

Administration of irinotecan has resulted in antitumor activity in mice bearing cancers of rodent origin and human carcinoma xenografts of various histological types.

Pharmacokinetics

After intravenous infusion of CAMPTOSAR in humans, irinotecan plasma concentrations decline in a multiexponential manner, with a mean terminal elimination half-life of about 6 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 hours. The half-lives of the lactone (active) forms of irinotecan and SN-38 are similar to those of total irinotecan and SN-38, as the lactone and hydroxy acid forms are in equilibrium.

Over the dose range of 50 to 350 mg/m^2, the AUC of irinotecan increases linearly with dose; the AUC of SN-38 increases less than proportionally with dose. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of CAMPTOSAR.

Irinotecan exhibits moderate plasma protein binding (30% to 68% bound). SN-38 is highly bound to human plasma proteins (approximately 95% bound). The plasma protein to which irinotecan and SN-38 predominantly binds is albumin.

Summary of Mean (± Standard Deviation) Irinotecan and SN-38 Pharmacokinetic Parameters in Patients With Metastatic Carcinoma of the Colon and Rectum

Dose (mg/m^2)	Irinotecan					SN-38		
	C_{max} (ng/mL)	AUC_{0-24} (ng·hr/mL)	$t_{½}$ (hr)	V_{area} (L/m^2)	CL (L/hr/m^2)	C_{max} (ng/mL)	AUC_{0-24} (ng·hr/mL)	$t_{½}$ (hr)
125 (N=64)	1,660 ± 797	10,200 ± 3,270	5.8 ± 0.7	110 ± 48.5	13.3 ± 6.01	26.3 ± 11.9	229 ± 106	10.4 ± 3.1

C_{max} - Maximum plasma concentration.
AUC_{0-24} - Area under the plasma concentration-time curve from time 0 to 24 hours after the end of the 90-minute infusion.
$t_{½}$ - Terminal elimination half-life.
V_{area} - Volume of distribution of terminal elimination phase.
CL - Total systemic clearance.

Metabolism and Excretion: The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver. SN-38 subsequently undergoes conjugation to form a glucuronide metabolite. SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines in vitro. The disposition of irinotecan has not been fully elucidated in humans. The urinary excretion of irinotecan is 11% to 20%; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of CAMPTOSAR in two patients ranged from approximately 25% (100 mg/m^2) to 50% (300 mg/m^2).

Pharmacokinetics in Special Populations

Geriatric: The terminal half-life of irinotecan was 6.0 hours in patients who were 65 years or older and 5.5 hours in patients younger than 65 years. Dose-normalized $AUC_{0\text{-}24}$ for SN-38 in patients who were at least 65 years of age was 11% higher than in patients younger than 65 years. No change in dosage and administration is recommended for geriatric patients.

Pediatric: The pharmacokinetics of irinotecan have not been studied in the pediatric population.

Gender: The pharmacokinetics of irinotecan do not appear to be influenced by gender.
Race: The influence of race on the pharmacokinetics of irinotecan has not been evaluated.

Hepatic Insufficiency: The influence of hepatic insufficiency on the pharmacokinetic characteristics of irinotecan and its metabolites has not been formally studied. Among patients with known hepatic tumor involvement (a majority of patients), irinotecan and SN-38 AUC values were somewhat higher than values for patients without liver metastases. For patients having liver metastases without decreased hepatic function, no change in dosage and administration is recommended.

Renal Insufficiency: The influence of renal insufficiency on the pharmacokinetics of irinotecan has not been evaluated.

Drug-Drug Interactions

Possible pharmacokinetic interactions of CAMPTOSAR with other concomitantly administered medications have not been formally investigated

CLINICAL STUDIES

In phase I studies of CAMPTOSAR Injection, the maximum-tolerated dose as a single agent in the treatment of patients with solid tumors was 120 to 150 mg/m^2 when administered once weekly for 4 weeks, followed by a 2-week rest period. The dose-limiting toxicities were diarrhea and neutropenia. In one study, use of granulocyte colony-stimulating factor (G-CSF) appeared to increase the tolerated dose from 120 to 145 mg/m^2.

Data from three open-label, phase 2, single-agent clinical studies, involving a total of 304 patients in 59 centers, support the use of CAMPTOSAR in the treatment of patients with metastatic cancer of the colon or rectum that has recurred or progressed following treatment with fluorouracil (5-FU)-based therapy. These studies were designed to evaluate tumor response rate and do not provide information on actual clinical benefit, such as effect on survival and disease related symptoms. In each study, CAMPTOSAR was administered in repeated 6-week courses consisting of a 90-minute intravenous infusion once weekly for 4 weeks, followed by a 2-week rest period. Starting doses of CAMPTOSAR in these trials were 100, 125, or 150 mg/m^2, but the 150-mg/m^2 dose proved poorly tolerated (unacceptably high rates of grade 4 late diarrhea and febrile neutropenia). Study 1 enrolled 48 patients and was conducted under the auspices of a single investigator at several regional hospitals. Study

2 was a multicenter study conducted by the North Central Cancer Treatment Group. All 90 patients enrolled in Study 2 received a starting dose of 125 mg/m^2. Study 3 was a multicenter study that enrolled 166 patients from 30 institutions. The initial dose in Study 3 was 125 mg/m^2 but was reduced to 100 mg/m^2 because the toxicity seen at the 125-mg/m^2 dose was perceived to be greater than that seen in previous studies. All patients in these studies had metastatic colorectal cancer, and the majority had disease that recurred or progressed following a 5-FU based regimen administered for metastatic disease.

The results of the individual studies are shown in the following table:

	Study			
	1	2	3	
Number of Patients	48	90	64	102
Dose (mg/m^2/wk x 4)	125*	125	125	100
Male (%)	54	64	50	49
Age <65 yr (%)	54	54	64	54
Ethnic Origin (%)				
White	79.2	95.6	81.3	91.2
African American	12.5	4.4	10.9	4.9
Hispanic	8.3	0.0	7.8	2.0
Oriental/Asian	0.0	0.0	0.0	2.0
Performance Status 0 (%)	60	38	59	44
Performance Status 1 (%)	38	48	33	51
Performance Status 2 (%)	2	14	9	5
Prior 5-FU Therapy (%)				
For Metastatic Disease	81.3	65.5	73.4	67.7
≤ 6 months after Adjuvant	14.6	6.7	26.6	27.5
> 6 months after Adjuvant	2.1	15.6	0.0	2.0
Classification Unknown	2.1	12.2	0.0	2.9
Primary Tumor %				
Colon	100	71	89	87
Rectum	0	29	11	8
Number of Courses of Camptosar (median)	3.5	3.0	3.0	3.0
Median Dose Intensity† (mg/m^2/wk)	62	56	61	54
Objective Response Rate (%)‡	20.8	13.3	14.1	7.8
[95% CI]	[9.3, 32.3]	[6.3, 20.4]	[5.5, 22.6]	[2.6, 13.1]
Time to Response (median, months)	2.6	2.1	2.8	2.8
Response Duration (median, months)	6.4	5.9	5.6	6.2
Survival (median, months)	10.4	8.1	10.7	9.3

*Nine patients received 150 mg/m^2 as a starting dose; 2 (22.2%) responded to CAMPTOSAR.
†Total dose administered in a course ÷ 6 (number of weeks in a course)
‡There were 2/304 complete responses; the remainder were partial responses.

In the intent-to-treat analysis of the pooled data across all three studies, 193 of the 304 patients began therapy at the recommended starting dose of 125 mg/m^2. Among these 193 patients, 2 complete and 27 partial responses were observed, for an overall response rate of 15.0% (95% Confidence Interval [CI], 10.0% to 20.1%) at this starting dose. A considerably lower response rate was seen with a starting dose of 100 mg/m^2. The majority of responses were observed within the first two courses of therapy, and all but one of the responses were observed by the fourth course of therapy (one response was observed after the eighth course). The response duration (median) for patients beginning therapy at 125 mg/m^2 was 5.8 months (range, 2.6 to 15.1 months).

Response rates to CAMPTOSAR were similar in males and females and among patients older and younger than 65 years. Rates were also similar in patients with cancer of the colon or cancer of the rectum and in patients with single and multiple metastatic sites. Response rate was 18.5% in patients with a performance status of 0 and 7.6% in patients with a performance status of 1 or 2. Patients with a performance status of 3 or 4 have not been studied. Over half of the patients responding to CAMPTOSAR had not responded to prior 5-FU-based treatment given for metastatic disease. Patients who had received previous irradiation to the pelvis also responded to CAMPTOSAR at approximately the same rate as those who had not previously received irradiation.

INDICATIONS AND USAGE

CAMPTOSAR Injection is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy.

CONTRAINDICATIONS

CAMPTOSAR is contraindicated in patients with a known hypersensitivity to the drug.

WARNINGS

Diarrhea:
CAMPTOSAR Injection can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Early diarrhea (occurring during or within 24 hours of administration of CAMPTOSAR) is cholinergic in nature. It can be severe but is usually transient. It may be preceded by complaints of diaphoresis and abdominal cramping. Early diarrhea may be ameliorated by administration of atropine (see PRECAUTIONS, General, for dosing recommendations for atropine).

Late diarrhea (occurring more than 24 hours after administration of CAMPTOSAR) can be prolonged, may lead to dehydration and electrolyte imbalance, and can be life-threatening. Late diarrhea should be treated promptly with loperamide (see PRECAUTIONS, Information for Patients, for dosing recommendations for loperamide). Patients with severe diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. National Cancer Institute (NCI) grade 3 diarrhea is defined as an increase of 7 to 9 stools daily, or incontinence, or severe cramping and NCI grade 4 diarrhea is defined as an increase of $\geq$ 10 stools daily, or grossly bloody stool, or need for parenteral support. If grade

3 or 4 late diarrhea occurs, administration of CAMPTOSAR should be delayed until the patient recovers and subsequent doses should be decreased (See DOSAGE AND ADMINISTRATION).

Myelosupression:
Deaths due to sepsis following severe myelosuppression have been reported in patients treated with CAMPTOSAR. Therapy with CAMPTOSAR should be temporarily discontinued if neutropenic fever occurs or if the absolute neutrophil count drops below 500/mm^3. The dose of CAMPTOSAR should be reduced if there is a clinically significant decrease in the total white blood cell count (<2000/mm^3), neutrophil count (<1000/mm^3), hemoglobin (<8 gm/dL), or platelet count (<100,000/mm^3) (see DOSAGE AND ADMINISTRATION). Routine administration of a colony-stimulating factor (CSF) is not necessary, but physicians may wish to consider CSF use in individual patients experiencing significant neutropenia.

Pregnancy:
CAMPTOSAR may cause fetal harm when administered to a pregnant woman. Radioactivity related to ^{14}C-irinotecan crosses the placenta of rats following intravenous administration of 10 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about 3 and 0.5 times, respectively, the corresponding values in patients administered 125 mg/m^2). Administration of 6 mg/kg/day intravenous irinotecan to rats (which in separate studies produced an irinotecan C_{max} and AUC about 2 and 0.2 times, respectively, the corresponding values in patients administered 125 mg/m^2) and rabbits (about one half the recommended human dose on a mg/m^2 basis) during the period of organogenesis, is embryotoxic as characterized by increased post-implantation loss and decreased numbers of live fetuses. Irinotecan was teratogenic in rats at doses greater then 1.2 mg/kg/day (which in separate studies produced an irinotecan C_{max} and AUC about 2/3 and 1/40th, respectively, of the corresponding values in patients administered 125 mg/m^2) and in rabbits at 6.0 mg/kg/day (about one half the recommended weekly human dose on a mg/m^2 basis). Teratogenic effects included a variety of external, visceral, and skeletal abnormalities. Irinotecan administered to rat dams for the period following organogenesis through weaning at doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights in the offspring. There are no adequate and well-controlled studies of irinotecan in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with CAMPTOSAR.

PRECAUTIONS

General

Care of Intravenous Site:
CAMPTOSAR is administered by intravenous infusion. Care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with sterile water and application of ice are recommended.

Premedication with Antiemetics:

Irinotecan is emetigenic. It is recommended that patients receive premedication with antiemetic agents In clinical studies, the majority of patients received 10 mg of dexamethasone given in conjunction with another type of antiemetic agent, such as a 5-HT_3 blocker (eg, ondansetron or granisetron). Antiemetic agents should be given on the day of treatment, starting at least 30 minutes before administration of CAMPTOSAR. Physicians should also consider providing patients with an antiemetic regimen (eg, prochlorperazine) for subsequent use as needed.

Treatment of Early Diarrhea:
Administration of 0.25 to 1 mg of intravenous atropine should be considered (unless clinically contraindicated) in patients experiencing diaphoresis, abdominal cramping, or early diarrhea (diarrhea occurring during or within 24 hours following administration of CAMPTOSAR).

Patients at Particular Risk:
Physicians should exercise particular caution in monitoring the effects of CAMPTOSAR in the elderly (≥65 years) and in patients who had previously received pelvic/abdominal irradiation (see ADVERSE REACTIONS).

Information for Patients

Patients and patients' caregivers should be informed of the expected toxic effects of CAMPTOSAR, particularly of its gastrointestinal manifestations, such as nausea, vomiting, and diarrhea. Each patient should be instructed to have loperamide readily available and to begin treatment for late diarrhea (occurring more than 24 hours after administration of CAMPTOSAR) 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. One dosage regimen for loperamide used in clinical trials consisted of the following (Note: This dosage regimen exceeds the usual dosage recommendations for loperamide.): 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. During the night, the patient may take 4 mg of loperamide every 4 hours. The patient should also be instructed to notify the physician if diarrhea occurs. Premedication with loperamide is not recommended.

The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to discuss any laxative use.

Patients should consult their physician if vomiting occurs, fever or evidence of infection develops, or if symptoms of dehydration, such as fainting, light-headedness, or dizziness, are noted following therapy with CAMPTOSAR.

Patients should be alerted to the possibility of alopecia.

Laboratory Tests

Careful monitoring of the white blood cell count with differential, hemoglobin, and platelet count is recommended before each dose of CAMPTOSAR.

Drug Interactions

The adverse effects of CAMPTOSAR, such as myelosuppression and diarrhea, would be expected to be exacerbated by other antineoplastic agents having similar adverse effects.

Patients who have previously received pelvic/abdominal irradiation are at increased risk of severe myelosuppression following the administration of CAMPTOSAR. The concurrent administration of CAMPTOSAR with irradiation has not been adequately studied and is not recommended.

Lymphocytopenia has been reported in patients receiving CAMPTOSAR, and it is possible that the administration of dexamethasone as antiemetic prophylaxis may have enhanced the likelihood of this effect. However, serious opportunistic infections have not been observed, and no complications have specifically been attributed to lymphocytopenia.

Hyperglycemia has also been reported in patients receiving CAMPTOSAR. Usually, this has been observed in patients with a history of diabetes mellitus or evidence of glucose intolerance prior to administration of CAMPTOSAR. It is probable that dexamethasone, given as antiemetic prophylaxis, contributed to hyperglycemia in some patients.

The incidence of akathisia in clinical trials was greater (8.5%, 4/47 patients) when prochlorperazine was administered on the same day as CAMPTOSAR than when these drugs were given on separate days (1.3%, 1/80 patients). The 8.5% incidence of akathisia, however, is within the range reported for use of prochlorperazine when given as a premedication for other chemotherapies

It would be expected that laxative use during therapy with CAMPTOSAR would worsen the incidence or severity of diarrhea, but this has not been studied.

In view of the potential risk of dehydration secondary to vomiting and/or diarrhea induced by CAMPTOSAR, the physician may wish to withhold diuretics during dosing with CAMPTOSAR and, certainly, during periods of active vomiting or diarrhea.

Drug-Laboratory Test Interactions

There are no known interactions between CAMPTOSAR and laboratory tests.

Carcinogenesis, Mutagenesis & Impairment of Fertility

Long-term carcinogenicity studies with irinotecan were not conducted. Rats were, however, administered intravenous doses of 2 mg/kg or 25 mg/kg irinotecan once per week for 13 weeks (in separate studies, the 25 mg/kg dose produced an irinotecan C_{max} and AUC that were about 7.0 times and 1.3 times the respective values in patients administered 125 mg/m^2) and were then allowed to recover for 91 weeks. Under these conditions, there was a significant linear trend with dose for the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas. Neither irinotecan or SN-38 was mutagenic in the in vitro Ames assay. Irinotecan was clastogenic both in vitro (chromosome aberrations in Chinese hamster ovary cells) and in vivo (micronucleus test in mice). No significant adverse effects on

fertility and general reproductive performance were observed after intravenous administration of irinotecan in doses of up to 6 mg/kg/day to rats and rabbits. However, atrophy of male reproductive organs was observed after multiple daily irinotecan doses both in rodents at 20 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about 5 and 1 times, respectively, the corresponding values in patients administered 125 mg/m^2) and dogs at 0.4 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about one half and 1/15th, respectively, the corresponding values in patients administered 125 mg/m^2).

Pregnancy

Pregnancy Category D - see WARNINGS.

Nursing Mothers

Radioactivity appeared in rat milk within 5 minutes of intravenous administration of radiolabeled irinotecan and was concentrated up to 65-fold at 4 hours after administration relative to plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving therapy with CAMPTOSAR.

Pediatric Use

The safety and effectiveness of CAMPTOSAR in pediatric patients have not been established.

ADVERSE REACTIONS

US Clinical Trials

In three clinical studies, 304 patients with metastatic carcinoma of the colon or rectum that had recurred or progressed following 5-FU-based therapy were treated with CAMPTOSAR. Seventeen of the patients died within 30 days of the administration of CAMPTOSAR; in five cases (1.6%, 5/304), the deaths were potentially drug-related. These five patients experienced a constellation of medical events that included known effects of CAMPTOSAR. One of these patients died of neutropenic sepsis without fever. Neutropenic fever, defined as NCI grade 4 neutropenia and grade 2 or greater fever, occurred in nine (3.0%) other patients; these patients recovered with supportive care. One hundred and nineteen (39.1%) of the 304 patients were hospitalized a total of 156 times because of adverse events; 81 (26.6%) patients were hospitalized for events judged to be related to administration of irinotecan. The primary reasons for drug-related hospitalization were diarrhea, with or without nausea and/or vomiting (18.4%); neutropenia/leukopenia, with or without diarrhea and/or fever (8.2%); and nausea and/or vomiting (4.9%). Adjustments in the dose of CAMPTOSAR were made during the course of treatment and for subsequent courses based on individual patient tolerance. The first dose of at least one course of CAMPTOSAR was reduced for 67% of patients who began the studies at the 125- mg/m^2 starting dose. Within-course dose reductions were required for 32% of the courses initiated at the 125-mg/m^2 dose level. The most common reasons for dose reduction were late diarrhea, neutropenia, and leukopenia. Thirteen (4.3%) patients discontinued treatment with CAMPTOSAR because of adverse events. The adverse

events in the following table are based on the experience of the 304 patients enrolled in the three studies described in the CLINICAL STUDIES section.

Adverse Events Occurring in >10% of 304 Previously Treated Patients with Metastatic Carcinoma of the Colon or Rectum

Body System & Event	% of Patients Reporting	
	NCI Grades 1-4	NCI Grades 3 & 4
GASTROINTESTINAL		
Diarrhea (late)*	87.8	30.6
7-9 stools/day (grade 3)	—	(16.4)
≥10 stools/day (grade 4)	—	(14.1)
Nausea	86.2	16.8
Vomiting	66.8	12.5
Anorexia	54.9	5.9
Diarrhea (early)†	50.7	7.9
Constipation	29.9	2.0
Flatulence	12.2	0
Stomatitis	11.8	0.7
Dyspepsia	10.5	0
HEMATOLOGIC		
Leukopenia	63.2	28.0
Anemia	60.5	6.9
Neutropenia	53.9	26.3
500 to <1000/mm^3 (grade 3)	—	(14.8)
<500/mm^3 (grade 4)	—	(11.5)
BODY AS A WHOLE		
Asthenia	75.7	12.2
Abdominal cramping/pain	56.9	16.4
Fever	45.4	0.7
Pain	23.7	2.3
Headache	16.8	0.7
Back pain	14.5	1.6
Chills	13.8	0.3
Minor Infection‡	14.5	0
Edema	10.2	1.3
Abdominal Enlargement	10.2	0.3
METABOLIC & NUTRITIONAL		
↓ Body weight	30.3	0.7
Dehydration	14.8	4.3
↑ Alkaline phosphatase	13.2	3.9
↑ SGOT	10.5	1.3
DERMATOLOGIC		
Alopecia	60.5	NA§
Sweating	16.4	0
Rash	12.8	0.7
RESPIRATORY		
Dyspnea	22.0	3.6
↑ Coughing	17.4	0.3
Rhinitis	15.5	0
NEUROLOGIC		
Insomnia	19.4	0
Dizziness	14.6	0
CARDIOVASCULAR		
Vasodilation (Flushing)	11.2	0

*Occurring >24 hours after administration of CAMPTOSAR
†Occurring ≤24 hours after administration of CAMPTOSAR
‡Primarily upper respiratory infections.
§ Not applicable; complete hair loss = NCI grade 2.

Gastrointestinal: Diarrhea, nausea, and vomiting were common adverse events following treatment with CAMPTOSAR and could be severe. These events occurred early (during or within 24 hours of administration of CAMPTOSAR) or late (more than 24 hours after administration of CAMPTOSAR). The median time to onset of late diarrhea was 11 days following administration of CAMPTOSAR. For patients starting treatment at the 125-mg/m^2 dose, the median duration of any grade of diarrhea was 3 days. Among those patients treated at the 125-mg/m^2 dose who experienced grade 3 or 4 diarrhea, the median duration of the entire episode of diarrhea was 7 days. The frequency of late grade 3 or 4 diarrhea was somewhat greater in patients starting treatment at 125 mg/m^2 than in patients given a 100 mg/m^2 starting dose (34% vs 24%). The frequency of grade 3 and 4 late diarrhea was significantly greater in patients ≥65 years than in patients <65 years of age (39.8% versus 23.4%; p = 0.0025). In Study 2, the frequency of grade 3 and 4 late diarrhea was significantly greater in male than in female patients (43.1% versus 15.6%; p=0.01). However, there were no gender differences in the frequency of grade 3 and 4 late diarrhea in the other two studies.

Hematology: CAMPTOSAR commonly caused neutropenia, leukopenia (including lymphocytopenia), and anemia. Serious thrombocytopenia was uncommon. Neutropenic fever (concurrent NCI grade 4 neutropenia and fever of grade 2 or greater) occurred in 3.0% of the patients; 5.6% of patients received G-CSF for the treatment of neutropenia. NCI grade 3 or 4 anemia was noted in 6.9% of the patients. Blood transfusions were given to 9.9% of the patients. The frequency of grade 3 and 4 neutropenia was significantly higher in patients who received previous pelvic/abdominal irradiation than in those who had not received irradiation (48.1% versus 24.1%; p = 0.0356). There were no significant differences in the frequency of grade 3 and 4 neutropenia by age or gender.

Body as a Whole: Asthenia, fever, and abdominal pain were the most common events of this type

Hepatic: NCI grade 3 or 4 liver enzyme abnormalities were observed in fewer than 10% of patients. These events typically occurred in patients with known hepatic metastases.

Dermatologic: Alopecia was reported during treatment with CAMPTOSAR. Rashes have also been reported but did not result in discontinuation of treatment.

Respiratory: Severe pulmonary events were infrequent; NCI grade 3 or 4 dyspnea was reported in 3.6% of patients. Over half the patients with dyspnea had lung metastases; the extent to which malignant pulmonary involvement or other preexisting lung disease may have contributed to dyspnea in these patients is unknown.

Neurologic: Insomnia and dizziness were observed, but were not usually considered to be directly related to the administration of CAMPTOSAR. Dizziness may sometimes have represented symptomatic evidence of orthostatic hypotension in patients with dehydration

Cardiovascular: Vasodilation (flushing) has been observed during administration of CAMPTOSAR but has not required intervention.

Non-US Clinical Trials

Irinotecan has been studied in over 1100 patients in Japan and in over 400 patients in France. Patients in these studies had a variety of tumor types, including cancer of the colon or rectum, and were treated with several different doses and schedules. In general, the types of toxicities observed were similar to those seen in US trials with CAMPTOSAR. There is some information from Japanese trials that patients with considerable ascites or pleural effusions were at increased risk for neutropenia or diarrhea. A potentially life-threatening pulmonary syndrome, consisting of dyspnea, fever, and a reticulonodular pattern on chest x-ray, was observed in a small percentage of patients in early Japanese studies. The contribution of irinotecan to these preliminary events was difficult to assess because these patients also had lung tumors and some had preexisting nonmalignant pulmonary disease. As a result of these observations, however, clinical studies in the United States have enrolled few patients with compromised pulmonary function, significant ascites, or pleural effusions.

OVERDOSAGE

In US phase I trials, single doses of up to 345 mg/m^2 of irinotecan injection were administered to patients with various cancers. Single doses of up to 750 mg/m^2 of irinotecan have been given in non-US trials. The adverse events in these patients were similar to those reported with the recommended dosage and regimen. There is no known antidote for overdosage of CAMPTOSAR. Maximum supportive care should be instituted to prevent dehydration due to diarrhea and to treat any infectious complications.

Lethality was observed after single intravenous irinotecan doses of approximately 111 mg/kg in mice and 73 mg/kg in rats (approximately 2.6 and 3.4 times the recommended human dose of 125 mg/m^2, respectively). Death was preceded by cyanosis, tremors, respiratory distress, and convulsions.

DOSAGE AND ADMINISTRATION

Starting Dose and Dose Modifications

The recommended starting dose of CAMPTOSAR Injection is 125 mg/m^2. All doses should be administered as an intravenous infusion over 90 minutes (see Preparation of Infusion Solution below). The recommended treatment regimen (one treatment course) is 125 mg/m^2 administered once weekly for 4 weeks, followed by a 2-week rest period. Thereafter, additional courses of treatment may be repeated every 6 weeks (4 weeks on therapy, followed by 2 weeks off therapy). Subsequent doses should be adjusted to as high as 150 mg/m^2 or to as low as 50 mg/m^2 in 25- to 50-mg/m^2 increments depending upon individual patient tolerance of treatment (see table below). Provided intolerable toxicity does not develop, treatment with additional courses of CAMPTOSAR may be continued indefinitely in patients who attain a response or in patients whose disease remains stable. Patients should be carefully monitored for toxicity.

The table below describes the recommended dose modifications during a course of therapy and at the start of each subsequent course of therapy. These recommendations are based on toxicities commonly observed with the administration of CAMPTOSAR. Therapy with CAMPTOSAR should be interrupted when grade 3 or 4 late diarrhea occurs (see PRECAUTIONS, Information for Patients) or when other intolerable toxicity is observed. Dose modifications for hematologic toxicities other than neutropenia (eg, leukopenia, anemia or thrombocytopenia, and platelets) during a course of therapy and at the start of a subsequent course of therapy are the same as recommended for neutropenia. Dose modifications for nonhematologic toxicities other than diarrhea (nausea, vomiting, etc) during a course of therapy are the same as those recommended for diarrhea. At the start of a subsequent course of therapy, the dose of CAMPTOSAR should be decreased by 25 mg/m^2, compared to the initial dose of the previous course, for other NCI grade 2 or by 50 mg/m^2 for other grade 3 or 4 nonhematologic toxicities. All dose modifications should be based on the worst preceding toxicity. A new course of therapy should not begin until the granulocyte count has recovered to $\geq 1500/mm^3$ and the platelet count has recovered to $\geq 100,000/mm^3$ and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicity. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing CAMPTOSAR.

Recommended Dose Modifications†

A new course of therapy should not begin until the granulocyte count has recovered to ≥1500/mm³, and the platelet count has recovered to ≥100,000/mm³, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing CAMPTOSAR.		
Toxicity NCI Grade* (Value)	**During a Course of Therapy†**	**At the Start of the Next Courses of Therapy† (After Adequate Recovery), Compared to the Starting Dose in the Previous Course**
No toxicity	Maintain dose level	↑ 25 mg/m² up to a maximum dose of 150 mg/m²
Neutropenia 1 (1500 to 1900/mm³) 2 (1000 to 1400/mm³) 3 (500 to 900/mm³) 4 (<500/mm³)	Maintain dose level ↓ 25 mg/m² Omit dose, then ↓ 25 mg/m² when resolved to ≤ grade 2 Omit dose, then ↓ 50 mg/m² when resolved to ≤ grade 2	Maintain dose level Maintain dose level ↓ 25 mg/m² ↓ 50 mg/m²
Neutropenic fever (grade 4 neutropenia & ≥grade 2 fever)	Omit dose, then ↓ 50 mg/m² when resolved	↓ 50 mg/m²
Other hematologic toxicities	Dose modifications for leukopenia, thrombocytopenia, and anemia during a course of therapy and at the start of subsequent courses of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.	
Diarrhea 1 (2-3 stools/day > pretx‡) 2 (4-6 stools/day > pretx) 3 (7-9 stools/day > pretx) 4 (≥ 10 stools/day > pretx)	Maintain dose level ↓ 25 mg/m² Omit dose, then ↓ 25 mg/m² when resolved to ≤ grade 2 Omit dose, then ↓ 50 mg/m² when resolved to ≤ grade 2	Maintain dose level Maintain, if the only grade 2 tox§ ↓ 25 mg/m², if the only grade 3 tox ↓ 50 mg/m²
Other nonhematologic toxicities 1 2 3 4	Maintain dose level ↓ 25 mg/m² Omit dose, then ↓ 25 mg/m² when resolved to ≤ grade 2 Omit dose, then ↓ 50 mg/m² when resolved to ≤ grade 2	Maintain dose level ↓ 25 mg/m² ↓ 50 mg/m² ↓ 50 mg/m²

*National Cancer Institute Common Toxicity Criteria.
†All dose modifications should be based on the worst preceding toxicity
‡Pretreatment
§Toxicity

It is recommended that patients receive premedication with antiemetic agents (see PRECAUTIONS, General).

Preparation & Administration Precautions

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions prepared from CAMPTOSAR Injection. The use of gloves is recommended. If a solution of CAMPTOSAR contacts the skin, wash the skin immediately

and thoroughly with soap and water If CAMPTOSAR contacts the mucous membranes, flush thoroughly with water Several published guidelines for handling and disposal of anticancer agents are available.[1-7]

Preparation of Infusion Solution

Inspect vial contents for particulate matter and repeat inspection when drug product is withdrawn from vial into syringe.

CAMPTOSAR Injection must be diluted prior to infusion. CAMPTOSAR should be diluted in 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final concentration range of 0 12 to 1.1 mg/mL. In most clinical trials, CAMPTOSAR was administered in 500 mL of 5% Dextrose Injection, USP.

The solution is physically and chemically stable for up to 24 hours at room temperature (approximately 25°C) and in ambient fluorescent lighting. Solutions diluted in 5% Dextrose Injection, USP, and stored at refrigerated temperatures (approximately 2° to 8°C), and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using 0.9% Sodium Chloride Injection, USP, is not recommended due to a low and sporadic incidence of visible particulates. **Freezing CAMPTOSAR and admixtures of CAMPTOSAR may result in precipitation of the drug and should be avoided.** Because of possible microbial contamination during dilution, it is advisable to use the admixture within 24 hours if refrigerated (2° to 8°C, 36° to 46°F) or within 6 hours if kept at room temperature (15° to 30°C, 59° to 86°F).

Other drugs should not be added to the infusion solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

Each mL of CAMPTOSAR Injection contains 20 mg irinotecan (on the basis of the trihydrate salt), 45 mg sorbitol, and 0.9 mg lactic acid. When necessary, pH has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid.

CAMPTOSAR Injection is available as single-dose vials in the following package size:

5-mL amber glass vial NDC 0009-7529-01

This is packaged in a backing/plastic blister to protect against inadvertent breakage and leakage. **The vial should be inspected for damage and visible signs of leaks before removing the backing/plastic blister. If damaged, incinerate the unopened package.**

Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light. It is recommended that the vial (and backing/plastic blister) should remain in the carton until the time of use.

Caution: Federal law prohibits dispensing without prescription.

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.

2. AMA Council Report. Guidelines for handling parenteral antineoplastics. JAMA 1985; 253(11):1590-2.

3. National Study Commission on Cytotoxic Exposure. Recommendations for handling cytotoxic agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.

4. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. M J Australia 1983;1:426-8.

5. Jones RB, et. al. Safe handling of chemotherapeutic agents: a report from the Mount Sinai Medical Center. CA-A Cancer J for Clinicians, 1983;Sept./Oct., 258-63.

6. American Society of Hospital Pharmacists Technical Assistance Bulletin on handling cytotoxic and hazardous drugs. Am J Hosp Pharm 1990;47:1033-49.

7. OSHA work-practice guidelines for personnel dealing with cytotoxic (antineoplastic) drugs Am J Hosp Pharm 1986;43:1193-1204.

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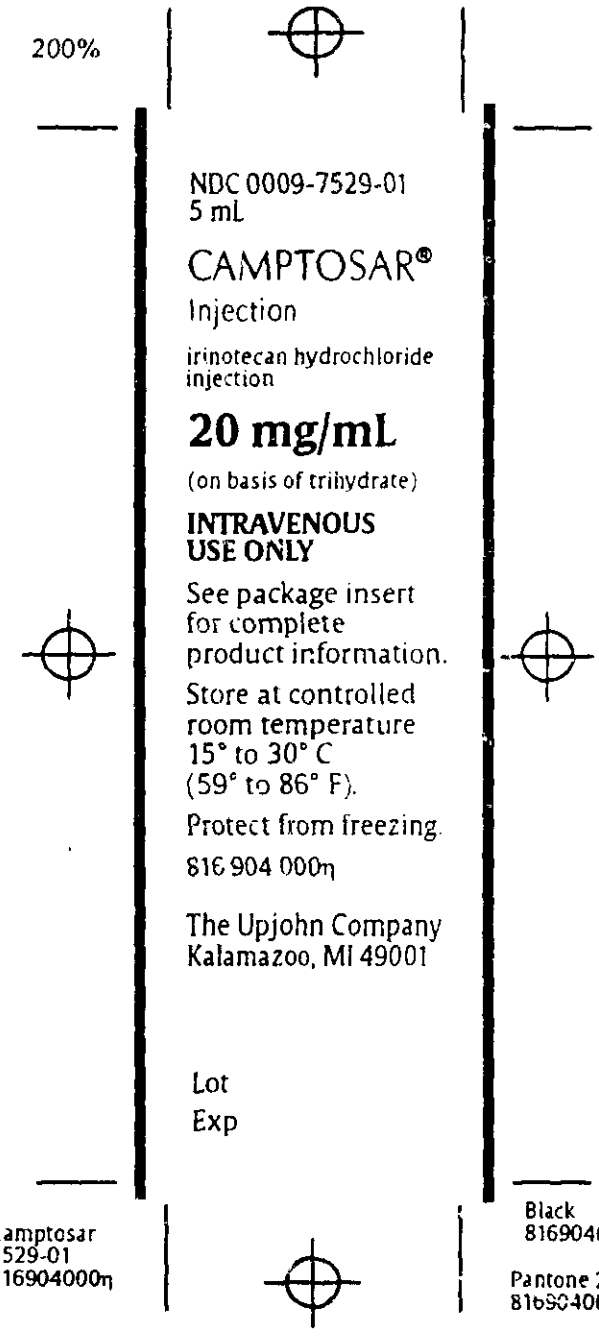
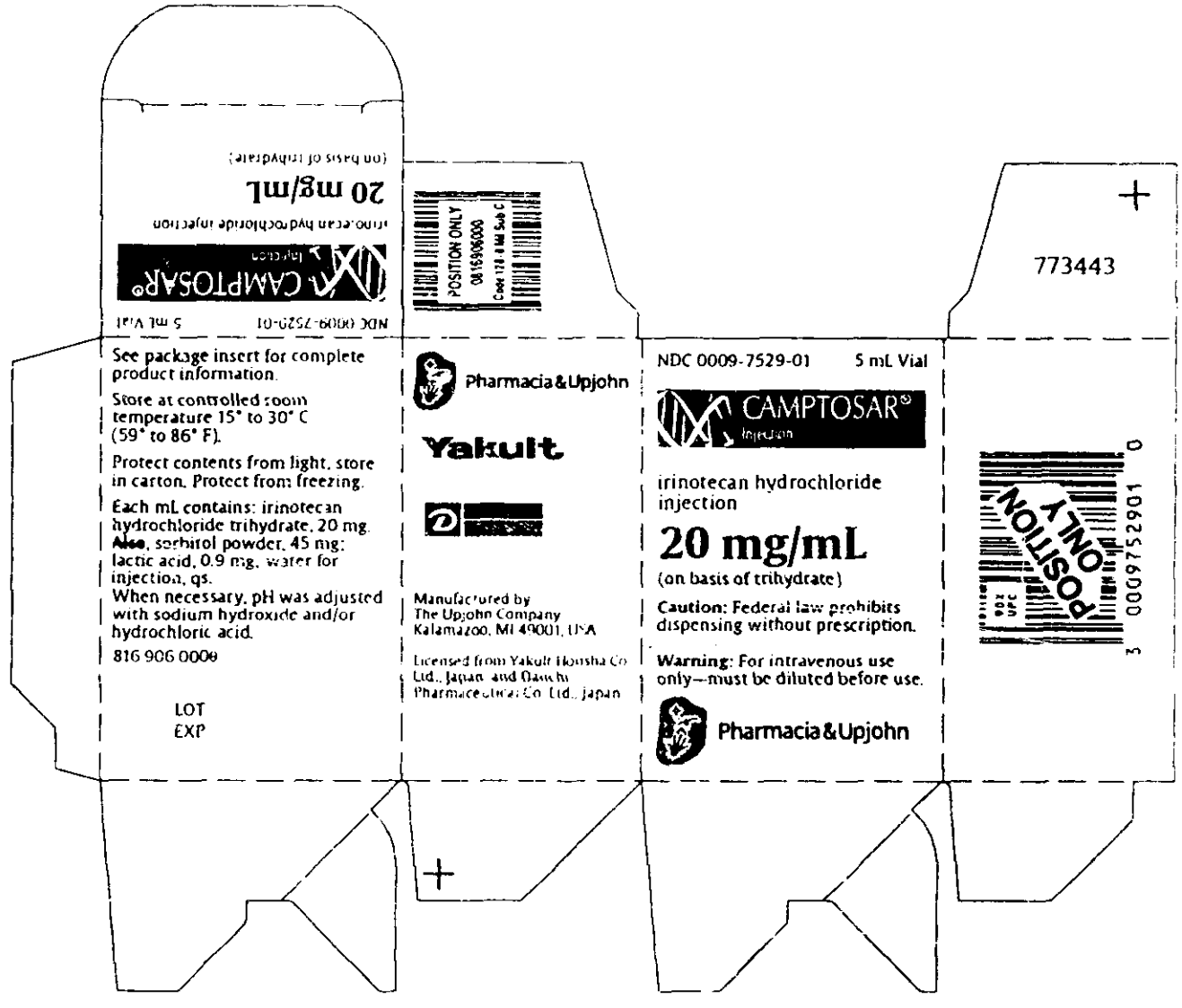

200%
NDC 0009-7529-01
5 mL
CAMPTOSAR®
Injection
irinotecan hydrochloride
injection
20 mg/mL
(on basis of trihydrate)
INTRAVENOUS
USE ONLY
See package insert
for complete
product information.
Store at controlled
room temperature
15° to 30° C
(59° to 86° F).
Protect from freezing.
816 904 000η
The Upjohn Company
Kalamazoo, MI 49001
Lot
Exp
EDP#690492
2.6875x.75 in.
Imp. area
.4375x.75 in.
Location:
left side
Camptosar
7529-01
816904000η
Black
816904000η
Pantone 287
816904000η

Vial Label



Camptosar
CPT-11
7529-01
816906000

Pantone 287

Plastic Blister

200%

NDC 0009-7529-01 5 mL

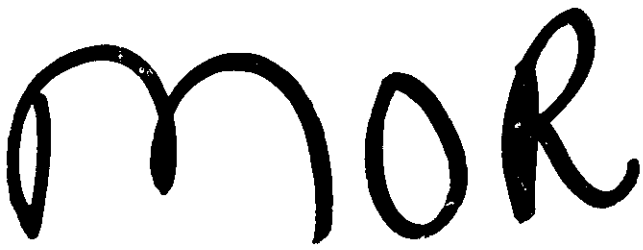
CAMPTOSAR® 20 mg/mL
Injection

irinotecan hydrochloride injection
Store at controlled room
temperature 15° to 30° C
(59° to 86° F)
Protect from freezing
IF CONTENTS ARE DAMAGED
AND/OR LEAKING INCINERATE
ENTIRE PACKAGE
The Upjohn Company

Printed Foil
EDP#691883
2.511 x 1.656 IN

Camptosar
7529-01

Black
8169050008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MEDICAL OFFICER REVIEW OF PROPOSED DRAFT LABELING

NDA #: 20-571

Drug Name: CAMPTOSAR™ Injection (Irinotecan HCl Injection)

Applicant: The Upjohn Company **Date Submitted:** 12/28/95

LABELING REVIEW

General Deficiencies (See attached marked-up labeling for specific changes)

1. Boxed WARNING is recommended.

2. CLINICAL STUDIES Section:

   a. Additional details regarding the design of the Phase 2 studies and rationale for the different doses has been included.

   b. Response results have been revised to be consistent with the information in the sponsor's "efficacy update" submitted April 15, 1996.

   c. Information regarding clinical benefit have been deleted because the NDA studies were not well-controlled to evaluate those parameters.

3. WARNINGS Section:

   Some of the information regarding diarrhea has been clarified.

4. PRECAUTIONS Section:

   In the Pediatric Use subsection, "the pediatric population" should be changed to "pediatric patients" to be consistent with current labeling guidelines.

5. ADVERSE REACTIONS Section:

   a. This section should be revised to include information on hospitalizations. The number of deaths potentially related to Irinotecan is corrected to based on the FDA assessment of the data in the NDA.

   b. The median duration of grade 3 or 4 diarrhea should be stated.

6. DOSAGE AND ADMINISTRATION Section:

   a. The Starting Dose and Dose Modifications subsection should be revised to emphasize that patients should recover from dose-limiting toxicities prior to beginning the next cycle of therapy.

7. REFERENCES Section:

   References 1 to 4 should be omitted.

VIII. RECOMMENDATIONS

The recommended changes in the submitted draft labeling based on the medical review of the NDA are shown in the marked-up version on the next page. These changes should be incorporated with those recommended by Chemistry, Biopharmacology, and Pharmacology/Toxicology. If the sponsor agrees to make the recommended changes, the labeling is otherwise approvable.

Anthony J. Murgo, M.D., M.S
Medical Officer
Division of Oncology
and Pulmonary Drug Products
HFD-150
May 29, 1996

JR Johnson, MD
5-30-96

cc:
Orig. NDA #20-571
HFD-150/Division File
HFD-150/A.J. Murgo, M.D.
HFD-151/L. Vaccari, R.N. (CSO)
HFD-710/T. Koutsoukos, Ph.D.
HFD-150/I. Chico, M.D.
HFD-150/P. Andrews, Ph.D.
HFD-860/G. Williams, Ph.D.

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FDA changes: Redline = additions; Strike-out = deletions
Comments regarding changes are in the footnotes.

CAMPTOSAR™
brand of Irinotecan hydrochloride injection

WARNINGS

1. CAMPTOSAR should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.
2. CAMPTOSAR can induce both an early and a late form of diarrhea that appear to be mediated by different mechanisms. Both forms of diarrhea may be severe. Early diarrhea (occurring during or within 24 hours of CAMPTOSAR administration) may be preceded by complaints of diaphoresis and abdominal cramping. There is evidence that early diarrhea may be ameliorated by administration of atropine. Late diarrhea (occurring more than 24 hours after administration of CAMPTOSAR) may be associated with dehydration and electrolyte imbalance and can be potentially life-threatening. Late diarrhea should be treated promptly with loperamide or other similar antidiarrheal agents. Administration of CAMPTOSAR should be interrupted in the presence of severe diarrhea, and patients with severe diarrhea should be carefully monitored and provided with fluid and electrolyte replacement if dehydration occurs. (see WARNINGS section).
3. Severe myelosuppression may occur (see WARNINGS Section).

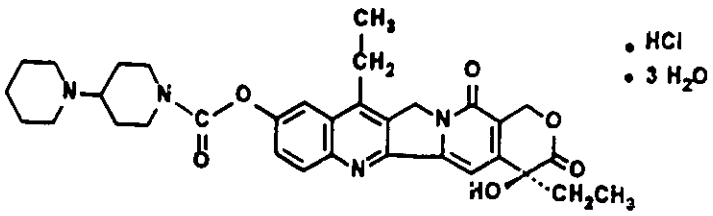
[1]Boxed WARNING should be included.

DESCRIPTION

CAMPTOSAR Injection (Irinotecan hydrochloride injection) is an antineoplastic agent, clinically investigated as CPT-11.

CAMPTOSAR is supplied as a sterile, pale yellow, clear, nonaqueous solution. It is available in 100-mg, single-dose, 5-mL vials. Each milliliter of solution contains 20 mg of Irinotecan trihydrate, 45 mg of sorbitol NF powder, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.0 to 4.0 with sodium hydroxide and hydrochloric acid. CAMPTOSAR is intended for dilution with 5% Dextrose Injection, USP (D5W) or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion.

Irinotecan is a semisynthetic derivative of camptothecin, an alkaloid extract from plants such as *Camptotheca acuminata*. The chemical name is (4*S*)-4,11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino)carbonyloxy]-1*H*-pyrano[3',4':6,7] indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)dione hydrochloride trihydrate. Its structural formula is as follows:



Irinotecan Hydrochloride

Irinotecan hydrochloride is a pale yellow to yellow crystalline powder, with the empirical formula $C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$ and a molecular weight of 677.19. It is soluble in water but sparingly soluble in organic solvents.

CLINICAL PHARMACOLOGY

Irinotecan is a derivative of camptothecin and belongs to a new class of cytotoxic chemotherapeutic agents with a unique mechanism of action. These drugs interact specifically with the enzyme topoisomerase I and are known as "topoisomerase I inhibitors." The function of topoisomerases is to maintain the proper three-dimensional conformation of DNA by removing supercoils (twists and kinks) during DNA replication and transcription.[1]– [2] The cytotoxicity of the camptothecins is due to double-stranded DNA damage produced when, during DNA synthesis (the S-phase), DNA replication enzymes collide with a ternary complex of drug, DNA, and topoisomerase I.[3]–This drug-induced damage is not efficiently repaired and apoptosis, a form of programmed cell death, ensues.

The therapeutic effects of Irinotecan have been attributed primarily to its active metabolite SN-38. Biochemical studies and in vitro cytotoxicity assays in human and rodent tumor cell lines consistently show SN-38 to be at least 1000-fold more potent as a topoisomerase I inhibitor than Irinotecan.[4]–SN-38 is formed from Irinotecan by

---

[2]References 1 to 4 should be deleted.

carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and the dipiperidino side chain. Thus, Irinotecan serves as a water-soluble prodrug of the lipophilic compound SN-38. Both Irinotecan and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. A pH-dependent equilibrium exists between the two forms such that an acid pH promotes the formation of the lactone while a more basic pH yields the hydroxy acid anion form.[4]

Irinotecan demonstrated marked activity when administered at well-tolerated doses to rodents bearing transplanted malignant tumors. In various models, activity was manifested by growth inhibition, shrinkage, or complete remission of tumors; prolongation of survival; and inhibition of metastasis. Antitumor activity was observed in mice bearing cancers of rodent origin and in human carcinoma xenografts of various histological types. Irinotecan was also active in multidrug-resistant tumor models that respond poorly to various clinically used drugs.

Pharmacokinetics

After intravenous infusion of CAMPTOSAR in humans, Irinotecan plasma concentrations decline in a multiexponential manner with a mean terminal elimination half-life of about 6 hours. The average systemic clearance of Irinotecan is approximately 13 L/hr/m^2 for total Irinotecan and 45 L/hr/m^2 for the lactone form. Although the pharmacokinetics of Irinotecan are highly variable among patients, they are linear with respect to the dose of CAMPTOSAR solution over the dose range of 50 to 350 mg/m^2. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of CAMPTOSAR. The mean terminal half-life of the total and lactone forms of SN-38 are slightly longer than corresponding values for Irinotecan (13.0 versus 7.9 hr for the total, and 11.5 versus 6.3 hr for the lactone). Maximum plasma SN-38 concentrations are approximately 2 to 5% of peak Irinotecan concentrations, while SN-38 area under the curve values are about 2 to 8% of those observed for Irinotecan.

Pharmacokinetic parameters for Irinotecan and SN-38 following 90-minute infusions of CAMPTOSAR at dose levels of 100 and 125 mg/m^2 were determined in a phase II study in patients with metastatic carcinoma of the colon or rectum and are summarized in the following Table:

Summary of Mean (± Standard Deviation) Irinotecan and SN-38 Pharmacokinetic Parameters in Patients With Metastatic Carcinoma of the Colon and Rectum

Dose (mg/m^2)	Irinotecan					SN-38		
	C_{max} (µg/mL)	AUC_{0-24} (µg·hr/mL)	$t_{½}$ (hr)	V_{area} (L/m^2)	CL (L/hr/m^2)	C_{max} (ng/mL)	AUC_{0-24} (ng·hr/mL)	$t_{½}$ (hr)
100 (N=98)	1.29 ± 0.488	8.20 ± 3.19	5.7	107 ± 29.4	13.2 ± 4.32	21.8 ± 10.1	206 ± 104	9.8
125 (N=64)	1.66 ± 0.797	10.2 ± 3.27	5.7	110 ± 48.5	13.3 ± 6.01	26.3 ± 11.9	229 ± 108	9.8

C_{max} - Maximum plasma concentration.
AUC_{0-24} - Area under the plasma concentration-time curve from time 0 to 24 hours after the end of the 90-minute infusion.
$t_{½}$ - Harmonic mean half-life.
V_{area} - Volume of distribution.
CL - Total systemic clearance.

Distribution: Irinotecan is extensively distributed to body tissues; estimates of the mean steady-state volume of distribution range from 105 L/m^2 to 266 L/m^2. Irinotecan exhibits moderate plasma protein binding (30 to 68% bound) over the concentration range achieved in clinical studies. SN-38 is highly bound to human plasma proteins (approximately 95% bound). The major plasma protein to which Irinotecan and SN-38 bind is albumin.[4]

Metabolism: The metabolic conversion of Irinotecan to SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver. SN-38 subsequently undergoes conjugation to form a glucuronide metabolite (SN-38 glucuronide). SN-38 was consistently at least 1000-fold more potent than Irinotecan and 100-fold more potent than SN-38 glucuronide in cytotoxicity assays using various lines of human and rodent tumor cells cultured in vitro.

Excretion: The disposition of Irinotecan has not been fully elucidated in humans. The urinary excretion of Irinotecan (11 to 20%), SN-38 (<1%), and SN-38 glucuronide (3%) is low. Thus, renal excretion does not represent a major route of elimination for Irinotecan and its known major circulating metabolites.

The cumulative biliary and urinary excretion of Irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of CAMPTOSAR in two patients ranged from approximately 25% (100 mg/m^2) to 50% (300 mg/m^2).

Pharmacokinetics in Special Populations

Geriatric: In a clinical trial of CAMPTOSAR in patients with metastatic carcinoma of the colon and rectum, the mean (± SD) systemic clearance of Irinotecan was 11.8 ± 3.50 L/hr/m^2 in 67 patients who were 65 years or older (mean, 71 ± 5 years) and 14.3 ± 5.74 L/hr/m^2 in 95 patients younger than 65 years (mean, 52 ± 10 years). The terminal half-life of Irinotecan was 6.0 hours in patients who were 65 years or older and 5.5 hours in patients younger than 65 years. Dose-normalized area under the curve ($AUC_{0\text{-}24}$) for SN-38 in patients who were at least 65 years of age was 11% higher than the $AUC_{0\text{-}24}$ determined in patients younger than 65 years.

Pediatric: The pharmacokinetics of Irinotecan have not been studied in the pediatric population.

Gender: The pharmacokinetics of Irinotecan do not appear to be influenced by gender. In clinical trials of CAMPTOSAR in patients with metastatic carcinoma of the colon or rectum who received a dose of 100 mg/m^2 or 125 mg/m^2, the mean (± SD) systemic clearance of Irinotecan was 13.6 ± 4.76 L/hr/m^2 in 80 male patients (mean age, 60 ± 11 years) and 12.9 ± 5.33 L/hr/m^2 in 82 female patients (mean age, 60 ± 13 years). The dose-normalized $AUC_{0\text{-}24}$ for SN-38 was 200 ± 95.9 ng•hr/mL in male patients and 194 ± 99.4 ng•hr/mL in female patients.

Race: The potential influence of race on the pharmacokinetics of Irinotecan has not been evaluated.

Hepatic Insufficiency: The influence of severe hepatic insufficiency on the pharmacokinetic characteristics of Irinotecan and its metabolites has not been formally studied. All patients with pharmacokinetic assessments in US clinical trials generally

had adequate liver function as measured by serum levels of hepatic enzymes and bilirubin. Among these patients with metastatic carcinoma of the colon or rectum, 77.2% had liver metastases and 22.8% did not have liver metastases. Irinotecan and SN-38 area-under-the-curve values were approximately 20% lower in patients without liver involvement by tumor than were values for patients with liver metastases.

Renal Insufficiency: Although the pharmacokinetics of Irinotecan have not been formally examined in patients with renal insufficiency, alterations in renal function would not be expected to have a major influence on the pharmacokinetics since renal excretion does not represent a major route of elimination for Irinotecan or its known major circulating metabolites.

Drug-Drug Interactions

The effect of the order of administration of CAMPTOSAR either immediately before or after fluorouracil (5-FU) and leucovorin has been studied. Mean Irinotecan and SN-38 pharmacokinetic parameters were within 10% of corresponding values observed when CAMPTOSAR was administered alone. Possible pharmacokinetic interactions of CAMPTOSAR with other concomitantly administered medications have not been formally investigated.

CLINICAL STUDIES

In a phase I study, the maximum tolerated dose of CAMPTOSAR as a single agent in the treatment of patients with solid tumors was 150 mg/m^2 when administered once weekly for 4 weeks, followed by a 2-week rest period. The dose-limiting toxicity was diarrhea. In a second phase I study of the same regimen, the maximum tolerated dose of CAMPTOSAR was 120 mg/m^2 without and 145 mg/m^2 with coadministration of G-CSF. The dose-limiting toxicities in this study were diarrhea and neutropenia.

Data from three open-label phase II [3] single-agent clinical studies, involving a total of 304 patients in 59 centers, support the use of CAMPTOSAR in the treatment of patients with metastatic cancer of the colon or rectum that has recurred or progressed following treatment with 5-FU-based therapy. In each study, CAMPTOSAR was administered in repeated 6-week courses comprising 90-minute IV infusions once weekly for 4 weeks, followed by a 2-week rest period. Starting doses of CAMPTOSAR in these trials were 100, 125, or 150 mg/m^2. Study I enrolled 48 patients and was conducted under the auspices of one investigator at several San Antonio regional institutions. This study initially used a starting dose of 150 mg/m^2. However, after nine patients had been enrolled, this dose level was found to have an unacceptably high rate of grade 4 late diarrhea and neutropenic fever. The subsequent 39 patients were treated at a starting dose of 125 mg/m^2. Study II was a multicenter study conducted by the North Central Cancer Treatment Group. All 90 patients enrolled in Study II received a starting dose of 125 mg/m^2. Study III a multicenter study that enrolled 166 patients and was conducted at 30 institutions. The first 64 patients in Study III received a starting dose of 125 mg/m^2. The starting dose for the subsequent 102 patients was reduced to 100 mg/m^2 because the toxicity seen at the 125 mg/m^2 dose was perceived to be greater than that seen in previous studies. [4]

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[3] Describe the design of the studies as open-label phase 2.

[4] Provides the rationale for the different doses utilized.

In the intent-to-treat analysis of the pooled data across all three studies, 193 of the 304 patients began therapy at the recommended starting dose of 125 mg/m^2. Among these 193 patients, 2 complete and 27 partial responses were observed for an overall response rate of 15.0% (95% Confidence Interval (CI), 10.0 to 20.1%) at this starting dose. The majority of responses were observed within the first two courses of therapy, and all of the responses were observed by the fourth course of therapy. The median duration of response for patients beginning therapy at 125 mg/m^2 was 5.8 months (range, 2.6 to 15.1 months).[5]

The individual by-study results for the overall intent-to-treat response rates are as follows: In Study 1 (N=48), the overall response rate was 20.8% (95% CI, 9.3 to 32.3%) for patients receiving a starting dose of 125 or 150 mg/m^2. Only nine patients were treated at the 150-mg/m^2 starting dose due to toxicity concerns. In Study 2 (N=90), the overall response rate was 13.3% (95% CI, 6.3 to 20.4%)[7] for patients receiving a starting dose of 125 mg/m^2. In Study 3, the overall response rate for patients receiving a starting dose of 125 mg/m^2 (N=64) was 14.1% (95% CI, 5.5 to 22.6%)[8] ; among patients in this study receiving a starting dose of 100 mg/m^2 (N=102), the response rate was somewhat lower at 7.8% (95% CI, 2.6 to 13.1%).

Response to CAMPTOSAR was observed in males and in females and among patients of all ages. Patients with cancer of the colon or cancer of the rectum responded to CAMPTOSAR, and responses occurred both in patients with single and multiple metastatic sites. Patients responded to CAMPTOSAR regardless of whether prior 5-FU treatment had been given as adjuvant therapy or for metastatic disease. Over half of the patients responding to CAMPTOSAR had not had responses to prior 5-FU-based treatment given for metastatic disease.

Patients who had received previous irradiation to the pelvis also responded to CAMPTOSAR.

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[5]Median response duration replaced with that from the April 15, 1996 update.

[6]The clinical relevance of this information is not established from the results of the phase II studies.

[7]According to FDA review of the NDA, one of the patients in Study 0003R (9015687) did not meet the criteria for response. However, we will allow the sponsor to include the results based on their analysis of the response data.

[8]Response rate is revised to include the additional responder (pt. 304) confirmed in the April 15, 1996 update..

[9]There are not sufficient data to support this claim and the information is superfluous.

INDICATIONS AND USAGE

CAMPTOSAR is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy.

CONTRAINDICATIONS

CAMPTOSAR is contraindicated in patients with a known hypersensitivity to the drug.

WARNINGS

CAMPTOSAR can induce both an early and a late form of diarrhea that appear to be mediated by different mechanisms. Early diarrhea (occurring during or within 24 hours of CAMPTOSAR administration) is cholinergic in nature. It can be severe but is usually transient. It may be preceded by complaints of diaphoresis and abdominal cramping. There is evidence that early diarrhea may be ameliorated by administration of atropine (see PRECAUTIONS, General, for dosing recommendations for atropine).

Late diarrhea (occurring more than 24 hours after administration of CAMPTOSAR) may be associated with dehydration and electrolyte imbalance and can be potentially life-threatening. Late diarrhea should be treated promptly with loperamide or other similar antidiarrheal agents (see PRECAUTIONS, Information for Patients, for dosing recommendations for loperamide). **If late diarrhea persists for longer than 3 days despite treatment with loperamide, therapy with CAMPTOSAR should be discontinued and the dose of CAMPTOSAR should be decreased once the patient has recovered (see DOSAGE AND ADMINISTRATION).** Patients with severe diarrhea should be carefully monitored and provided with fluid and electrolyte replacement if dehydration occurs. Administration of CAMPTOSAR should be interrupted in the presence of National Cancer Institute (NCI) grade 3 or 4 late diarrhea **(grade 3 diarrhea = increase of 7-9 stools daily, or incontinence, or severe cramping; grade 4 diarrhea = increase of ≥ 10 stools daily, or grossly bloody stool, or need for parenteral support).**

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[10]Information regarding clinical benefit should be deleted since the NDA studies were not well controlled to adequately evaluate these parameters.

[11]Moved to Boxed WARNINGS

[12]The paragraph has been restructured for clarity. Definitions of grade 3 and 4 diarrhea according to the NCI CTC are provided.

Deaths due to sepsis following severe myelosuppression have been reported in patients treated with CAMPTOSAR. Therapy with CAMPTOSAR should be temporarily discontinued if neutropenic fever occurs or if the absolute neutrophil count drops below 500/mm^3. The dose of CAMPTOSAR should be reduced if there is a clinically significant decrease in the total white blood cell count (< 2000/mm^3), neutrophil count (< 1000/mm^3), hemoglobin (< 8 gm/dL), or platelet count (< 100,000/mm^3) (see DOSAGE AND ADMINISTRATION). Routine administration of a colony-stimulating factor (CSF) is not necessary, but physicians may wish to consider CSF use in individual patients experiencing problems related to neutropenia.

CAMPTOSAR may cause fetal harm when administered to a pregnant woman. CAMPTOSAR has been shown to be teratogenic in rats and rabbits at a dose of 6 mg/kg/day. Treatment-related changes in the fetuses included external and visceral abnormalities, skeletal variations, and skeletal abnormalities. There are no adequate and well-controlled studies in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with CAMPTOSAR.

PRECAUTIONS

General

CAMPTOSAR is administered by intravenous infusion. Care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with sterile water and the application of ice are recommended.

It is recommended that patients receive premedication with antiemetic agents. In clinical studies, premedication has often consisted of 10 mg of dexamethasone given in conjunction with another type of antiemetic agent. Antiemetic agents should be given on the day of treatment, starting at least 30 minutes before administration of CAMPTOSAR. Physicians should also consider providing patients with an antiemetic regimen for subsequent use as needed.

Administration of 0.25 to 1 mg of intravenous atropine should be considered (unless clinically contraindicated) in patients experiencing diaphoresis, abdominal cramping, or early diarrhea occurring during or within 24 hours following administration of CAMPTOSAR.

Physicians should exercise caution in treating and monitoring patients older than 65 years and those with the following conditions: active infections, preexisting myelosuppression, preexisting diarrhea, intestinal obstruction, chronic inflammatory bowel disease, compromised pulmonary function, excessive ascites or pleural effusion, diabetes mellitus, or poor performance status.

Information for Patients

Patients and patient care givers should be informed of the expected toxic effects of CAMPTOSAR, particularly of its gastrointestinal manifestations, such as nausea, vomiting, and diarrhea. Each patient should be instructed to have antidiarrheal medication readily available and begin treatment for late diarrhea (occurring more than

24 hours after administration of CAMPTOSAR) 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. One dosage regimen for loperamide used in clinical trials consisted of the following (Note: This dosage regimen exceeds the usual dosage recommendations for loperamide.): 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea free for at least 12 hours. During the night, the patient may take 4 mg of loperamide every 4 hours. The patient should also be instructed to notify the physician if diarrhea occurs. Premedication with loperamide is not recommended. While agents other than loperamide may have utility in the treatment of late diarrhea, the experience in US clinical trials with such medications is limited.

The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to discuss any laxative use.

Patients should consult their physician if vomiting occurs, fever or evidence of infection develop, or if symptoms of dehydration such as fainting, light-headedness, or dizziness are noted following therapy with CAMPTOSAR.

Patients should be alerted to the possibility of alopecia.

Laboratory Tests

Careful monitoring of the white blood cell count with differential, hemoglobin, and platelet count is recommended before each dose of CAMPTOSAR.

Drug Interactions

Adverse events due to CAMPTOSAR, such as myelosuppression and diarrhea, may be enhanced by combination with other antineoplastic agents having similar adverse events.

Data from clinical trials with CAMPTOSAR suggest the potential for an interaction between prior irradiation to major bone-marrow–containing areas and CAMPTOSAR in enhancing myelosuppression. Patients receiving CAMPTOSAR and concurrent irradiation may also be at increased risk for myelosuppression, diarrhea, or other toxicities.

Lymphocytopenia has been reported in patients receiving CAMPTOSAR, and it is possible that the administration of dexamethasone as antiemetic prophylaxis may have enhanced the likelihood of this effect. However, serious opportunistic infections have not been observed, and no complications have specifically been attributed to lymphocytopenia.

Hyperglycemia has also been reported in patients receiving CAMPTOSAR. Usually, this has been observed in patients with a history of diabetes mellitus or evidence of glucose intolerance prior to administration of CAMPTOSAR. It is probable that dexamethasone, given as antiemetic prophylaxis, may have contributed to hyperglycemia in some patients.

The incidence of akathisia in clinical trials was somewhat greater (8.5%, 4/47 patients) when prochlorperazine was administered on the same day as CAMPTOSAR than when these drugs were given on separate days (1.3%, 1/80 patients). However, the 8.5% incidence of akathisia is within the range reported for use of prochlorperazine when given as a premedication for other chemotherapies.

It is possible that laxative use during therapy with CAMPTOSAR may worsen the incidence or severity of diarrhea.

In view of the potential risk of dehydration secondary to vomiting and/or diarrhea induced by CAMPTOSAR, the physician may wish to withhold diuretics during dosing with CAMPTOSAR, and certainly during periods of active vomiting or diarrhea.

Minor bleeding has infrequently been noted when patients receiving CAMPTOSAR were treated with warfarin. The data do not appear to indicate a propensity for bleeding that is greater than that observed with warfarin alone.

Drug-Laboratory Test Interactions

There are no known interactions between CAMPTOSAR and laboratory tests.

Carcinogenesis, Mutagenesis & Impairment of Fertility

Irinotecan was not carcinogenic in the rat bioassay when administered at doses of 2 mg/kg or 25 mg/kg once per week for 13 weeks, with a subsequent 91-week observation period. Irinotecan was not mutagenic in the in vitro Ames assay. However, in the in vitro Chinese hamster cell chromosomal aberration assay, Irinotecan produced a significant increase in the incidence of chromosomal aberrations in a concentration-dependent manner. Additionally, in the in vivo mouse micronucleus assay, a single dose of Irinotecan over the dosage range of 2.5 to 200 mg/kg, administered intraperitoneally, caused a significant and dose-dependent increase in micronucleated polychromatic erythrocytes and a decrease in the reticulocyte/erythrocyte ratio in bone marrow cells. No significant adverse effects on fertility and general reproductive performance were observed after intravenous administration of Irinotecan in doses of up to 6 mg/kg/day to rats and rabbits (see WARNINGS).

Pregnancy

Pregnancy Category D - see WARNINGS.

Nursing Mothers

It is not known whether Irinotecan is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving therapy with CAMPTOSAR.

Pediatric Use

The safety and effectiveness of CAMPTOSAR in pediatric patients have not been established.[13]

ADVERSE REACTIONS

US Clinical Trials

In three clinical studies, 304 patients with metastatic carcinoma of the colon or rectum that had recurred or progress following 5-FU-based therapy were treated with CAMPTOSAR. Seventeen of the patients died within 30 days of the administration of CAMPTOSAR; six deaths were potentially drug related (2.0%, 6/304).[14] Neutropenic fever, defined as NCI grade 4 neutropenia and grade 2 or greater fever, occurred in nine (3.0%) patients; one of these patients died of neutropenic sepsis and the remaining eight patients recovered with supportive care. One hundred and nineteen (39.1%) of the 304 patients were hospitalized a total of 156 times because of medical events. Eighty-one (26.6%) patients were hospitalized for events judged to be related to administration of CPT-11. The primary reasons for drug-related hospitalizations were diarrhea, with or without nausea and/or vomiting (18.4%), neutropenia/leukopenia, with or without diarrhea and/or fever (8.2%), and nausea and/or vomiting (4.6%).[15] Thirteen (4.3%) patients discontinued treatment with CAMPTOSAR because of medical events. The adverse events in the following Table are based on the experience of the 304 patients enrolled in the three studies.

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[13]Terminology consistent with current FDA policy.

[14]FDA review of the narratives and CRFs of the patients who died on study found evidence that the deaths of six patients (198212 [study 0001]; 9011327, 9009864 [study 0003R]; 308, 534, 903 [study 0006]) were potentially related to CPT-11.

[15]Include information on hospitalizations due to adverse event.

Adverse Events Occurring in > 10% of 304 Previously Treated Patients with Metastatic Carcinoma of the Colon or Rectum

Event	% of Patients	% NCI Grade 3 & 4
Gastrointestinal		
Diarrhea (late)*	87.8	30.6
7-9 stools/day (grade 3)	–	16.4
≥10 stools/day (grade 4)	–	14.1
Nausea	86.2	16.8
Vomiting	66.1	12.5
Anorexia	54.6	5.9
Diarrhea (early)†	50.3	7.9
Constipation	29.3	2.0
Flatulence	12.2	0
Stomatitis	11.2	0.7
Dyspepsia	10.5	0
Hematologic		
Leukopenia	62.8	27.6
Anemia	60.5	6.9
Neutropenia	53.3	26.3
500 to <1000/mm³ (grade 3)	–	14.8
<500/mm³ (grade 4)	–	11.5
Body as a Whole		
Asthenia	75.7	12.2
Abdominal pain	56.9	15.8
Fever	45.1	0.7
Pain	23.4	2.3
Headache	16.8	0.7
Back pain	14.5	1.3
Chills	13.8	0.3
Infection	13.8	0
Edema	12.5	1.3
Metabolic & Nutritional		
↓ Body weight	30.3	0.7
Dehydration	14.5	4.3
↑ Alkaline phosphatase	13.2	3.9
↑ SGOT	10.5	1.3
Dermatologic		
Alopecia	60.5	0
Sweating	16.1	0
Rash	12.2	0.7
Respiratory		
Dyspnea	22.0	3.6
↑ Coughing	17.4	0.3
Rhinitis	15.5	0
Neurologic		
Insomnia	19.4	0
Dizziness	14.8	0
Cardiovascular		
Vasodilation	11.2	0

* Occurring > 24 hours after administration of CAMPTOSAR.
† Occurring ≤ 24 hours after administration of CAMPTOSAR.

Gastrointestinal: Diarrhea, nausea, and vomiting were common adverse events following treatment with CAMPTOSAR and could be severe. These events occurred early (during or within 24 hours of administration of CAMPTOSAR) or late (more than 24 hours after administration of CAMPTOSAR). The median time to onset of late diarrhea was 11 days following administration of CAMPTOSAR. The median duration of grade 3 or 4 late diarrhea for the patients treated at the 125 mg/m^2 starting dose was 7 days (range, 1 to 97 days).[16]

Hematology: Typical adverse hematologic events of CAMPTOSAR included neutropenia, leukopenia (including lymphocytopenia), and anemia. Serious thrombocytopenia was uncommon. Neutropenic fever (concurrent NCI grade 4 neutropenia and fever of grade 2 or greater) occurred in 3.0% of the patients. Only 5.6% of patients received G-CSF for the treatment of neutropenia. NCI grade 3 or 4 anemia was noted in 6.9% of the patients. Blood transfusions were given to 9.9% of the patients.

Body as a Whole: Asthenia, fever, and abdominal pain were the most common events of this type.

Hepatic: NCI grade 3 or 4 liver enzyme abnormalities were observed in less than 10% of patients. These events typically occurred in patients with known hepatic metastases.

Dermatologic: Alopecia, usually transient, was reported during treatment with CAMPTOSAR. Transient rashes have also been reported but did not result in discontinuation of treatment.

Respiratory: Severe pulmonary events were infrequent; NCI grade 3 or 4 dyspnea was reported in 3.6% of patients with previously treated cancer of the colon or rectum. Over half the patients with dyspnea had lung metastases; the extent to which malignant pulmonary involvement or other preexisting lung disease may have contributed to dyspnea in these patients is unknown.

Neurologic: Insomnia and dizziness were observed, but were not usually considered to be directly related to the administration of CAMPTOSAR. Dizziness may sometimes have represented symptomatic evidence of orthostatic hypotension in patients with dehydration.

Cardiovascular: Vasodilation (flushing) has been observed during administration of CAMPTOSAR but has not required intervention.

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[16]Information is provided regarding the duration of grade 3 or 4 diarrhea.

Non-US Clinical Trials

Irinotecan has been studied in over 1100 patients in Japan and in over 400 patients in France. Patients in these studies had a variety of tumor types, including cancer of the colon or rectum, and were treated with several different doses and schedules. In general, the clinical activity in patients with previously treated cancer of the colon and rectum, and the types of toxicities observed, were similar to those seen in US trials with CAMPTOSAR. There is some information from Japanese trials that patients with considerable ascites or pleural effusions were at increased risk for neutropenia or diarrhea. A potentially life-threatening pulmonary syndrome, consisting of dyspnea, fever, and a reticulonodular pattern on chest x-ray, was observed in a small percentage of patients in early Japanese studies. The contribution of Irinotecan to these preliminary events was difficult to assess because these patients also had lung tumors and some had preexisting nonmalignant pulmonary disease. As a result of these observations, clinical studies in the United States have enrolled limited numbers of patients with compromised pulmonary function, significant ascites, or pleural effusions.

OVERDOSAGE

In US phase I trials, single doses of up to 345 mg/m^2 of CAMPTOSAR were administered to patients with various cancers. Single doses of up to 750 mg/m^2 of Irinotecan have been given in non-US trials. The adverse events in these patients were similar to those reported with the recommended dosage and regimen. There is no known antidote for overdosage of CAMPTOSAR. Maximum supportive care should be instituted to prevent dehydration due to diarrhea and to treat any infectious complications.

Acute toxicity in rodents consists of tremors, convulsions, respiratory distress, and death. Subacute toxicity studies show that Irinotecan affects tissues with rapid cell proliferation (bone marrow, intestinal epithelia, thymus, spleen, lymph nodes, and testes). The acute intravenous toxicity of Irinotecan in animals is shown below:

Species	LD_{50} (mg/kg)
Mouse	132.4-134.1
Rat	83.6-85.1
Dog	40-80

DOSAGE AND ADMINISTRATION

Starting Dose and Dose Modifications

The recommended starting dose of CAMPTOSAR Injection is 125 mg/m^2. All doses should be administered as an intravenous infusion over 90 minutes (see Preparation of Infusion Solution below). The recommended treatment regimen (one treatment course) is 125 mg/m^2 administered once weekly for 4 weeks, followed by a 2-week rest period. Thereafter, additional courses of treatment may be repeated every 6 weeks (4 weeks on therapy followed by 2 weeks off therapy). It is recommended that subsequent doses be adjusted to as high as 150 mg/m^2 or to as low as 50 mg/m^2 in 25 to 50 mg/m^2 increments depending upon individual patient tolerance of treatment (see Table below). Provided intolerable toxicity does not develop, treatment with additional courses of CAMPTOSAR

may be continued indefinitely in patients who attain a response or in patients whose disease remains stable. Patients should be carefully monitored for toxicity.

The Table below describes the recommended dose modifications during a course of therapy and at the start of each subsequent course of therapy. These recommendations are based on toxicities commonly observed with the administration of CAMPTOSAR. Therapy with CAMPTOSAR should be interrupted when diarrhea persists longer than 3 days despite appropriate treatment with loperamide (see PRECAUTIONS, Information for Patients) or when other intolerable toxicity is observed. Dose modifications for hematologic toxicities other than neutropenia (eg, leukopenia, anemia or thrombocytopenia, and platelets) during a course of therapy and at the start of a subsequent course of therapy are the same as recommended for neutropenia. Dose modifications for nonhematologic toxicities other than diarrhea (nausea, vomiting, etc) during a course of therapy are the same as those recommended for diarrhea. At the start of a subsequent course of therapy, the dose of CAMPTOSAR should be decreased by 25 mg/m^2 for other NCI grade 2 or by 50 mg/m^2 for other grade 3 or 4 nonhematologic toxicities. All dose modifications should be based on the worst preceding toxicity. A new course of therapy should not begin until the granulocyte count has recovered to $\geq$1500/mm^3 and the platelet count has recovered to $\geq$100,000/mm^3 and treatment-related diarrhea is fully resolved. Treatment should be delayed one to two weeks to allow for recovery from treatment-related toxicity. If the patient has not recovered after a two-week delay, consideration should be given to discontinuing CAMPTOSAR. [17]

[17]Clarifies that a patients should recover from dose-limiting toxicity prior to beginning a new cycle of therapy.

Recommended Dose Modifications[18]

A new course of therapy should not begin until the granulocyte count has recovered to ≥ 1500/mm³ and the platelet count has recovered to ≥ 100,000/mm³ and treatment-related diarrhea is fully resolved. Treatment should be delayed one to two weeks to allow for recovery from treatment related toxicities. If the patient has not recovered after a two-week delay, consideration should be given to discontinuing CAMPTOSAR.

Toxicity NCI Grade* (Value)	During a Course of Therapy[18]	At the Start of Subsequent the Next Courses of Therapy[18] - After Adequate Recovery (see above)
No toxicity	Maintain dose level	↑ 25 mg/m² up to a maximum dose of 150 mg/m²
Neutropenia 1 (1500 to 1900/mm³) 2 (1000 to 1400/mm³) 3 (500 to 900/mm³) 4 (< 500/mm³)	Maintain dose level ↓ 25 mg/m² Omit dose, then ↓ 25 mg/m² when resolved to ≤ grade 2 Omit dose, then ↓ 50 mg/m² when resolved to ≤ grade 2	Maintain dose level Maintain dose level ↓ 25 mg/m² ↓ 50 mg/m²
Neutropenic fever (grade 4 neutropenia & ≥ grade 2 fever)	Omit dose, then ↓ 50 mg/m² when resolved	↓ 50 mg/m²
Other hematologic toxicities	Dose modifications for leukopenia, thrombocytopenia and anemia during a course of therapy and at the start of subsequent courses of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.	
Diarrhea 1 (2-3 stools/day > pretx†) 2 (4-6 stools/day > pretx) 3 (7-9 stools/day > pretx) 4 (≥ 10 stools/day > pretx)	Maintain dose level ↓ 25 mg/m² Omit dose, then ↓ 25 mg/m² when resolved to ≤ grade 2 Omit dose, then ↓ 50 mg/m² when resolved to ≤ grade 2	Maintain dose level Maintain, if the only grade 2 toxicity ‡ ↓ 25 mg/m², if the only grade 3 toxicity ‡ ↓ 50 mg/m²
Other nonhematologic toxicities 1 2 3 4	Maintain dose level ↓ 25 mg/m² Omit dose, then ↓ 25 mg/m² when resolved to ≤ grade 2 Omit dose, then ↓ 50 mg/m² when resolved to ≤ grade 2	Maintain dose level ↓ 25 mg/m² ↓ 50 mg/m² ↓ 50 mg/m²

*National Cancer Institute Common Toxicity Criteria
†Pretreatment
‡Toxicity
□All dose modifications should be based on the worst preceding toxicity.

It is recommended that patients receive premedication with antiemetic agents (see PRECAUTIONS, General).

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[18]Emphasizes that a patients should recover from dose-limiting toxicity prior to beginning a new cycle of therapy. This information should be placed in the table or text or, preferably, in both places.

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions containing CAMPTOSAR. The use of gloves is recommended. If CAMPTOSAR solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If CAMPTOSAR contacts the mucous membranes, flush thoroughly with water. Several published guidelines for handling and disposal of anticancer agents are available [1-7]

Preparation of Infusion Solution

CAMPTOSAR Injection must be diluted prior to infusion. CAMPTOSAR should be diluted in 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final concentration range of 0.12 to 1.1 mg/mL. In most clinical trials, CAMPTOSAR was administered in 500 mL of 5% Dextrose Injection, USP.

The solution is physically and chemically stable for up to 24 hours at room temperature (approximately 25°C) and in ambient fluorescent lighting. Solutions diluted in 5% Dextrose Injection, USP and stored at refrigerated temperatures (approximately 2° to 8°C) and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using 0.9% Sodium Chloride Injection, USP, is not recommended due to a low and sporadic incidence of visible particulates. **Freezing CAMPTOSAR and admixtures of CAMPTOSAR may result in precipitation of the drug and should be avoided.** Because of possible microbial contamination during dilution, it is advisable to use the admixture within 24 hours if refrigerated (2° to 8°C, 36° to 46°F) or within 6 hours if kept at room temperature (15° to 30°C, 59° to 86°F).

Other drugs should not be added to the infusion solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

Each mL of CAMPTOSAR Injection contains 20 mg irinotecan (on the basis of the trihydrate salt); 45 mg sorbitol; 0.9 mg lactic acid. When necessary, pH has been adjusted to 3.5 with sodium hydroxide and/or hydrochloric acid.

CAMPTOSAR Injection is available as single-dose vials in the following package size:

5-mL amber glass vial NDC 0009-7529-01

This is packaged in a foil/plastic blister to protect against inadvertent breakage and leakage. **The vial should be inspected for damage and visible signs of leaks before removing the foil/plastic blister. If damaged, incinerate the unopened package.**

Store at controlled room temperature 15° to 30°C (59° to 86°F). Although the product is supplied in an amber glass vial that offers some light protection, it is recommended that the vial (and foil/plastic blister) should remain in the carton until the time of use

Caution: Federal law prohibits dispensing without prescription.

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.

2. AMA Council Report. Guidelines for handling parenteral antineoplastics. JAMA 1985; 253(11):1590-1592.

3. National Study Commission on Cytotoxic Exposure. Recommendations for handling cytotoxic agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.

4. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. Med J Australia 1983;1:426-428.

5. Jones RB, et. al. Safe handling of chemotherapeutic agents: a report from the Mount Sinai Medical Center. CA-A Cancer J for Clinicians, 1983;Sept./Oct., 258-263.

6. American Society of Hospital Pharmacists Technical Assistance Bulletin on handling cytotoxic and hazardous drugs. Am J Hosp Pharm 1990;47:1033-1049.

7. OSHA work-practice guidelines for personnel dealing with cytotoxic (antineoplastic) drugs. Am J Hosp Pharm 1986;43:1193-1204.

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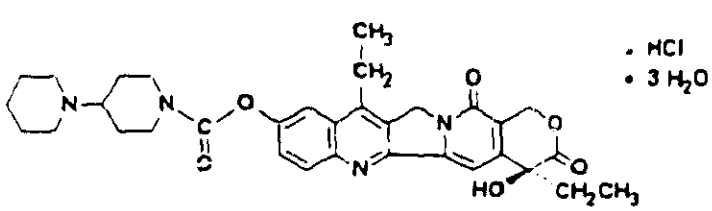
[19]Delete references 1 to 4.

A. Annotated Proposed Package Insert

The proposed package insert has been annotated to the volume and page number of the specific Item (as identified on FDA form 356h) and the technical sections.

DRAFT PACKAGE INSERT	Location in Summary and Technical Sections
CAMPTOSAR™ **brand of irinotecan hydrochloride injection** **DESCRIPTION** CAMPTOSAR Injection (irinotecan hydrochloride injection) is an antineoplastic agent, clinically investigated as CPT-11. CAMPTOSAR is supplied as a sterile, pale yellow, clear, nonaqueous solution. It is available in 100-mg, single-dose, 5-mL vials. Each milliliter of solution contains 20 mg of irinotecan trihydrate, 45 mg of sorbitol NF powder, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.0 to 4.0 with sodium hydroxide and hydrochloric acid. CAMPTOSAR is intended for dilution with 5% Dextrose Injection, USP (D5W) or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion. Irinotecan is a semisynthetic derivative of camptothecin, an alkaloid extract from plants such as *Camptotheca acuminata*. The chemical name is (4*S*)-4,11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino)carbonyloxy]-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)dione hydrochloride trihydrate. Irinotecan hydrochloride is a pale yellow to yellow crystalline powder, with the empirical formula $C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$ and a molecular weight of 677.19. It is soluble in water but sparingly soluble in organic solvents. Its structural formula is as follows:  **Irinotecan Hydrochloride**	Item 3.II. Vol 1.3, pgs 3/2/1 - 35, pg 3/2/64 Item 3.IA. Vol 1.2, pgs 3/1/40 - 42 Item 3.IA.2. Vol 1.2, pg 3/1/41

CLINICAL PHARMACOLOGY	
Irinotecan is a derivative of camptothecin and belongs to a new class of cytotoxic chemotherapeutic agents with a unique mechanism of action. These drugs interact specifically with the enzyme topoisomerase I and are known as "topoisomerase I inhibitors." The function of topoisomerases is to maintain the proper three-dimensional conformation of DNA by removing supercoils (twists and kinks) during DNA replication and transcription.[1] The cytotoxicity of the camptothecins is due to double-stranded DNA damage produced when, during DNA synthesis (the S-phase), DNA replication enzymes collide with a ternary complex of drug, DNA, and topoisomerase I.[2] This drug-induced damage is not efficiently repaired and apoptosis, a form of programmed cell death, ensues.	Item 5.C.2.b. Vol 1.14, pg 5/1/49
The therapeutic effects of irinotecan have been attributed primarily to its active metabolite SN-38. Biochemical studies and in vitro cytotoxicity assays in human and rodent tumor cell lines consistently show SN-38 to be at least 1000-fold more potent as a topoisomerase I inhibitor than irinotecan.[1] SN-38 is formed from irinotecan by carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and the dipiperidino side chain. Thus, irinotecan serves as a water-soluble prodrug of the lipophilic compound SN-38. Both irinotecan and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. A pH-dependent equilibrium exists between the two forms such that an acid pH promotes the formation of the lactone while a more basic pH yields the hydroxy acid anion form.[4]	Item 5.C.4. Vol 1.14, pg 5/1/59 Item 5.E.1.d. Vol 1.14, pg 5/1/163
Irinotecan demonstrated marked activity when administered at well-tolerated doses to rodents bearing transplanted malignant tumors. In various models, activity was manifested by growth inhibition, shrinkage, or complete remission of tumors; prolongation of survival; and inhibition of metastasis. Antitumor activity was observed in mice bearing cancers of rodent origin and in human carcinoma xenografts of various histological types. Irinotecan was also active in multidrug-resistant tumor models that respond poorly to various clinically used drugs.	Item 5.C.3. Vol 1.14, pg 5/1/51.
Pharmacokinetics	
After intravenous infusion of CAMPTOSAR in humans, irinotecan plasma concentrations decline in a multiexponential manner with a mean terminal elimination half-life of about 6 hours. The average systemic clearance of irinotecan is approximately 13 L/hr/m^2 for total irinotecan and 45 L/hr/m^2 for the lactone form. Although the pharmacokinetics of irinotecan are highly variable among patients, they are linear with respect to the dose of CAMPTOSAR solution over the dose range of 50 to 350 mg/m^2. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of CAMPTOSAR. The mean terminal half-life of the total and lactone forms of SN-38 are slightly longer than corresponding values for irinotecan (13.0 versus 7.9 hr for the total, and 11.5 versus 6.3 hr for the lactone). Maximum plasma SN-38 concentrations are approximately 2 to 5% of peak irinotecan concentrations, while SN-38 area under the curve values are about 2 to 8% of those observed for irinotecan.	Item 6.E.1.b. Vol 1.36 pgs 6/1/19 - 23 Item 6.E.1.f. Vol 1.36 pgs 6/1/29 - 32 Item 6.E.1.b. Vol 1.36 pgs 6/1/19 - 23
Pharmacokinetic parameters for irinotecan and SN-38 following 90-minute infusions of CAMPTOSAR at dose levels of 100 and 125 mg/m^2 were determined in a phase II study in patients with metastatic carcinoma of the colon or rectum and are summarized in the following Table:	Item 6.E.1.b. Vol 1.36, pg 6/1/28

Summary of Mean (± Standard Deviation) Irinotecan and SN-38 Pharmacokinetic Parameters in Patients With Metastatic Carcinoma of the Colon and Rectum

Dose (mg/m^2)	Irinotecan					SN-38		
	C_{max} (µg/mL)	AUC_{0-24} (µg·hr/mL)	$t_{1/2\beta}$ (hr)	V_{area} (L/m^2)	CL ($L/hr/m^2$)	C_{max} (ng/mL)	AUC_{0-24} (ng·hr/mL)	$t_{1/2\beta}$ (hr)
100 (N=98)	1.29 ± 0.488	8.20 ± 3.19	5.7	107 ± 29.4	13.2 ± 4.32	21.8 ± 10.1	206 ± 104	9.8
125 (N=64)	1.66 ± 0.797	10.2 ± 3.27	5.7	110 ± 48.5	13.3 ± 6.01	26.3 ± 11.9	229 ± 108	9.8

C_{max} - Maximum plasma concentration.
AUC_{0-24} - Area under the plasma concentration-time curve from time 0 to 24 hours after the end of the 90-minute infusion.
$t_{1/2\beta}$ - Harmonic mean half-life
V_{area} - Volume of distribution.
CL - Total systemic clearance.

Distribution: Irinotecan is extensively distributed to body tissues; estimates of the mean steady-state volume of distribution range from 105 L/m^2 to 266 L/m^2. Irinotecan exhibits moderate plasma protein binding (30 to 68% bound) over the concentration range achieved in clinical studies. SN-38 is highly bound to human plasma proteins (approximately 95% bound). The major plasma protein to which irinotecan and SN-38 bind is albumin.[4]

Item 6.E.1.c.
Vol 1.36
pgs 6/1/24 - 25

Item 6.E.1.d.
Vol 1.36
pgs 6/1/26 - 27

Metabolism: The metabolic conversion of irinotecan to SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver. SN-38 subsequently undergoes conjugation to form a glucuronide metabolite (SN-38 glucuronide). SN-38 was consistently at least 1000-fold more potent than irinotecan and 100-fold more potent than SN-38 glucuronide in cytotoxicity assays using various lines of human and rodent tumor cells cultured in vitro.

Item 5.C.5.
Vol 1.14, pg 5/1/61

Item 5.C.6.
Vol 1.14, pg 5/1/68

Excretion: The disposition of irinotecan has not been fully elucidated in humans. The urinary excretion of irinotecan (11 to 20%), SN-38 (<1%), and SN-38 glucuronide (3%) is low. Thus, renal excretion does not represent a major route of elimination for irinotecan and its known major circulating metabolites

Item 6.E.1.e.
Vol 1.36,
pgs 6/1/27 - 28

The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of CAMPTOSAR in two patients ranged from approximately 25% (100 mg/m^2) to 50% (300 mg/m^2).

Item 6 E.1.e.
Vol 1.36, pg 6/1/28

Pharmacokinetics in Special Populations	
Geriatric: In a clinical trial of CAMPTOSAR in patients with metastatic carcinoma of the colon and rectum, the mean (± SD) systemic clearance of irinotecan was 11.8 ± 3.50 L/hr/m² in 67 patients who were 65 years or older (mean, 71 ± 5 years) and 14.3 ± 5.74 L/hr/m² in 95 patients younger than 65 years (mean, 52 ± 10 years). The terminal half-life of irinotecan was 6.0 hours in patients who were 65 years or older and 5.5 hours in patients younger than 65 years. Dose-normalized area under the curve (AUC_{0-24}) for SN-38 in patients who were at least 65 years of age was 11% higher than the AUC_{0-24} determined in patients younger than · years.	Item 6.E.2.a.2. Vol 1.36 pgs 6/1/33 - 34
Pediatric: The pharmacokinetics of irinotecan have not been studied in the pediatric population.	
Gender: The pharmacokinetics of irinotecan do not appear to be influenced by gender. In clinical trials of CAMPTOSAR in patients with metastatic carcinoma of the colon or rectum who received a dose of 100 mg/m² or 125 mg/m², the mean (± SD) systemic clearance of irinotecan was 13.6 ± 4.76 L/hr/m² in 80 male patients (mean age, 60 ± 11 years) and 12.9 ± 5.33 L/hr/m² in 82 female patients (mean age, 60 ± 13 years). The dose-normalized AUC_{0-24} for SN-38 was 200 ± 95.9 ng·hr/mL in male patients and 194 ± 99.4 ng·hr/mL in female patients.	Item 6.E.2.a.1. Vol 136 pgs 6/1/32 - 33
Race: The potential influence of race on the pharmacokinetics of irinotecan has not been evaluated.	
Hepatic Insufficiency: The influence of severe hepatic insufficiency on the pharmacokinetic characteristics of irinotecan and its metabolites has not been formally studied. All patients in US clinical trials had adequate liver function as measured by serum levels of hepatic enzymes and bilirubin. In a clinical trial in patients with metastatic carcinoma of the colon or rectum, 77.2% of patients had liver metastases and 22.8% did not have liver metastases. Among those patients without known hepatic tumor involvement, irinotecan and SN-38 area-under-the-curve values were approximately 20% lower than values for patients wth liver metastases.	Item 6.E.2.a.4. Vol 1.36, pg 6/1/35
Renal Insufficiency: Alt..ough the pharmacokinetics of irinotecan have not been formally examined in patients with renal insufficiency, alterations in renal function would not be expected to have a major influence on the pharmacokinetics since renal excretion does not represent a major route of elimination for irinotecan or its known major circulating metabolites.	Item 6.E.2.a.3. Vol 1.36, pg 6/1/34
Drug-Drug Interactions	
The effect of the order of administration of CAMPTOSAR either immediately before or after fluorouracil (5-FU) and leucovorin has been studied. Mean irinotecan and SN-38 pharmacokinetic parameters were within 10% of corresponding values observed when CAMPTOSAR was administered alone. Possible pharmacokinetic interactions of CAMPTOSAR with other concomitantly administered medications have not been formally investigated.	Item 6.E.2.b Vol 1.36, pg 6/1/36

CLINICAL STUDIES

In a phase I study, the maximum tolerated dose of CAMPTOSAR as a single agent in the treatment of patients with various tumors was 150 mg/m² when administered once weekly for 4 weeks, followed by a 2-week rest period. The dose-limiting toxicity was diarrhea. In a second phase I study of the same regimen, the maximum tolerated dose of CAMPTOSAR was 120 mg/m² without and 145 mg/m² with coadministration of G-CSF. The dose-limiting toxicities in this study were diarrhea and neutropenia.

Item 8.G.3.
Vol 1.45, pg 8/3/31

TR 7216-95-006
Vol 1.58, pg 8/16/1

TR 7216-95-011
Vol 1.62 , pg 8/20/1

Data from three single-agent clinical studies, involving a total of 304 patients in 59 centers, support the use of CAMPTOSAR in the treatment of patients with metastatic cancer of the colon or rectum that has recurred or progressed following treatment with 5-FU-based therapy. In each study, CAMPTOSAR was administered in repeated 6-week courses comprising 90-minute IV infusions once weekly for 4 weeks, followed by a 2-week rest period. Starting doses of CAMPTOSAR in these trials were 100, 125, or 150 mg/m².

Item 8.F.2.a.
Vol 1.44, pg 8/2/8
Item 8.F.2.b.
Vol 1.44, pg 8/2/9

TR 7216-95-007
Vol 1.65, pg 8/23/1
TR 7216-95-008
Vol 1.69, pg 8/27/1
TR 7216-95-010
Vol 1.74, pg 8/32/1

In the intent-to-treat analysis of the pooled data across all three studies, 193 of the 304 patients began therapy at the recommended starting dose of 125 mg/m². Among these 193 patients, 2 complete and 26 partial responses were observed for an overall response rate of 14.5% (95% Confidence Interval (CI), 9.5 to 19.5%) at this starting dose. The majority of responses were observed within the first two courses of therapy, and all of the responses were observed by the fourth course of therapy. The median duration of response for patients beginning therapy at 125 mg/m² was 5.2 months (range, 2.6 to 15.1 months). An additional 53.9% (104/193) of the patients treated at a starting dose of 125 mg/m² achieved a best response of stable disease by formal response criteria, but many of these patients experienced substantial reductions in their total tumor burden at some time during the study.

Item 8.F.c.(6) - (9),
Vol 1.44,
pgs 8/2/33 - 48

The individual by-study results for the overall intent-to-treat response rates are as follows: In Study 1 (N=48), the overall response rate was 20.8% (95% CI, 9.3 to 32.3%) for patients receiving a starting dose of 125 or 150 mg/m². Only nine patients were treated at the 150-mg/m² starting dose due to toxicity concerns. In Study 2 (N=90), the overall response rate was 13.3% (95% CI, 6.3 to 20.4%) for patients receiving a starting dose of 125 mg/m². In Study 3, the overall response rate for patients receiving a starting dose of 125 mg/m² (N=64) was 12.5% (95% CI, 4.4 to 20.6%); among patients in this study receiving a starting dose of 100 mg/m² (N=102), the response rate was somewhat lower at 7.8% (95% CI, 2.6 to 13.1%).

Item 8.F.c.(7)
Vol 1.44, pg 8/2/34

Response to CAMPTOSAR was observed in males and in females and among patients of all ages. Patients with cancer of the colon or cancer of the rectum responded to CAMPTOSAR, and responses occurred both in patients with single and multiple metastatic sites. Patients responded to CAMPTOSAR regardless of whether prior 5-FU treatment had been given as adjuvant therapy or for metastatic disease. Over half of the patients responding to CAMPTOSAR had not had responses to prior 5-FU-based treatment given for metastatic disease. Response to CAMPTOSAR could be observed in patients who had received more than one prior chemotherapy regimen. Patients who had received previous irradiation to the pelvis also responded to CAMPTOSAR.

Item 8.F.c.(7)
Vol 1.44, pg 8/2/34

The majority of patients treated with CAMPTOSAR had an increase in or stabilization of body weight and an improvement or maintenance of performance status. Among responding patients with tumor-related symptoms, the majority experienced amelioration of these symptoms during CPT-11 treatment. Moreover, some patients had a longer time to tumor progression after treatment with CAMPTOSAR than they had experienced during their prior 5-FU-based therapy.	Item 8.F.C.(12) (a) and (c), Vol 1.44 pgs 8/2/66 and 78 TR 7216-95-017 Vol 1.84, pg 8/42/1
INDICATIONS AND USAGE CAMPTOSAR is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy.	Item 8.F.1. Vol 1.44, pg 8/2/5
CONTRAINDICATIONS CAMPTOSAR is contraindicated in patients with a known hypersensitivity to the drug.	
WARNINGS CAMPTOSAR should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available. CAMPTOSAR can induce both an early and a late form of diarrhea that appear to be mediated by different mechanisms. Early diarrhea (occurring during or within 24 hours of CAMPTOSAR administration) is cholinergic in nature. It can be severe but is usually transient. It may be preceded by complaints of diaphoresis and abdominal cramping. There is evidence that early diarrhea may be ameliorated by administration of atropine (see PRECAUTIONS, General, for dosing recommendations for atropine). Late diarrhea (occurring more than 24 hours after administration of CAMPTOSAR) may be associated with dehydration and electrolyte imbalance and can be potentially life-threatening. Late diarrhea should be treated promptly with loperamide or other similar antidiarrheal agents (see PRECAUTIONS, Information for Patients, for dosing recommendations for loperamide). Patients with severe diarrhea should be carefully monitored and provided with fluid and electrolyte replacement if dehydration occurs. Administration of CAMPTOSAR should be interrupted in the presence of National Cancer Institute (NCI) grade 3 or 4 late diarrhea. If late diarrhea persists for longer than 3 days despite treatment with loperamide, therapy with CAMPTOSAR should be discontinued and the dose of CAMPTOSAR should be decreased once the patient has recovered (see DOSAGE AND ADMINISTRATION). Deaths due to sepsis following severe myelosuppression have been reported in patients treated with CAMPTOSAR. Therapy with CAMPTOSAR should be temporarily discontinued if neutropenic fever occurs or if the absolute neutrophil count drops below 500/mm^3. The dose of CAMPTOSAR should be reduced if there is a clinically significant decrease in the total white blood cell count (< 2000/mm^3), neutrophil count (< 1000/mm^3), hemoglobin (< 8 gm/dL), or platelet count (< 100,000/mm^3) (see DOSAGE AND ADMINISTRATION). Routine administration of a colony-stimulating factor (CSF) is not necessary, but physicians may wish to consider CSF use in individual patients experiencing problems related to neutropenia.	Item 8.G.15.b. Vol 1.45, pg 8/3/241 Item 8.G.7.c.(1)(b) Vol 1.45, pg 8/3/210 Item 8.G.15.b.(2)(a) and (b) Vol 1.45, pg 8/3/242 Item 8.G.7.c.(2)(a) Vol 1.45, pg 8/3/212 Item 8.G.15.b.(2)(a) Vol 1.45, pg 8/3/242 TR 7216-95-007 Vol 1.65, pg 8/23/1 TR 7216-95-008 Vol 1.69, pg 8/27/1 TR 7216-95-010 Vol 1.74, pg 8/32/1 Item 8.G.4.f.(8) Vol 1.45, pg 8/3/83 Item 8.G.15.b.(2) Vol 1.45, pg 8/3/242

CAMPTOSAR may cause fetal harm when administered to a pregnant woman. CAMPTOSAR has been shown to be teratogenic in rats and rabbits at a dose of 6 mg/kg/day. Treatment-related changes in the fetuses included external and visceral abnormalities, skeletal variations, and skeletal abnormalities. There are no adequate and well-controlled studies in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with CAMPTOSAR.	Item 5.D.5.a. Vol 1.14, pg 5/1/138
PRECAUTIONS **General** CAMPTOSAR is administered by intravenous infusion. Care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with sterile water and the application of ice are recommended. It is recommended that patients receive premedication with antiemetic agents. In clinical studies, premedication has often consisted of 10 mg of dexamethasone given in conjunction with another type of antiemetic agent. Antiemetic agents should be given on the day of treatment, starting at least 30 minutes before administration of CAMPTOSAR. Physicians should also consider providing patients with an antiemetic regimen for subsequent use as needed. Administration of 0.25 to 1 mg of intravenous atropine should be considered (unless clinically contraindicated) in patients experiencing diaphoresis, abdominal cramping, or early diarrhea occurring during or within 24 hours following administration of CAMPTOSAR. Physicians should exercise caution in treating and monitoring patients older than 65 years and those with the following conditions: active infections, preexisting myelosuppression, preexisting diarrhea, intestinal obstruction, chronic inflammatory bowel disease, compromised pulmonary function, excessive ascites or pleural effusion, diabetes mellitus, or poor performance status.	Item 8.G.4.g.(8) Vol 1.45, pg 8/3/99 Item 8.G.4.a(6)(c) Vol 1.45, pg 8/3/45 Item 8.G.15.b.(2)(c) Vol 1.45, pg 8/3/244 Item 8.G.15.b.(2)(b) Vol 1.45, pg 8/3/243 Item 8.G.11. Vol 1.45, pg 8/3/234 Item 8.G.15.b. Vol 1.45, pg 8/3/241

Information for Patients	
Patients and patient care givers should be informed of the expected toxic effects of CAMPTOSAR, particularly of its gastrointestinal manifestations, such as nausea, vomiting, and diarrhea. Each patient should be instructed to have antidiarrheal medication readily available and begin treatment for late diarrhea (ocurring more than 24 hours after administration of CAMPTOSAR) 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. One dosage regimen for loperamide used in clinical trials consisted of the following (Note: This dosage regimen exceeds the usual dosage recommendations for loperamide.): 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea free for at least 12 hours. During the night, the patient may take 4 mg of loperamide every 4 hours. The patient should also be instructed to notify the physician if diarrhea occurs. Premedication with loperamide is not recommended. While agents other than loperamide may have utility in the treatment of late diarrhea, the experience in US clinical trials with such medications is limited.	Item 8.G.15.b. Vol 1.45, pg 8/3/241
The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to discuss any laxative use.	Item 8.G.10.b.(5) Vol 1.45, pg 8/3/232
Patients should consult their physician if vomiting occurs, fever or evidence of infection develop, or if symptoms of dehydration such as fainting, light-headedness, or dizziness are noted following therapy with CAMPTOSAR.	Item 8.G.4.g. Vol 1.45, 8/3/55
Patients should be alerted to the possibility of alopecia.	Item 8.G.4.f.(1) and (2), Vol 1.45, pgs 8/3/55 - 64
Laboratory Tests	
Careful monitoring of the white blood cell count with differential, hemoglobin, and platelet count is recommended before each dose of CAMPTOSAR.	TR 7216-95-007 Vol 1.65, pg 8/23/1 TR 7216-95-008 Vol 1.69, pg 8/27/1 TR 7216-95-010 Vol 1.74, pg 8/32/1

Drug Interactions	
Adverse events due to CAMPTOSAR, such as myelosuppression and diarrhea, may be enhanced by combination with other antineoplastic agents having similar adverse events.	Item 8.G.10.b.(2) Vol 1.45, pg 8/3/231
Data from clinical trials with CAMPTOSAR suggest the potential for an interaction between prior irradiation to major bone-marrow–containing areas and CAMPTOSAR in enhancing myelosuppression. Patients receiving CAMPTOSAR and concurrent irradiation may also be at increased risk for myelosuppression, diarrhea, or other toxicities.	Item 8.G.10.b.(1) Vol 1.45, pg 8/3/231
Lymphocytopenia has been reported in patients receiving CAMPTOSAR, and it is possible that the administration of dexamethasone as antiemetic prophylaxis may have enhanced the likelihood of this effect. However, serious opportunistic infections have not been observed, and no complications have specifically been attributed to lymphocytopenia.	Item 8.G.10.b.(3) Vol 1.45, pg 8/3/232
Hyperglycemia has also been reported in patients receiving CAMPTOSAR. Usually, this has been observed in patients with a history of diabetes mellitus or evidence of glucose intolerance prior to administration of CAMPTOSAR. It is probable that dexamethasone, given as antiemetic prophylaxis, may have contributed to hyperglycemia in some patients.	Item 8.G.15.b.(5) Vol 1.45, pg 8/3/246
The incidence of akathisia in clinical trials was somewhat greater (8.5%, 4/47 patients) when prochlorperazine was administered on the same day as CAMPTOSAR than when these drugs were given on separate days (1.3%, 1/80 patients). However, the 8.5% incidence of akathisia is within the range reported for use of prochlorperazine when given as a premedication for other chemotherapies.	Item 8.G.10.b.(4) Vol 1.45, pg 8/3/232
It is possible that laxative use during therapy with CAMPTOSAR may worsen the incidence or severity of diarrhea.	Item 8.G.10.b.(5) Vol 1.45, pg 8/3/232
In view of the potential risk of dehydration secondary to vomiting and/or diarrhea induced by CAMPTOSAR, the physician may wish to withhold diuretics during dosing with CAMPTOSAR, and certainly during periods of active vomiting or diarrhea.	Item 8.G.10.b.(6) Vol 1.45, pg 8/3/232
Minor bleeding has infrequently been noted when patients receiving CAMPTOSAR were treated with warfarin. The data do not appear to indicate a propensity for bleeding that is greater than that observed with warfarin alone.	Item 8.G.10.b.(7) Vol 1.45, pg 8/3/232
Drug-Laboratory Test Interactions	
There are no known interactions between CAMPTOSAR and laboratory tests.	

Carcinogenesis, Mutagenesis & Impairment of Fertility Irinotecan was not carcinogenic in the rat bioassay when administered at doses of 2 mg/kg or 25 mg/kg once per week for 13 weeks, with a subsequent 91-week observation period. Irinotecan was not mutagenic in the in vitro Ames assay. However, in the in vitro Chinese hamster cell chromosomal aberration assay, irinotecan produced a significant increase in the incidence of chromosomal aberrations in a concentration-dependent manner. Additionally, in the in vivo mouse micronucleus assay, a single dose of irinotecan over the dosage range of 2.5 to 200 mg/kg, administered intraperitoneally, caused a significant and dose-dependent increase in micronucleated polychromatic erythrocytes and a decrease in the reticulocyte/erythrocyte ratio in bone marrow cells. No significant adverse effects on fertility and general reproductive performance were observed after intravenous administration of irinotecan in doses of up to 6 mg/kg/day to rats and rabbits (see WARNINGS).	Item 5.D.4. Vol 1.14, pg 5/1/138 Item 5.D.6. Vol 1.14, pg 5/1/141 Item 5.D.7. Vol 1.1.4, pg 5/1/141
Pregnancy Pregnancy Category D - see WARNINGS.	
Nursing Mothers It is not known whether irinotecan is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving therapy with CAMPTOSAR.	
Pediatric Use The safety and effectiveness of CAMPTOSAR in the pediatric population have not been established.	
ADVERSE REACTIONS **US Clinical Trials** In three clinical studies, 304 patients with metastatic carcinoma of the colon or rectum that had recurred or progress following 5-FU-based therapy were treated with CAMPTOSAR. Seventeen of the patients died within 30 days of the administration of CAMPTOSAR; only one death (due to neutropenic sepsis) was judged to be potentially drug related (0.3%, 1/304). Neutropenic fever, defined as NCI grade 4 neutropenia and grade 2 or greater fever, occurred in nine (3.0%) other patients; these patients recovered with supportive care. Thirteen (4.3%) patients discontinued treatment with CAMPTOSAR because of medical events. The adverse events in the following Table are based on the experience of the 304 patients enrolled in the three studies.	TR 7216-95-007 Vol 1.65, pg 8/23/1 TR 7216-95-008 Vol 1.69, pg 8/27/1 TR 7216-95-010 Vol 1.74, pg 8/32/1 Item 8.G.4.f.(5) and (8), Vol 1.45, pgs 8/3/80 and 83 Item 8.G.4.g.(6)(b) Vol 1.45, pg 8/3/96 Item 8.G.4.f.(1) and (3), Vol 1.45, pgs 8/3/55 and 64

Adverse Events Occurring in > 10% of 304 Previously Treated Patients with Metastatic Carcinoma of the Colon or Rectum

Event	% of Patients	% NCI Grade 3 & 4
Gastrointestinal		
Diarrhea (late)*	87.8	30.6
7-9 stools/day (grade 3)	--	16.4
≥10 stools/day (grade 4)	--	14.1
Nausea	86.2	16.8
Vomiting	66.1	12.5
Anorexia	54.6	5.9
Diarrhea (early)†	50.3	7.9
Constipation	29.3	2.0
Flatulence	12.2	0
Stomatitis	11.2	0.7
Dyspepsia	10.5	0
Hematologic		
Leukopenia	62.8	27.6
Anemia	60.5	6.9
Neutropenia	53.3	26.3
500 to <1000/mm^3 (grade 3)	--	14.8
<500/mm^3 (grade 4)	--	11.5
Body as a Whole		
Asthenia	75.7	12.2
Abdominal pain	56.9	15.8
Fever	45.1	0.7
Pain	23.4	2.3
Headache	16.8	0.7
Back pain	14.5	1.3
Chills	13.8	0.3
Infection	13.8	0
Edema	12.5	1.3
Metabolic & Nutritional		
↓ Body weight	30.3	0.7
Dehydration	14.5	4.3
↑ Alkaline phosphatase	13.2	3.3
↑ SGOT	10.5	1.3
Dermatologic		
Alopecia	60.5	0
Sweating	16.1	0
Rash	12.2	0.7
Respiratory		
Dyspnea	22.0	3.6
↑ Coughing	17.4	0.3
Rhinitis	15.5	0
Neurologic		
Insomnia	19.4	0
Dizziness	14.8	0
Cardiovascular		
Vasodilation	11.2	0

* Occurring > 24 hours after administration of CAMPTOSAR.
† Occurring ≤ 24 hours after administration of CAMPTOSAR.

Gastrointestinal: Diarrhea, nausea, and vomiting were common adverse events following treatment with CAMPTOSAR and could be severe. These events occurred early (during or within 24 hours of administration of CAMPTOSAR) or late (more than 24 hours after administration of CAMPTOSAR). The median time to onset of late diarrhea was 11 days following administration of CAMPTOSAR.	Item 8.G.4.g.(1) - (3) Vol 1.45, pgs 8/3/85 - 92
Hematology: Typical adverse hematologic events of CAMPTOSAR included neutropenia, leukopenia (including lymphocytopenia), and anemia. Serious thrombocytopenia was uncommon. Neutropenic fever (concurrent NCI grade 4 neutropenia and fever of grade 2 or greater) occurred in 3.0% of the patients. Only 5.6% of patients received G-CSF for the treatment of neutropenia. NCI grade 3 or 4 anemia was noted in 6.9% of the patients. Blood transfusions were given to 9.9% of the patients.	Item 8.G.4.f.(1) and (3), Vol 1.45, pgs 8/3/55 and 64 Item 8.G.4.g.(6) and (7), Vol 1.45, pgs 8/3/93 - 99 Item 8.G.4.i.(1) Vol 1.45, pg 8/3/100
Body as a Whole: Asthenia, fever, and abdominal pain were the most common events of this type.	Item 8.G.4.f.(1) Vol 1.45, pg 8/3/55
Hepatic: NCI grade 3 or 4 liver enzyme abnormalities were observed in less than 10% of patients. These events typically occurred in patients with known hepatic metastases.	Item 8.G.4.i.(2)(a) Vol 1.45, pg 8/3/102
Dermatologic: Alopecia, usually transient, was reported during treatment with CAMPTOSAR. Transient rashes have also been reported but did not result in discontinuation of treatment.	Item 8.G.4.f.(1) and (5), Vol 1.45, pgs 8/3/55 and 80
Respiratory: Severe pulmonary events were infrequent; NCI grade 3 or 4 dyspnea was reported in 3.6% of patients with previously treated cancer of the colon or rectum. Over half the patients with dyspnea had lung metastases; the extent to which malignant pulmonary involvement or other preexisting lung disease may have contributed to dyspnea in these patients is unknown.	Item 8.G.4.g.(5) Vol 1.45, pg 8/3/93 Item 8.G.4.f.(1) and (2), Vol 1.45, pgs 8/3/55 and 64
Neurologic: Insomnia and dizziness were observed, but were not usually considered to be directly related to the administration of CAMPTOSAR. Dizziness may sometimes have represented symptomatic evidence of orthostatic hypotension in patients with dehydration.	Item 8.G.17.(b) Vol 1.45, pg 8/3/269
Cardiovascular: Vasodilation (flushing) has been observed during administration of CAMPTOSAR but has not required intervention.	Item 8.G.4.f.(1) Vol 1.45, pg 8/3/55 Item 8.G.4.h.(1) Vol 1.45, pg 8/3/99

Non-US Clinical Trials Irinotecan has been studied in over 1100 patients in Japan and in over 400 patients in France. Patients in these studies had a variety of tumor types, including cancer of the colon or rectum, and were treated with several different doses and schedules. In general, the clinical activity in patients with previously treated cancer of the colon and rectum, and the types of toxicities observed, were similar to those seen in US trials with CAMPTOSAR. There is some information from Japanese trials that patients with considerable ascites or pleural effusions were at increased risk for neutropenia or diarrhea. A potentially life-threatening pulmonary syndrome, consisting of dyspnea, fever, and a reticulonodular pattern on chest x-ray, was observed in a small percentage of patients in early Japanese studies. The contribution of irinotecan to these preliminary events was difficult to assess because these patients also had lung tumors and some had preexisting nonmalignant pulmonary disease. As a result of these observations, clinical studies in the United States have enrolled limited numbers of patients with compromised pulmonary function, significant ascites, or pleural effusions.	Item 8.G.7. Vol 1.45, pg 8/3/180
OVERDOSAGE In US phase I trials, single doses of up to 345 mg/m^2 of CAMPTOSAR were administered to patients with various cancers. Single doses of up to 750 mg/m^2 of irinotecan have been given in non-US trials. The adverse events in these patients were similar to those reported with the recommended dosage and regimen. There is no known antidote for overdosage of CAMPTOSAR. Maximum supportive care should be instituted to prevent dehydration due to diarrhea and to treat any infectious complications. Acute toxicity in rodents consists of tremors, convulsions, respiratory distress, and death. Subacute toxicity studies show that irinotecan affects tissues with rapid cell proliferation (bone marrow, intestinal epithelia, thymus, spleen, lymph nodes, and testes). The acute intravenous toxicity of irinotecan in animals is shown below: Species — LD_{50} (mg/kg) Mouse — 132.4-134.1 Rat — 83.6-85.1 Dog — 40-80	Item 8.H. Vol 1.50, pg 8/8/217

DOSAGE AND ADMINISTRATION **Starting Dose and Dose Modifications** The recommended starting dose of CAMPTOSAR Injection is 125 mg/m^2. All doses should be administered as an intravenous infusion over 90 minutes (see Preparation of Infusion Solution below). The recommended treatment regimen (one treatment course) is 125 mg/m^2 administered once weekly for 4 weeks, followed by a 2-week rest period. Thereafter, additional courses of treatment may be repeated every 6 weeks (4 weeks on therapy followed by 2 weeks off therapy). It is recommended that subsequent doses be adjusted to as high as 150 mg/m^2 or to as low as 50 mg/m^2 in 25 to 50 mg/m^2 increments depending upon individual patient tolerance of treatment (see Table below). Provided intolerable toxicity does not develop, treatment with additional courses of CAMPTOSAR may be continued indefinitely in patients who attain a response or in patients whose disease remains stable. Patients should be carefully monitored for toxicity.	Item 8.G.9.b.(2) Vol 1.45, pg 8/3/228
The Table below describes the recommended dose modifications during a course of therapy and at the start of each subsequent course of therapy. These recommendations are based on toxicities commonly observed with the administration of CAMPTOSAR. Therapy with CAMPTOSAR should be interrupted when diarrhea persists longer than 3 days despite appropriate treatment with loperamide (see PRECAUTIONS, Information for Patients) or when other intolerable toxicity is observed. Dose modifications for hematologic toxicities other than neutropenia (eg, leukopenia, anemia or thrombocytopenia, and platelets) during a course of therapy and at the start of a subsequent course of therapy are the same as recommended for neutropenia. Dose modifications for nonhematologic toxicities other than diarrhea (nausea, vomiting, etc) during a course of therapy are the same as those recommended for diarrhea. At the start of a subsequent course of therapy, the dose of CAMPTOSAR should be decreased by 25 mg/m^2 for other NCI grade 2 or by 50 mg/m^2 for other grade 3 or 4 nonhematologic toxicities. All dose modifications should be based on the worst preceding toxicity.	TR 7216-95-007 Vol 1.65, pg 8/23/1 TR 7216-95-008 Vol 1.69, pg 8/27/1 TR 7216-95-010 Vol 1.74, pg 8/32/1

Recommended Dose Modifications		
Toxicity NCI Grade* (Value)	**During a Course of Therapy**	**At the Start of Subsequent Courses of Therapy**
No toxicity	Maintain dose level	↑ 25 mg/m² up to a maximum dose of 150 mg/m²
Neutropenia		
1 (1500 to 1900/mm³)	Maintain dose level	Maintain dose level
2 (1000 to 1400/mm³)	↓ 25 mg/m²	Maintain dose level
3 (500 to 900/mm³)	Omit dose, then ↓ 25 mg/m² when resolved to ≤ grade 2	↓ 25 mg/m²
4 (< 500/mm³)	Omit dose, then ↓ 50 mg/m² when resolved to ≤ grade 2	↓ 50 mg/m²
Neutropenic fever (grade 4 neutropenia & ≥ grade 2 fever)	Omit dose, then ↓ 50 mg/m² when resolved	↓ 50 mg/m²
Other hematologic toxicities	Dose modifications for leukopenia, thrombocytopenia and anemia during a course of therapy and at the start of subsequent courses of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.	
Diarrhea		
1 (2-3 stools/day > pretx†)	Maintain dose level	Maintain dose level
2 (4-6 stools/day > pretx)	↓ 25 mg/m²	Maintain, if the only grade 2 tox‡
3 (7-9 stools/day > pretx)	Omit dose, then ↓ 25 mg/m² when resolved to ≤ grade 2	↓ 25 mg/m², if the only grade 3 tox
4 (≥ 10 stools/day > pretx)	Omit dose, then ↓ 50 mg/m² when resolved to ≤ grade 2	↓ 50 mg/m²
Other nonhematologic toxicities		
1	Maintain dose level	Maintain dose level
2	↓ 25 mg/m²	↓ 25 mg/m²
3	Omit dose, then ↓ 25 mg/m² when resolved to ≤ grade 2	↓ 50 mg/m²
4	Omit dose, then ↓ 50 mg/m² when resolved to ≤ grade 2	↓ 50 mg/m²

*National Cancer Institute Common Toxicity Criteria.
†Pretreatment
‡Toxicity

It is recommended that patients receive premedication with antiemetic agents (see PRECAUTIONS, General).	Item 8.G.15.b.(2)(c) Vol 1.45, pg 8/3/244
Preparation & Administration Precautions As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions containing CAMPTOSAR. The use of gloves is recommended. If CAMPTOSAR solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If CAMPTOSAR contacts the mucous membranes, flush thoroughly with water. Several published guidelines for handling and disposal of anticancer agents are available.[5-11]	

Preparation of Infusion Solution CAMPTOSAR Injection must be diluted prior to infusion. CAMPTOSAR should be diluted in 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final concentration range of 0.12 to 1.1 mg/mL. In most clinical trials, CAMPTOSAR was administered in 500 mL of 5% Dextrose Injection, USP.	Item 8.F.2.b.(2) Vol 1.44, 8/2/11
The solution is physically and chemically stable for up to 24 hours at room temperature (approximately 25°C) and in ambient fluorescent lighting. Solutions diluted in 5% Dextrose Injection, USP and stored at refrigerated temperatures (approximately 2° to 8°C) and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using 0.9% Sodium Chloride Injection, USP, is not recommended due to a low and sporadic incidence of visible particulates. **Freezing CAMPTOSAR and admixtures of CAMPTOSAR may result in precipitation of the drug and should be avoided.** Because of possible microbial contamination during dilution, it is advisable to use the admixture within 24 hours if refrigerated (2° to 8°C, 36° to 46°F) or within 6 hours if kept at room temperature (15° to 30°C, 59° to 86°F). Other drugs should not be added to the infusion solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.	Item 3.II.H. Vol 1.4, pg 3/3/112
HOW SUPPLIED Each mL of CAMPTOSAR Injection contains 20 mg irinotecan (on the basis of the trihydrate salt); 45 mg sorbitol; 0.9 mg lactic acid. When necessary, pH has been adjusted to 3.5 with sodium hydroxide and/or hydrochloric acid.	Item 3.II.C. Vol 1.3, pg 3/2/36
CAMPTOSAR Injection is available as single-dose vials in the following package size: 5-mL amber glass vial NDC 0009-7529-01 This is packaged in a foil/plastic blister to protect against inadvertent breakage and leakage. **The vial should be inspected for damage and visible signs of leaks before removing the foil/plastic blister. If damaged, incinerate the unopened package.** Store at controlled room temperature 15° to 30°C (59° to 86°F). Although the product is supplied in an amber glass vial that offers some light protection, it is recommended that the vial (and foil/plastic blister) should remain in the carton until the time of use. **Caution:** Federal law prohibits dispensing without prescription.	Item 3.II.F. Vol 1.3, pg 3/2/64

REFERENCES

1. Maxwell A, Gellert M. Mechanistic aspects of DNA topoisomerases. Adv Protein Chem 1986:38;69-107.

2. Holm C, Covey JM, Kerrigan D, Pommier Y. Differential requirement of DNA replication for the cytotoxicity of DNA topoisomerase I and II inhibitors in Chinese hamster DC3F cells. Cancer Res 1989;49:6365-68.

3. Kawato Y, Aonuma M, Hirota Y, Kuga H, Sato K. Intracellular roles of SN-38, a metabolite of the camptothecin derivative CPT-11, in the antitumor effect of CPT-11. Cancer Res 1991;51(16):4187-91.

4. Burke TG, Mi Z. The structural basis of camptothecin interactions with human serum albumin: impact on drug stability. J Med Chem 1994;37(1):40-6.

5. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.

6. AMA Council Report. Guidelines for handling parenteral antineoplastics. JAMA 1985; 253(11):1590-1592.

7. National Study Commission on Cytotoxic Exposure. Recommendations for handling cytotoxic agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.

8. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. Med J Australia 1983;1:426-428.

9. Jones RB, et. al. Safe handling of chemotherapeutic agents: a report from the Mount Sinai Medical Center. CA-A Cancer J for Clinicians, 1983;Sept./Oct., 258-263.

10. American Society of Hospital Pharmacists Technical Assistance Bulletin on handling cytotoxic and hazardous drugs. Am J Hosp Pharm 1990;47:1033-1049.

11. OSHA work-practice guidelines for personnel dealing with cytotoxic (antineoplastic) drugs. Am J Hosp Pharm 1986;43:1193-1204.

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L. Larcada
JUN 6 1996

MEDICAL OFFICER REVIEW NDA EFFICACY UPDATE

NDA #: 20-571

Drug Name: CAMPTOSAR™ (Irinotecan)

Applicant: Upjohn **Date Submitted**: 4/15/96

Comments regarding efficacy update:

This unsolicitied report updates response variables, time to disease progression, survival, and some of the other secondary endpoints. The survival information includes data through March 12, 1996, and the remainder of the efficacy data are updated only through December 31, 1995.

One additional patient , on Study 0006 was confirmed to have a partial response to treatment. The information in the data listings and CRF are consistent with this assessment. Based on the intent-to-treat population, the total number of patients who responded to treatment was 39/304 for an overall response rate of 12.8% (95% CI, 9.1% to 16.6%). There were two complete and 37 partial responses. The additional follow-up resulted in fewer censored data and allowed medians for time to response, time to progression, and survival to be estimated by Kaplan-Meier methods. This resulted in minor changes in the time to event analyses as shown in the following table:

TIME TO EVENT (months)	MARCH 31, 1995	DECEMBER 31, 1995
time to response	2.6 (0.9 to 5.5)	2.7 (0.9 to 11.0)
duration of response	5.8 (2.6 to 15.1)	6.0 (2.6 to 15.1)
time to progression	3.2 (0.1 to 19.9)	4.0 (0.1 to 19.9)
survival	8.3 (0.3 to 26.7)	9.0 (0.3 to 35.8)

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HFD-151/L. Vaccari (CSO)

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MAY 23 1996

MEDICAL OFFICER NDA REVIEW

NDA #: 20-571 **Drug Name:** CAMPTOSAR™ Injection
Applicant: The Upjohn Company **Date Submitted:** 12/28/95

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MEDICAL OFFICER NDA REVIEW

NDA #: 20-571

Drug Name: Irinotecan Hydrochloride injection (CPT-11)
CAMPTOSAR™ Injection

Applicant: The Upjohn Company **Date Submitted:** 12/28/95

I. GENERAL INFORMATION

A. Drug Name and Chemical Characteristics

1. Generic Name: Irinotecan Hydrochloride injection (CPT-11; U-101440E)

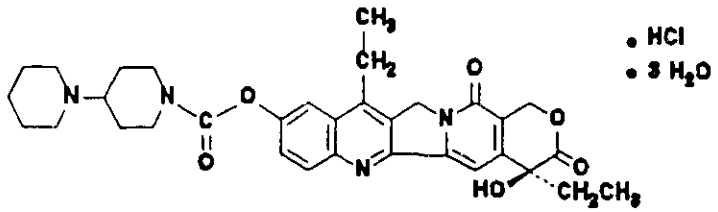
2. Trade Name: CAMPTOSAR™ Injection

3. Chemical Name: (4*S*)-4,11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino)carbonyloxy]-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)dione hydrochloride trihydrate

4. Chemical formula: $C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$

5. Molecular weight: 677.2

6. Structural formula:



Irinotecan Hydrochloride

Both irinotecan and SN-38 exist in an active lactone form and inactive hydroxy acid anion form. A pH-dependent equilibrium exists between the two forms such that acid pH promotes the formation of the lactone while a more basic pH yields the hydroxy acid form.

B. Pharmacologic Category: Topoisomerase I inhibitor

C. Proposed indication(s): Colorectal cancer patients with disease that has

progressed or recurred following 5-FU based chemotherapy.

D. Dosage form(s) and route(s) of administration:

Irinotecan hydrochloride is a pale yellow to yellow crystalline powder for dilution in 500 mL of 5% Dextrose Injection (D5W) and infused IV over 90 minutes once weekly for four consecutive weeks.

E. Related drugs: Other topoisomerase I inhibitors (topotecan, campothecin)

II. MANUFACTURING CONTROLS (refer to Chemistry Review)

Irinotecan is a semisynthetic derivative of camptothecin, an alkaloid extract from plants such as *Camptotheca acuminata*. CPT-11 drug product changed during the clinical development phases. CPT-11 was originally synthesized

The drug is under joint development in
European development of the drug has been licensed to
and US development has been licensed to The Upjohn Company. The vast majority of the patients in the controlled studies were treated with the drug product which differs from the Upjohn product that is proposed for marketing in that is uses terminal heat sterilization. It is as yet unclear whether the sterilization process effects the quantity of "impurities" particularly that of the very potent CPT-11 metabolite SN-38. If the sterilization procedure does substantially changes the content of SN-38 then we will need clinical bridging data to support the safety and efficacy of the Upjohn product to be marketed.

III. PHARMACOLOGY (refer to Pharmacology Review)

A. Pharmacodynamics

CPT-11 is an inhibitor of topoisomerase I. The function of topoisomerases is to maintain the proper three-dimensional conformation of DNA by removing supercoils (twists and kinks) during DNA replication and transcription. The cytotoxicity of the campothecins is due to double-stranded DNA damage produced when, during DNA synthesis (the S-phase), DNA replication enzymes collide with a ternary complex of drug, DNA, and topoisomerase I. DNA damage of this type appears to be difficult for cells to repair and results in programmed cell death.

CPT-11 is a prodrug that is rapidly metabolized in vivo to its active metabolite SN-38. In preclinical testing, CPT-11 showed antitumor activity in a broad spectrum of experimental tumor models and against pleiotropically drug-resistant tumor-cell lines. Additionally, in an in vitro, drug-sensitivity assay, CPT-11 showed strong activity against many tumor cell types, including colon, breast, non-small-cell lung, ovarian, and mesothelioma.

B. Pharmacokinetics

CPT-11 serves as a water-soluble prodrug for the poorly soluble SN-38 (7-ethyl-10-hydroxycamptothecin) which is formed from CPT-11 by carboxyl esterase-mediated cleavage of the bond between the camptothecin moiety

and the piperidinopiperidine (PP) side chain. Carboxyl esterases are most concentrated in liver tissue and are widely distributed in other tissues such as kidney, lung, intestine, brain, blood cells, etc. The Carboxyl esterases are predominantly microsomal enzymes of which multiple isoforms with overlapping substrate specificities are often observed. The liver is believed to be the major site of bioactivation. SN-38 is subsequently metabolized to a glucuronide conjugate (SN-38 glucuronide; SN-38G). In studies of the mechanism of camptothecin- and SN-38-induced cell killing, the inhibitory potency of SN-38 was approximately . fold greater than of CPT-11.

The following table summarizes some of the PK properties of CPT-11 and SN-38 in patients with colorectal cancer:

Mean (± SD) CPT-11 and SN-38 Pharmacokinetic Parameters Following Infusion (90-minute) of 125 or 150 mg/m^2 CPT-11 in Patients with Colorectal Cancer on Week 1 of Therapy (Source: Table 1, sect. g.txt).

Parameter	125 mg/m^2 [N=26]	150 mg/m^2 [N=9]	p Value[a]
CPT-11:			
Tmax (hr)	1.59 (0.099)	1.59 (0.076)	0.7622
Cmax (µg/mL)	1.38 (0.304)	1.73 (0.392)	0.0235
$AUC_{0\text{-}24}$ (µg•hr/mL)	13.5 (3.66)	17.1 (2.64)	0.0097
CL (L/hr/m^2)	9.90 (3.91)	8.60 (1.19)	0.4850
Vz (L/m^2)	73.8 (36.5)	68.6 (20.3)	0.8949
$t_{½}$ (hr)[b]	5.03	5.31	—
SN-38:			
Tmax (hr)	2.31 (0.960)	2.20 (0.892)	0.8649
Cmax (ng/mL)	34.4 (15.0)	29.1 (13.6)	0.4391
$AUC_{0\text{-}24}$ (ng•hr/mL)	459 (218)[c]	359 (112)	0.1976
Metabolic Ratio (%):[d]	3.74 (2.37)[c]	2.16 (0.781)	0.0236

[a] Wilcoxon Rank Sum test.
[b] Harmonic mean half-life.
[c] N=25.
[d] Ratio of SN-38 to CPT-11 $AUC_{0\text{-}24}$ expressed as a percent.

CPT-11 clearance was 17% lower in patients aged 65 years or older (mean, 71 ± 5 years) than in patients younger than 65 years (mean, 52 ± 10 years). The terminal half-life of CPT-11 was 5.5 hours in patients younger than 65 years and 6.0 hours in patients 65 years or older. Statistically

significant differences in mean SN-38 parameters between the two age groups were not observed.

Urinary excretion of CPT-11, SN-38, and SN-38 glucuronide is low, generally 11% to 20%, <1%, and 3% of the dose, respectively. Thus, renal excretion does not represent a major route of elimination for CPT-11 or its two known major circulating metabolites. CPT-11 clearance and dose-normalized SN-38 AUC_{0-24} were independent of creatinine clearance over the range of values (mL/min) estimated in patients with metastatic colorectal cancer. While the pharmacokinetics of CPT-11 have not been formally examined in patients with severe renal insufficiency, alterations in renal function would not be expected to have a major influence on the CPT-11 or SN-38 pharmacokinetics, since renal excretion does not represent a major route of excretion for these compounds.

CPT-11 and SN-38 AUC_{0-24} values (dose-normalized) were 21% and 23% higher, respectively, in patients with liver metastases than in those without liver metastases. While these results are consistent with the hypothesis that liver dysfunction may impair the metabolism of both CPT-11 and SN-38, all patients in this analysis had adequate hepatic function (i.e, serum total bilirubin $\leq$ 2 mg/dL and SGOT (AST) $\leq$ 3 times the upper limit of the normal range, unless the liver was involved with the tumor, in which case the SGOT value must have been $\leq$ 5 times the upper limit of the normal range). Formal investigations of CPT-11 and SN-38 pharmacokinetics in patients with severe hepatic impairment is being undertaken.

CPT-11 is 30% to 68% plasma protein bound ,while SN-38 is 95%. The major plasma protein to which CPT-11 and SN-38 bind is albumin.

Gupta et al (*Cancer Res 1994:54: 3723–3725*) have hypothesized that late diarrhea is associated with intestinal accumulation of SN-38 and that biliary concentrations of SN-38 may be predictive of gastrointestinal toxicity induced by CPT-11. An empiric pharmacokinetic parameter called the SN-38 "biliary index" was used as a measure of the extent of SN-38 secretion into the bile. Biliary index values, which were calculated by multiplying the relative AUC ratio of SN-38 to SN-38G by the CPT-11 AUC, were significantly greater in patients experiencing grade 3 to 4 diarrhea. Since glucuronidation represents the major detoxification pathway of SN-38, patients deficient in this enzyme activity may have a greater susceptibility to diarrhea. Additional studies to further evaluate the relationship between glucuronidation and CPT-11-induced gastrointestinal toxicity are in progress in larger patient populations.

Summary of the results of PK studies with CPT-11:

- The clearance of CPT-11 appears to be independent of dose. The relationship between CPT-11 dose and SN-38 AUC appears to be linear at doses less than 150 mg/m^2.

- The mean half-life of total CPT-11 was approximately 8 hours, while the half-life of the active metabolite, SN-38, was about 13 hours.

- The ratio of the lactone AUC to total AUC appears to remain relatively constant over the entire dose range for both CPT-11 and SN-38.

- Renal excretion is not a major route of elimination for either CPT-11 or SN-38 and SN-38 glucuronide..

- Plasma protein binding was independent of concentration with about 68% of CPT-11 and 96% of SN-38 bound to protein.

- The active lactone forms of CPT-11 and SN-38 account for a large proportion of total drug exposure; mean lactone AUCs were 44% and 51%, respectively, of the AUCs for total CPT-11 and SN-38.

- The relatively long half-life for SN-38 suggests that cytotoxic concentrations may be sustained for long durations.

- Large interindividual variability in the pharmacokinetic behavior of CPT-11 and SN-38 has been observed. Pharmacokinetic variability may be accentuated at higher doses which could increase the likelihood for toxicity in susceptible individuals.

- Neither the symptom complex consisting of diarrhea and abdominal cramps nor the symptom complex of nausea, vomiting, and anorexia could be related to C_{max} or $AUC_{0-\infty}$ values for total or lactone forms of either CPT-11 or SN-38.

- No relationship was observed between hematologic toxicity and either C_{max} or $AUC_{0-\infty}$ values for total or lactone forms of CPT-11.

- Individual patient differences as well as dose-dependency in the SN-38 glucuronidation pathway may have a major influence on SN-38 disposition.

- Biliary index values are greater in patients who experienced grade 3 to 4 diarrhea than in patients who experienced grade 0 to 2 diarrhea.

- The relatively higher biliary index values, suggestive of higher biliary

concentrations of SN-38, are possibly due to low glucuronidation rates. Since glucuronidation represents the major detoxification pathway of SN-38, patients deficient in this enzyme activity may have a greater susceptibility to diarrhea.

C. Toxicology

Please refer to the Pharmacology review for the preclinical toxicology data.

IV. CLINICAL BACKGROUND

Colorectal cancer affects one person in 20 in the United States, resulting in approximately 138,200 new cases diagnosed and 55,300 deaths yearly in the United States. This disease is the third most common cancer after prostate and lung cancers in men and after breast and lung cancer in women. Colorectal cancer accounts for approximately 15% of cancer-related mortality.

The primary therapy of early stage primary colorectal cancer is surgery. However, in 50% of cases, the disease has already metastasized at the time of diagnosis or there is a high risk of local recurrence.

Currently, the most effective, first-line systemic treatment for patients with metastatic colorectal cancer is combination therapy with 5-FU and leucovorin. Recently, in an attempt to study modulation of 5-FU, the Southwest Oncology Group (SWOG) conducted a seven-arm, phase II study [*Leichman CG, et al. Phase II study of fluorouracil and its modulation in advanced colorectal cancer: a Southwest Oncology Group study. J Clin Oncol 1995;13:1303-11*]. In that study, all regimens—5-FU plus or minus leucovorin, 5-FU plus or minus phosphonacetyl-L-aspartate (PALA), continuous 5-FU infusion, and 5-FU bolus—produced comparable confirmed response rates (13% to 24%).

There is no approved or standard second-line therapy for patients whose disease has progressed following 5-FU therapy. The sponsor conducted a literature review of experimental, second-line single-agent therapies for the treatment of patients with colorectal cancer and found an overall response rate of 3.0% (39/1279) in patients with colorectal cancer who have received previous 5-FU-based therapies (the compete set of references can be found in the NDA). Most of these studies reported response rates in the range of 0% to 5%; only one study with streptozotocin reported a response rate of greater than 10%. Median duration of response ranged from 1.5 months to 7.0 months, and median survival time ranged from 2.9 months to 7.0 months. There is clearly a need for effective second-line therapy for the treatment of patients whose disease recurs or progresses following 5-FU-based therapy.

In clinical studies in Japan utilizing various dosing regimens, CPT-11 demonstrated antitumor activity in patients with colorectal, gastric, pancreatic, cervical, ovarian, breast, or lung cancers, as well as in patients with non-Hodgkin's lymphoma, leukemia, or squamous cell carcinoma of the skin. Gastrointestinal (primarily diarrhea and nausea/vomiting) and

hematologic (primarily neutropenia and leukopenia) events were the primary adverse events associated with the administration of CPT-11.

CPT-11 was approved for clinical use in Japan in January 1994 for the indications of lung cancer, uterine-cervical cancer, and ovarian cancer. A supplemental New Drug Application (sNDA) was subsequently submitted in Japan, and approval to market the drug for the additional indications of colorectal cancer, gastric cancer, breast cancer, lymphomas, and squamous cell carcinoma of the skin was granted in September 1995. In May 1995, CPT-11 was approved in France for the treatment of patients with inoperable advanced colorectal cancer previously treated with adjuvant or palliative 5-FU-based chemotherapy.

In a phase I study, the maximum tolerated dose of CPT-11 as a single agent in patients with solid tumors was 150 mg/m^2 when administered once weekly for 4 weeks, followed by a 2-week rest period. The dose-limiting toxicity was diarrhea. In another phase I study of the same regimen, the maximum tolerated dose of CAMPTOSAR was 120 mg/m^2 without and 145 mg/m^2 with coadministration of G-CSF. The dose-limiting toxicities in this study were diarrhea and neutropenia.

V. CLINICAL STUDIES

A. Controlled studies

The controlled clinical studies submitted in support of the NDA consist of the results of three Phase II trials of CPT-11 in patients with metastatic colorectal cancer who have previously received 5-FU. For the purposes of the NDA, the studies are designated M/6475/0001 (0001), M/6475/0003R (0003R) and M/6475/0006 (0006). The studies differ somewhat from their original design. For example, study 0003R represents a subset of patients from a Mayo Clinic/NCCTG study that included both previously treated and previously untreated patients; 0003R is the subgroup of previously treated patients. The Mayo Clinic/NCCTG study was stratified by no prior therapy versus prior therapy. Unless otherwise indicated, the studies are described as they were written in the protocols. All the patients in each controlled NDA study were to have disease that was considered refractory to prior chemotherapy with a 5-FU based regimen (i.e., disease that progressed on therapy or that recurred within 6 months of adjuvant therapy).

Reviewer comment: *These notations "Reviewer comment" represent the FDA reviewer commentary and evaluation of the study. These are found throughout this NDA review to point out differences in the interpretation of the study results, discrepancies in the data, or to emphasize certain aspects of the study that may be relevant to marketing approval and/or the approved labeling of CPT-11.*

A1. Study M/6475/0001: A Phase II Trial of CPT-11 in Patients with Metastatic Colorectal Carcinoma. (San Antonio protocol # D92-2108)

Study P.I. : Mace L. Rothenberg, MD
Cancer Therapy & Research Center
San Antonio, TX

Protocol dates:

Original:	11/13/92
Amendments:	01/05/93, 02/09/93, 07/23/93, 11/23/93

As of the data cutoff date (03/31/95) for the NDA, all patients were off this study.

Enrollment of first patient: January 8, 1993
Completion of last patient: September 6, 1994

Brief description of Protocol Amendments:

- Amendment 1, dated January 5, 1993, revised to include an additional tumor measurement to confirm response.

- Amendment 2, dated February 9, 1993, reduced the starting dose from 150 mg/m^2 to 125 mg/m^2 and excluded patients with prior pelvic/abdominal radiation.

- Amendment 3, dated July 23, 1993, specifically identified the primary and secondary objectives of the study. Additionally, this amendment revised the efficacy data analysis section to 1) state the number of patients who would be enrolled in the study, 2) define the rules for terminating the study, and 3) define the manner in which the 95% confidence interval for median time to response and duration of response would be calculated.

- Amendment 4, dated November 23, 1993, allowed treatment with the next course of therapy to begin on day 36, rather than on day 42, in those patients whose treatment was withheld because of toxicity on week 4 if all toxicities had returned to a grade 0 or 1 by day 36. The sponsor of the study was changed from
to The Upjohn Company (Kalamazoo, Michigan, USA).

Unless otherwise indicated, the protocol is described as it was written is its final version:

1. Objectives of the study: (Study 0001)

- The primary objective is to estimate the antitumor activity (response rate) of CPT-11 in patients with metastatic colorectal carcinoma that has recurred following 5-FU-based chemotherapy.

- The secondary objectives are to evaluate the onset and duration of antitumor responses and to evaluate the qualitative and quantitative toxicities of CPT-11.

Reviewer Comment: *The reviewer interprets the first objective to mean: CPT-11 will be evaluated in patients who have metastatic disease and who have received a prior 5-FU-based regimen for metastatic or adjuvant disease. Patients with*

disease that had progressed or recurred following adjuvant therapy were eligible (i.e., they need no: have received prior therapy for metastatic disease; see Eligibility Criteria, below).

2. Rationale for the study: (Study 0001)

The lack of effective treatments for patients with refractory colorectal cancer, combined with its poor prognosis, was the major rationale for conducting a Phase II study in this disease.

3. Experimental Design: (Study 0001)

Open-label, phase II study in patients with metastatic colorectal cancer that progressed or recurred following a 5FU containing regiment. The study used a modified Gehan two-stage accrual design (14 + 31 patients).

a. Patient Population: (Study 0001)

(I) Inclusion criteria: (Study 0001)

- Histologic diagnosis of metastatic colorectal cancer.
- Measurable disease (bidimensional or unidimensional).
- Progressive disease after at least one 5-FU-based regimen for metastatic colorectal carcinoma or recurrent disease within 6 months of treatment with an adjuvant 5-FU-based regimen. (Protocol was amended on February 9, 1993 to exclude patients who had received prior radiation therapy to the abdomen or pelvis).
- No chemotherapy for at least 28 days before study entry.
- Performance status of 0 (asymptomatic) to 2 (symptomatic, in bed less than 50% of day) based on Eastern Cooperative Oncology Group (ECOG) criteria.
- Pretreatment granulocyte count of $\geq$ 1500/mm^3 and pretreatment platelet count of $\geq$ 100,000/mm^3.
- Adequate renal function, as defined by a value of $\leq$ 2 mg/dL for serum creatinine.
- Adequate hepatic function, as defined by a value of $\leq$ 2 mg/dL for serum total bilirubin, regardless of whether liver involvement was secondary to the tumor, and a value of $\leq$ 3 times the upper limit of the normal range for serum glutamic-oxaloacetic transaminase (SGOT; AST).
- Ability to understand the study and willingness to sign a written informed consent statement.

(ii) Exclusions: (Study 0001)

- Previous radiation therapy to the abdomen or pelvis.
- Active uncontrolled infection.
- Psychiatric disorders that would interfere with the patient's ability to give informed consent or to complete follow-up visits.
- History of myocardial infarction within the previous six months or current clinical evidence of congestive heart failure.
- Severe underlying diseases that, in the investigator's judgement, were inappropriate for entry into this study.
- Central nervous system metastasis.
- Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer or other cancer from which the patient had been disease-free for at least five years.
- Pregnancy or lactation.
- Reproductive potential (male or female), unless an effective contraceptive method was used.

(iii) Procedure: (Study 0001)

DRUG ADMINISTRATION

Drug supply:

The drug was manufactured and supplied by

Reviewer Comment: *All the patients in this study were treated with the drug product. This product differs from the Upjohn product proposed for marketing in that it was prepared with sterilization whereas the Upjohn product is prepared without sterilization. The chemists need to evaluate whether the sterilization process effects the quantity of "impurities" particularly that of the very potent CPT-11 metabolite SN-38. This may or not be an important issue.*

Starting Dose and Schedule (0001)

The recommended daily starting dose of CPT-11 was 125 mg/m^2 (note that the starting dose was reduced in an amendment dated February 9, 1993

from 150 mg/m^2 because of excessive toxicity). The dose of CPT-11 was to be calculated using body surface area, as determined from actual body weight, and rounded to the nearest 2 mg. The appropriate dose of CPT-11 was to be diluted and mixed in 500 mL of 5% Dextrose Injection (D5W) and infused IV over 90 minutes once weekly for four consecutive weeks. The protocol clearly states in capital letters "NOTE: DO NOT USE NORMAL SALINE TO DILUTE CPT-11". The four-week treatment period was to be followed by a two-week rest period, during which no CPT-11 was administered; this six-week period constituted one course of therapy. Treatment courses were to be repeated at 42-day intervals, unless dose omissions were needed because of toxicity.

Dose Modifications (Study 0001)

The toxicity of CPT-11 was to be assessed according to the NCI Common Toxicity Criteria. If multiple toxicities occurred, decreases in the recommended dose of CPT-11 were to be made for subsequent doses based on the most severe toxicity that the patient experienced. No dose modifications were to be made for alopecia or for decreases in hemoglobin, hematocrit, or lymphocytes. Dose modifications were to be made for nausea and vomiting only if these events occurred despite maximal antiemetic therapy.

Dose Modifications at the Start of Each Course of Therapy

Before each new course of therapy was begun, values for hematologic and serum chemistry tests were required to be within the limits specified at study entry. If values were outside acceptable limits, treatment was to be delayed for up to two weeks to allow values to return to within acceptable limits. If values were not within acceptable limits after this time, the patient was to be discontinued from the study, unless it could be documented that the cause of the abnormal laboratory values was unrelated to treatment with CPT-11 or to the underlying cancer.

If the dose of CPT-11 was modified at any time during a course of therapy for any toxicity other than grade 4 diarrhea, the next course of therapy was to be initiated at one dose level below the dose level at which the toxicity occurred. If grade 4 diarrhea occurred, the next course of therapy was to be initiated at two dose levels below the dose level at which the grade 4 diarrhea occurred. The CPT-11 dose levels are summarized in the Table below.

Dose Levels (Study 0001)

Starting Dose:	125 mg/m²/wk	150 mg/m²/wk*
One-Dose Level Reduction:	100 mg/m²/wk	125 mg/m²/wk
Two-Dose Level Reduction:	75 mg/m²/wk	100 mg/m²/wk
Three-Dose Level Reduction:	50 mg/m²/wk	75 mg/m²/wk

* Only the initial nine patients were treated at this dose.

Treatment courses were to be repeated at 42-day intervals. However, if treatment was withheld on week 4, the next course of therapy could begin one week earlier (i.e, on day 36) if all toxicities were of grade 0 or 1 by that time (note that this latter stipulation was added in an amendment dated November 23, 1993).

Dose Modifications during Therapy (Weeks 2, 3, and 4) (Study 0001)

Dose modifications were to be made during therapy based toxicities that were present at the time of the scheduled administration of drug. Dosage decreases were to be based on the worst grade of the toxicities that had occurred since administration of the last dose of CPT-11. If the CPT-11 dose was reduced during a course of therapy, the reduced dose was to be administered on each of the remaining weeks of treatment in that course, unless further dose reductions were required.

(Study 0001)
Dose Modifications Due to Hematologic Toxicity at Time of Scheduled Treatment on Week 2, 3, or 4

Absolute Granulocyte Count (/mm³)	Platelet Count (/mm³)	Dose Reduction
≥ 1500	≥ 100,000	None
1000-1499	≥ 100,000	1 Dose Level
< 1000	< 100,000	Omit Dose

(Study 0001)

Dose Modifications Due to Diarrhea at the Time of Scheduled Treatment on Week 2, 3, or 4

Toxicity Grade[a]	Immediate Dose Reduction	Next Dose Reduction
0-1	None	None
2	1 Dose Level	1 Dose Level
3	Omit Dose	1 Dose Level
4	Omit Dose	2 Dose Levels

[a] NCI Common Toxicity Criteria

Note: If a patient experienced grade 2 or 3 diarrhea, the next course of therapy was to be initiated at one dose level below the initial dose of the preceding course. Any remaining doses in the same course, after recovery, were also to be administered at one dose level below the initial dose. If a patient experienced grade 4 diarrhea, the next course of therapy was to be initiated at two dose levels below the initial dose of the preceding course. Any remaining doses in the same course, after recovery, were also to be administered at two dose levels below the initial dose.

(Study 0001)

Dose Modifications Based on Other Toxicities

Toxicity Grade[a,b]	Dose Reduction
0-1	None
2	1 Dose Level
3	2 Dose Levels
4	Omit Dose

[a] NCI Common Toxicity Criteria (See Appendix A).

[b] Patients who entered the study with a grade 2 elevation in SGOT were to receive full doses of CPT-11. Worsening of this toxicity to grade 3 necessitated a reduction of 2 dose levels.

Additional Courses of Therapy: (Study 0001)

Patients who obtained a partial response or whose disease remained stable could continue to receive treatment with CPT-11 indefinitely unless unacceptable toxicity occurred. Patients who developed progressive disease

or unacceptable toxicity were to be taken off study.

Concomitant Medications: (Study 0001)

Antidiarrheal Therapy

The protocol provided some instructions on the treatment of diarrhea which was to be initiated at the earliest sign of diarrhea. Diarrhea that occurred during infusion of CPT-11 (early onset diarrhea) was to be treated with 1 mg of atropine IV. The protocol contained information on experience with treating late onset diarrhea (occurring more than 24 hours after the administration) with loperamide and diphenhydramine. The sponsor states that after a published report by Abigerges et al. appeared in May 1993 [*Abigerges D, Armand JP, Chabot GG, Cote C, Rougier P, Concalves E, et al. High-dose intensity of CPT-11 administered as single dose every 3 weeks. Proc Soc Clin Oncol 1993;12:a332.*], the following standardized approach was instituted to treat late diarrhea: 4 mg of loperamide orally at the first sign of diarrhea, then 2 mg of loperamide orally every two hours (not to exceed 16 mg per day) and diphenhydramine 25 to 50 mg every six hours as needed until resolution of the diarrhea for at least 12 hours.

Reviewer Comment: *I could not find a protocol amendment that contained such explicit instructions for the management of late-onset diarrhea. The assumption is that this approach was routinely used by the investigator's in this study beginning some time after May 1993. It should also be noted that the use of diphenhydramine (in combination with loperamide) was not recommended in Study 0003R.*

Other Medications

Treatment with standard analgesic and antiemetics was permitted to control pain and nausea and vomiting, respectively. A recommendation regarding the use of granulocyte colony-stimulating factor (G-CSF) was added in the February 9, 1993 amendment and read as follows: The following treatment regimen is recommended but may be modified if medically indicated: G-CSF 5 μg/kg/day sc for grade 4 neutropenia lasting > 5 days or for patients who develop fever and/or documented infection in the setting of grade 4 neutropenia.

CLINICAL EVALUATIONS

Please refer to the table below for an outline of the evaluations to be done at baseline and during the study:

(Study 0001)
Schedule of Activities and Evaluations

Evaluation	Pre-Study[a]	Before Each CPT-11 Dose	Before Starting New Course of CPT-11	Before Starting Every Other Course of CPT-11	Study Completion[b]
History & Physical	X	X[f]	X[f]		X
Weight	X		X		X
ECOG Performance Status	X	X	X		X
Review of Systems (Toxicity Assessment)	X	X	X		X
Tumor Measurements	X		X[g]	X[g]	X
Chemistry Profile[c]	X		X		X[h]
CBC with Differential	X	X	X		X[h]
Platelet Count	X	X	X		X[h]
Pregnancy Test[d]	X				
Vital Signs	X	X	X		X
DLCO	X				X
Chest X-Ray	X		X		X
Pharmacokinetics[e]					

a Prestudy evaluations were to be done within 14 days prior to the start of the first course of therapy.
b Evaluations were to be done within three weeks after administration of the final dose of CPT-11.
c To include creatinine, total bilirubin, and SGOT.
d Women of childbearing potential only.
e Limited pharmacokinetic evaluations were to be done on weeks 1 and 3 of the first course of therapy only.
f Brief physical examination.
g To be obtained in all patients after the first and second courses of therapy. If disease remained stable, measurements were to be obtained after every other course of therapy. If ≥ 50% reduction in tumor size occurred, one additional measurement was to be obtained after the next course of therapy to confirm the response. Thereafter, measurements were to be done after every other course of therapy.
h To be repeated until values were within normal limits.
Abbreviations: CBC = complete blood count; DLCO = diffusion capacity of the lung for carbon monoxide; ECOG = Eastern Cooperative Oncology Group

Abnormal laboratory tests were to be repeated until values were within

normal limits. Patients were to be followed until death to assess survival time from the date of initial treatment. The protocol included limited PK sampling in order to correlate peak plasma concentration AUC with response and toxicity.

4. Safety considerations: (Study 0001)

a. Monitoring for Toxicity: (Study 0001)

The NCI Common Toxicity Criteria were used to grade the toxicity of CPT-11. The toxicity grades were assigned to reflect the most severe degree of toxicity that occurred during the evaluation period. The protocol called for evaluating patients for toxicity before each dose of CPT-11 and at the end of study (see previous section of this report).

Any medical event that was reported by the patient or observed by the investigator during the study was to be reported on the CRF, regardless of whether the event was considered to be related to use of the study medication. Among other things, investigators were required to classify the event by seriousness, record the maximum NCI toxicity grade, record the relationship to the study drug (unrelated, unlikely, possible, probable, definite), and record the outcome (recovered, still under treatment, alive with sequelae, died).

Diffusion Capacity of the Lung for Carbon Monoxide (DLCO) measurements were to be obtained at baseline and at the end of the study. This measure of pulmonary function was included because of reports of pneumonitis in Japanese phase II studies in patients with lung cancer (*Fukuoka M, et al. J Clin Oncol 1992;10(1):16-20; Masuda N, et al. J Clin Oncol 1992;10(8):1225-9*).

b. Criteria for Removal from the Study:

The criteria for removal from the study included: progressive disease, unacceptable toxicity in the absence of an objective response, patient's decision to withdraw, intercurrent, noncancer-related reason, which prevented continuation of therapy or regular follow-up, or general or specific changes in the patient's condition which render the patient unacceptable for further treatment in the judgement of the investigator.

c. Dose Modifications: (Please refer to the section on Procedures, above.

5. Efficacy considerations: (Study 0001)

a. Tumor Measurements

Please refer to subsection 3 (above) for the scheduling of on-study evaluations. Tumor measurements were to be obtained for all patients after the first and second courses of therapy. If disease remained stable, measurements were to be obtained after every other course of therapy. If ≥ 50% reduction in tumor size occurred, one additional measurement was to be obtained after the next course of therapy to confirm the response. Thereafter, measurements were to be done after every other course of therapy (i.e., every 12 weeks). Body weight and ECOG performance status were assessed before each course of CPT-11.

Reviewer Comment: *Follow-up evaluations of tumor measurements after the second course of therapy (with the exception of confirming a response) were to be done at 12 week intervals. This needs to be kept in mind when interpreting the response duration and time-to-progression results particularly in regards to censoring of time-to-event data and to how well the investigators adhered to the protocol.*

b. Efficacy Endpoints (Study 0001)

The primary efficacy endpoint in the protocol was tumor response (complete plus partial response) rate. The protocol indicated that 95% confidence interval for median time to response and duration of response would be constructed from the results but the FDA reviewer could not find in the protocol specific reference to other endpoints. The protocol defined response duration as the time from the onset of a partial response (even if the patient later attains a complete response) until there is objective evidence of disease progression (see below). The sponsor provided the following definitions in the NDA study report (2/1/170): 1) duration of response, defined as the period from date of first objective documentation of response to the date of first objective documentation of disease progression or to the off-study date, whichever came first; 2) time to response, defined as the period from first dose of CPT-11 to the first objective documentation of response; 3) time to disease progression, defined as the period from the date of initial treatment to the date of first objective documentation of disease progression or to the off-study date, whichever came first; 4) survival, defined as the period from the date of initial CPT-11 to the last date known alive; and 5) ECOG performance status.

Reviewer Comment: *In regards to the sponsor's definitions of the secondary endpoints, which were made retrospectively, particular*

attention needs to be placed on the choice of the date for censoring the time-to-event data (i.e., use of off-study date). This will be discussed later in the Results Section.

c. Tumor Response Criteria (Study 0001)

This protocol included definitions for both bidimensionally measurable and unidimensionally measurable disease which are defined below:

- *Bidimensionally Measurable Disease* (i.e, lymph nodes, pulmonary nodules on X-ray, or subcutaneous masses): All tumor measurements must consist of the longest diameter and the perpendicular diameter at the widest portion of the tumor, recorded in centimeters. The product of the two measurements was used to evaluate response. If more than one lesion was followed, the sum of the products was used.

- *Unidimensionally Measurable Disease* (ie, liver enlargement or abdominal masses that could only be measured in one dimension): Hepatic enlargement was to be recorded in centimeters as the overall liver size in both mid-clavicular lines (measured below the costal margin) and the midline. The sum of these three measurements was to be used to evaluate response in hepatic enlargement. The liver must have been palpable at least 5 cm below the costal margin in the mid-clavicular line(s) or below the xiphoid process on quiet respiration.

Protocol response criteria:

- Complete Response (CR): Total disappearance of all tumors for at least one month.

- Partial Response (PR): For bidimensional tumors, at least a 50% reduction in the sum of the products of the longest perpendicular diameters of measurable lesions with no new lesions for at least one month. For unidimensional hepatic lesions, ≥ 30% decrease in the sum of the distances below the costal margin, with no new lesions for at least one month.

- Stable Disease (SD): For bidimensional tumors, less than a 50% reduction or less than a 25% increase in the sum of the products of the longest perpendicular diameters of measured lesions with no new lesions for at least one month. For unidimensional hepatic lesions, less than a 30% reduction or less than a 25% increase in the sum of the distances below the costal margin, with no new lesions for at least one month.

- Progressive Disease (PD): For bidimensional tumors, at least a 25% increase in the sum of the products of the longest perpendicular diameters of measured lesions or the appearance of new lesions. For unidimensional

hepatic lesions, ≥ 25% increase in the sum of the distances below the costal margin or the appearance of new lesions.

Reviewer comment: *These are fairly standard tumor response criteria. It is important to note that the IND sponsor (Theradex at that time) did not consult with the FDA prior to the protocol submission on the adequacy of the study design to provide sufficient data to support marketing approval (i.e., provide substantial evidence of safety and efficacy).*

Levels of CEA were not required in the protocol. However, CEA levels were obtained in some patients but were not used to evaluate disease response.

d. ECOG Performance Status Criteria: (Study 0001)

The protocol CRF used an ECOG Performance Status scale. An appendix to the protocol was entitled ECOG PERFORMANCE STATUS but included a table with information on both ECOG and Karnofsky PS as shown below:

Performance Status Scale		
ECOG (Zubrod)	Karnofsky	Definitions
0	100	Asymptomatic
1	80-90	Symptomatic, fully ambulatory
2	60-70	Symptomatic, in bed less than 50% of day
3	40-50	Symptomatic, in bed more than 50% of the day, but not bedridden
4	20-30	Bedridden

Reviewer Comment: *The sponsor's study report provides a similar table but with somewhat more detailed definitions.*

6. Results of statistical consultation: (Study 0001)

See Biometrics Division review (T. Koutsoukos). The statistical aspects of this submission are mainly descriptive. Dr. Koutsoukos used the electronic

data base provided by the sponsor to verify the time to event results.

7. Results of study: (Study 0001)

Sponsor's Monitoring of data (Study 0001)

In the NDA submission, Upjohn describes the procedures of data collection and auditing. Please note that US development of CPT-11 was licensed to The Upjohn Company in November 1993. Data monitoring prior to that time was primarily performed by . Only those details relating to the auditing of the efficacy results will be included in this report.

The scans of the patients who were judged by the investigators to have attained an objective response to CPT-11 therapy (ie, a complete or partial response) were reviewed at a central location by an independent review committee of three physicians (one radiologist and two oncologists) who were selected based on their expertise in the treatment of patients with gastrointestinal cancers. The members of the independent review committee were as follows: Janet L. Potter, MD (Department of Radiology, The University of Texas Health Center at San Antonio, San Antonio, TX), Kathy Lyn Christman, MD (Department of Hematology-Medical Oncology, Lackland Air Force Base, Lackland, TX), and Margaret Ann Tempero, MD (University of Nebraska Medical Center, Omaha, NE). The same independent review committee reviewed scans and clinical records to determine whether CPT-11 responders were progressing during or after 5-FU therapy but before receiving CPT-11. If the lesion(s) that was measured for response by the investigator was not clearly identified, the reviewers selected lesions for measurement. The panel made tumor measurements from films taken at the following times: baseline, initial response, confirmation of response, and disease progression. The review was conducted at the . on April 11 and April 18, 1995.

Roviewer Comment: *The panel audit appears acceptable in regards to verifying that an objective response was achieved. However, the audit was not adequately designed to verifying the time to event endpoints (e.g., time to response, response duration).*

As assessed by the investigator, ten patients met the criteria for an objective tumor response on this study (one complete response and nine partial responses). The radiographic films were not available for one of the patients at the time of the panel review. This patient was included as a responder in all analyses. For the nine other patients, all the responses were

verified by the panel.

Patient Enrollment and Disposition (Study 0001)

Number of patients:

Patients (48 total) were enrolled from two study sites in San Antonio:
Brooke Army Medical Center (8 patients)
Cancer Therapy & Research Center (40 patients)

There were 26 males and 22 female patients enrolled.

Disposition by dose:

All 48 patients enrolled received at least one dose of CPT-11. Patients received from 1 to 13 courses of therapy; the median number of courses was 3.5. The disposition of patients is summarized by course in the table below:

Patient Disposition (Study 0001)
(Source: modified from Table 8; m0001.txt)

Classification		No.	%
Enrolled		48	100
Treated with CPT-11		48	100
No. of Patients by Course:			
Course N	1	48	100.0
	4	24	50.0
	6	12	25.0
	10	4	8.3
	13	1	2.1
Intent-to-Treat Patients		48	100
Evaluable Patients		43	89.6

Protocol deviations:

The following deviations from the protocol were identified:

- One patient had received adjuvant treatment with 5-FU and had experienced disease progression more than six months after stopping 5-FU therapy. This patient was, therefore, ineligible for the study. However, her data were included in the analyses, but she did not attain an objective response to CPT-11 therapy.

- The protocol designated that patients were to have received one prior

5-FU-based therapy. Three patients were found who had received more than one chemotherapy regimen before initiating protocol treatment with CPT-11.

- Although dose increases were not to be made within a course of therapy, the dose of CPT-11 was increased from 50 to 75 mg/m^2 within a course for two patients

- The starting dose for one patient who was obese, was calculated according to a formula different than that described in the protocol. As a some of her doses were lower than allowed by the protocol.

- Additional subgroups analyses of efficacy based on age, gender, performance status, prior 5-FU therapy, and prior response to 5-FU were included in the analyses based on FDA suggestions. (*I am not sure if we insisted on this, but I don't think that by doing this it should substantially effect the results of the study but will be interested in what they come up with*).

- The protocol indicated that the secondary objectives of this trial were to evaluate the onset and the duration of antitumor responses. Additional secondary endpoints of time to response, response duration, time to disease progression, survival and performance status were evaluated.

These deviations from the planned protocol were not judged by the sponsor to have had any substantial effect on the conclusions drawn from the study.

Demographics:

For additional information regarding demographics, please also refer to the Integrated Summary. The following is an abbreviated summary of the demographics for Study 0001).

Age and Baseline Performance Status: (Study 0001)

The median age of patients on this study was 63 years (range, 29-78). Baseline PS was 0 or 1 for 60.4% and 37.5% of patients, respectively. The one remaining patient had a PS of 2.

Pretreatment Disease-Related Characteristics: (Study 0001)

All of the patients had cancer of the colon. The majority (87.5%) had two or more metastatic disease sites. The most common sites of metastases were the liver (66.7%), lung (25.0%), and pelvis (25.0%). In about half of the patients, the largest metastatic tumor sites were less than 20 cm^2.

The time from first diagnosis to the first CPT-11 infusion ranged from 4 to 67 months (mean, 18 months; median, 12 months).

Prior Therapy:

The most common previous 5-FU-based chemotherapeutic regimen was 5-FU/leucovorin which was received by 72.9% of the patients. The majority of patients (79.2%) had experienced progressive metastatic disease during or within three months after stopping therapy.

TREATMENT ADMINISTRATION

Number of Courses Delivered:

A total of 210 courses of therapy was delivered. The median number of courses was 3.5 (range, 1 to 13) for a median of 21 weeks on therapy.

Dose Adjustments within Patients: (Study 0001)

After four of the first nine patients who received the 150-mg/m^2 starting dose developed grade 4 diarrhea with dehydration and were hospitalized for supportive care (all recovered without sequelae), the protocol was amended to reduce the starting dose to 125 mg/m^2, and the remaining 39 patients who were enrolled in the study received this starting dose.

Fifteen (38.5%) of the 39 patients who received the 125-mg/m^2 starting dose required no adjustment during the study, the remainder of the patients required reductions in the starting dose.

Dose Adjustments of CPT-11 within Courses: (Study 0001)

The CPT-11 dose was to be adjusted within courses based on the toxicities that were present at the time of scheduled treatment on week 2, 3, or 4. The table below summarizes the distribution of the first and last CPT-11 dose within courses. No adjustments in the course starting dose were made within 62 (73.8%) of the courses that were initiated at the 125-mg/m^2 dose. The distribution of the doses administered are shown in the table below. A total of 55 doses were omitted during the study.

Distribution of Doses Administered[a] (0001)

(Source: m 0001.txt Table 22)

Dose (mg/m^2)	No.	%
150	17	2.3
125	282	37.6
100	266	35.5
75	164	21.9
50	21	2.8
All	750	100

[a] Does not include 55 doses that were omitted.

Treatment Modifications for Diarrhea and Neutropenia/Leukopenia:

The number of courses that were associated with a decrease in dose because of diarrhea, neutropenia, or leukopenia is summarized in the table below.

Frequency of Dosage Adjustments due to Late Diarrhea, Neutropenia, or Leukopenia by Course (Study 0001)

(Source: m0001.txt Table 23)

Reason for Dosage Modification	No. & % of Courses with Event N=210		No. & % of Courses Requiring Dosage Modification for Event N=210	
	No.	%	No.	%
Diarrhea (late)[a]	122	58.1	37	17.6
Neutropenia	125	59.5	47	22.4
Leukopenia	137	65.2	36	17.1

[a] Occurred more than 24 hours after administration of CPT-11.

Dose Intensity:

The projected dose intensity was 100 mg/m^2/week for the 150-mg/m^2

starting dose and 83.3 mg/m^2/week for the 125-mg/m^2 starting dose. The median dose intensity for all 48 patients for the entire duration of treatment was 62.0 mg/m^2/week (range, 31.3 to 85.4 mg/m^2/week). Median dose intensity decreased from 72.9 mg/m^2/week to 66.7 mg/m^2/week between courses 1 and 2, remained relatively constant at 62.5 to 66.7 mg/m^2 from courses 2 to 5, and then decreased to 50.0 mg/m^2 and remained relatively constant over the remainder of the courses.

Reviewer Comment: *In regards to dose-intensity during the study, keep in mind that the number of patients at risk decreases with time (e.g., only approximately half of the patients make it to course 4)*

EFFICACY RESULTS: (Study 0001)

Analyses of the Data: (Study 0001)

All 48 enrolled patients received at least one dose of CPT-11 and were included in the intent-to-treat efficacy and safety analyses. Forty-three (89.6%) of the 48 patients completed at least one course of therapy and were included in the evaluable-patient efficacy analyses. The reasons in the five patients for not completing the first course of therapy and for exclusion from the evaluable-patient efficacy analyses are: personal request . progression intercurrent illness and death due to cardiopulmonary arrest of unknown etiology

Reviewer comment: *According to the sponsor's narrative in the NDA, the autopsy pathology report on the last patient stated, "The patient was medically debilitated secondary to his metastatic colonic adenocarcinoma, predisposing him to infection." and that it was presumed that the already existing chronic myocardial ischemia was exacerbated by his development of pneumonia, leading to cardiopulmonary failure and eventually death. In this case, drug association can not be ruled out.*

Because of a decline in performance status patient requested to be removed from study which was done on 10/10/93. The patient died of her malignancy on 01/04/94. No autopsy was performed.

Reviewer Comment: *Please note that the results of Study 0001 were*

published by Rothenberg et al in the April 1996 issue of the J Clin Oncol. In that publication, the efficacy results are presented for only those 43 patients who received at least one course of CPT-11. According to the publication, the reasons for the five patients not completing at least one course of CPT-11 were intercurrent illness (4 patients) and withdrawal of consent (1 patient). No mention of progressive disease or death as a reason for not completing at least one course. This is not totally consistent with the information in the NDA study report.

Duration of response, time to response, time to disease progression, and survival time were analyzed using Kaplan-Meier methods. If the exact date for an event was not available for the time-to-event analysis, the observation was censored as follows: 1) If the date of disease progression was not known, both the time to progression and duration of response were censored. The date used in the analyses was the off-study date. 2) If the date of death was not available, survival time was censored. The date used in the analyses was the last available date the patient was known to be alive (even if this was after the March 31, 1995, data cutoff date), the off-study date, or March 31, 1995.

Reviewer Comment: *The use of the off-study date for censoring data can bias the duration or response and time to progression results, and the bias may be in favor of the drug if there is unsatisfactory monitoring (i.e., less often objective tumor assessments to document progression).*

Performance status was evaluated at various times during a course. Shift tables were prepared to summarize the change from baseline in performance status at the beginning of each course. The first value for the performance status in each course was listed by patient. During data analysis, the sites were asked to provide further information from the medical records on each patient's prior 5-FU regimen, and these data were used to further clarify the prestudy status of each patient. Classifications of prior 5-FU therapy for CPT-11 responders were those of the independent review committee.

Objective Tumor Responses: (Study 0001)

Based on the investigator's assessment 10 of the 48 patients in this study achieved an objective response (1 CR and 9 PR); all 10 responses were verified by the Reviewer Panel. These responding patients are listed below:

Responses in Study M/6475/Study 0001
(N = 10)

Patient No.	Investigator's Response	Review Panel's Response
	PR	PR
	PR	PR
	PR	PR
	PR	NR[a]
	PR	PR
	PR	PR
	PR	PR
	PR	PR
	CR	CR
	PR	PR

[a] NR = Not reviewed

Reviewer Comment: *The following is based on the FDA reviewer evaluation of the CRFs and data listings of the patients who the sponsor assessed as responding to CPT-11.*

Reviewer evaluation of the response data:

The was fairly good agreement between the sponsor's assessment of objective response and the information in the NDA data listings and CRFs. Discrepancies were found in the data for two of the 10 patients . Patient had palpable hepatomegaly but these measurements were not included in the response evaluation. Only the CT measurements of lesions were used. This omission did not appear to affect the assessment of response. In regards to Patient according to the panel review of the pelvic lesion measurement, there was evidence for PD on 01/17/94 (46% increase compared to the previous measurement on 10/25/93). However, the listings have 4/11/94 as the date of PD. CRF note dated 4/11/94 indicates CT scan of abd and pelvis shows "interval development of extensive pericaval and RT periaortic adenopathy in the region of the pancreas". PD on

1/17/93 would reduce the duration of response for this patient by 12 weeks.

Reviewer comment: *There was one complete response in this study. Since complete responses in colorectal cancer are uncommonly achieved, a brief synopsis of this case is warranted.*

Brief synopsis of the one patient in whom a CR was achieved following treatment with CPT-11:

The one patient who achieved a CR on this study was a 57-year-old male underwent a sigmoid colon resection on 12/10/92 for Dukes' D colon cancer with metastases to the liver. Histopathologic examination revealed full-thickness penetration of the primary tumor into the bowel wall with adherence to the adjacent peritoneal surface but fourteen mesenteric lymph nodes were negative for tumor metastases. He was treated with 5-FU and leucovorin from 1/4/93 to 6/4/93. The patient had progression of his liver metastases while on 5-FU/leucovorin which was noted on CT scan in 6/93. He received nine courses of CPT-11 from 7/6/93 to 5/31/94. The independent panel review of the radiology films confirmed the following: at baseline (pre-CPT-11) there was only one metastatic lesion in the liver (rather than 2) which measured only 1.8 x 1.8 cm = 3.24 cm^2 (the other lesion measuring 1.5 x 1.5 was not confirmed by the independent panel); a partial response to CPT-11 occurred on 9/21/93 with the one measurable lesion equaling 30.8% of the baseline measurements. A complete response occurred on 3/8/94, and this was confirmed on the scan dated 5/31/94. On 8/1/94 there was evidence of progression with both reappearance of the pre-existing lesions in addition to other new lesions.

Actually, the investigator identified two measurable lesions in the liver at baseline (1.8 x 1.8 cm and 1.5 x 1.5 cm) but only one of the lesions was confirmed by the expert panel, the smaller of the two was not confirmed. This raises some question as to the nature of the hepatic lesion(s) in this patient (i.e., benign versus malignant). Also note that the patient had no disease related symptoms reported at baseline.

There were no apparent differences in response rate based on age, sex, number of involved tumor sites, or classification of previous 5-FU therapy;

however, a baseline performance score of 0 tended to be associated with a better response to therapy than a baseline performance score of ≥ 1 (31% vs. 9.3%; p=0.065).

Reviewer Comment: *There are too few patients to draw any firm conclusions from these retrospective subset analyses of demographic characteristics. A relatively higher response rate in patients with very good PS is not surprising.*

According to the information provided by the sponsor in the NDA, none of the eight CPT-11 responders who had received previous 5-FU therapy for metastatic disease had responded to their prior 5-FU regimen. Seven (70%) of these eight patients had experienced disease progression during or within three months after stopping 5-FU therapy.

Reviewer comment: *Please note that the details regarding prior therapy and response of prior therapy were obtained retrospectively.*

Duration of Response: (Study 0001)

The median duration of response for the ten patients who obtained an objective response was 6.4 months (range, 2.7 to 13.7 months); the sponsor reports that no response data from this group of patients were censored.

Reviewer comment: *As noted above, based on the FDA review of the response data, the date of progression for one of the responding patients was about 12 weeks earlier than according to the sponsor's evaluation. If the FDA evaluation of the response data were used to calculate duration of response, the duration of response would be approximately 1.6 months (range, 2.7 to 13.7 months).*

Time to Disease Progression: (Study 0001)

For all 48 patients, the median time to disease progression was 3.9 months (range, 0.5 to 16.6 months); data from nine patients were censored for this observation.

Reviewer Comment: ***As noted previously, tumor measurements were obtained at baseline, after the first and second courses, after the third course if a ≥ 50% response was observed after the first or second course, and then after every other course. Therefore, unless to confirm a response, tumor***

measurements were only to be performed every 12 weeks. That means, for uncensored data the time to event (duration of response or time to progression), for each case, falls somewhere between the time of documented progression and 3 months earlier.

Survival: (Study 0001)

Of the 48 patients, 38 (79.2%) had died and 10 (20.8%) were still known to be alive at the time of last follow-up. Thus, estimates of survival time include censored data for these ten patients. The median survival time for the 48 patients was 10.4 months (range, 1.0 to 26.7 months). The median survival time was longer in the patients who attained a complete or partial response to therapy (20.9 months) than in those whose best response to therapy was stable (10.4 months) or progressive disease (3.2 months).

Reviewer comment: *In regards to time to progression and survival, the effects of CPT-11 can not be adequately evaluated without a concomitant control group.*

Please refer to the FDA Statistician's (Tony Koutsoukos, Ph.D.) Review. He worked on confirming the time to event results using the sponsor's electronic data base.

Carcinoembryonic Antigen: (Study 0001)

As noted previously, CEA measurements were not a formal part of this protocol. Serum levels of CEA were determined at baseline and at least once during treatment for only 17 (35.4%) of the 48 patients. Of these 17 patients, 12 (70.6%) had a decrease in CEA level at some time during CPT-11 therapy. Based on the sponsor's evaluation, four of the ten responders had decreases from baseline in CEA levels while on therapy; baseline CEA levels were not obtained in the remaining six responders.

Clinical Benefit: (Study 0001)

See Integrated Summary of Efficacy for summary data on PS and body weight.

Reviewer comment:

There is a paucity of information in the NDA data listings regarding disease related symptoms. According to the data listings, only two of

the 10 patients (20%) who achieved an objective response (i.e., CR or PR) had what were reported to be disease related symptoms prior to starting CPT-11. Patient had "hot flashes" and back pain, and patient had constipation. The symptoms were reported to improve after treatment with CPT-11.

It is not possible to draw any conclusions about clinical benefit from these retrospectively collected data in only two patients. It is difficult to attribute hot flashes in a 46 year old woman (patient to colorectal cancer. Since an expected side effect of CPT-11 is diarrhea, the value of improvement of constipation as evidence of clinical benefit is very questionable.

According to the data listings, 11 of the 30 patients whose best objective tumor response to CPT-11 was stable disease were reported to have disease related symptoms at baseline Only one of those 11 patients were reported to have improvement of those disease related symptoms on CPT-11; the 10 other patients were reported not to have improvement of symptoms.

SAFETY RESULTS (Study 0001)

Data analysis: (Study 0001)

Medical events were summarized by COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms) body system and primary term. All medical events that were judged by the investigators to be drug-related were summarized by maximum NCI toxicity grade. Medical events were displayed by patient and by course. Information related to late diarrhea (occurring > 24 hours after administration of CPT-11), neutropenia, and leukopenia was summarized by sex, age, baseline performance status, previous pelvic/abdominal radiation, number of involved tumor sites, and CPT-11 starting dose. The frequency of neutropenic fever, defined as grade 4 neutropenia and ≥ grade 2 fever, was tabulated by patient and course, as was the frequency of the simultaneous occurrence of neutropenia and diarrhea.

Reviewer comment: *The use of grade 4 neutropenia (i.e., < 500 cells/mm^3) to define febrile neutropenia is somewhat liberal, but acceptable. Some investigators use grade 3 neutropenia to define febrile neutropenia. It should be noted, however, that in the recent topotecan application (presented at the ODAC in April, 1996), grade 4*

neutropenia was used.

Reasons for Discontinuation of Study Medication: (Study 0001)

Patients were to continue to receive treatment with CPT-11 until disease progression, unacceptable toxicity occurred, or the patient requested to stop treatment. As of the cutoff date for this report, all 48 patients had discontinued from the study, primarily due to disease progression (77.1%). The reasons for discontinuing therapy are listed in the table below:

Reasons for Discontinuation (Study 0001)
(Source: Table 9; m 0001.txt)

Reason	No.	%
Disease Progression	37	77.1
Personal Request[a]	5	10.4
Death	2	4.2
Medical Events	1	2.1
Other	3	6.3
—Completed planned treatment with complete response[a]	(1)	(2.1)
—Patient desired a break in therapy[b]	(1)	(2.1)
—Intercurrent illness[c]	(1)	(2.1)
Total	48	100

[a] Experienced fatigue with treatment and wished to try shark cartilage, felt weak and did not wish to remain on study, or did not wish/declined further therapy.

[b] This patient chose to withdraw from the study because, with the improvement he experienced in his condition as a result of CPT-11 therapy, he wished to travel extensively and, therefore, could not adhere to the protocol-specified treatment plan.

[c] Biliary sepsis and bowel obstruction

Discontinuations due to death or adverse events: (Study 0001)

Deaths while on treatment or within 30 days of last dose of CPT-11

Three (6.3%) of the 48 patients died while on study. One of these deaths was felt by the investigator to have been the result of disease progression 74 yrs.). The second patient died of cardiopulmonary arrest of unknown etiology 71 yrs.). The third patient 54 yrs.) died of disease progression within 30 days after administration of the last CPT-11 dose. According to the sponsor's narrative in the NDA, the latter patient developed liver failure that was considered due to disease

progression. None of the on-study deaths were judged by the investigators to be related to treatment with CPT-11. However, the death in one patient was judged by the medical monitor to be possibly related to treatment with CPT-11 because the patient experienced grade 4 neutropenia and septic shock before death. All three patients received a starting dose of 125 mg/m^2.

Reviewer comment: *According to the sponsor's narrative in the NDA, the autopsy pathology report on patient stated, "The patient was medically debilitated secondary to his metastatic colonic adenocarcinoma, predisposing him to infection." and that it was presumed that the already existing chronic myocardial ischemia was exacerbated by his development of pneumonia, leading to cardiopulmonary failure and eventually death. This death is possibly related to CPT-11 treatment. The FDA review of the information in the CRF agrees with the sponsor's assessment of patient , that the death was related to CPT-11.*

Discontinuations Due to Medical Events

One (2.1%) patient 78 yrs.) discontinued treatment due to grade 4 neutropenia associated with grade 2 fever, which was judged by the investigator to be related to administration of CPT-11. The patient required supportive care with antibiotics and growth factors. Previously, this patient had also developed grade 4 neutropenia associated with grade 2 fever and grade 4 diarrhea requiring hospitalization.

Discontinuations for Other Reasons:

Five (10.4%) patients withdrew from the study for personal reasons, and three (6.3%) withdrew for other miscellaneous personal reasons. Patient no. (please note that in the text of the NDA referring to this patient the number is mistakenly given as the table in the NDA shows the correct number), who had a complete response to therapy, chose to withdraw from the study because he wanted to travel extensively and, therefore, could not adhere to the protocol-specified treatment schedule. At the time of last follow-up, his survival time was 20.9 months.

Reviewer comment: *A brief synopsis of patient was provided previously in this review. This patient had only one measurable metastatic lesion in the liver (confirmed by the expert panel), and at baseline this lesion measured*

only 1.8 x 1.8 cm. Actually, the investigator identified two measurable lesions in the liver at baseline (1.8 x 1.8 cm and 1.5 x 1.5 cm) but only one of the lesions was confirmed by the expert panel, the smaller of the two was not confirmed. This raises some question as to the nature of the hepatic lesion(s) in this patient (i.e., benign versus malignant). Also note that the patient had no disease related symptoms reported at baseline. Furthermore, this patient also was reported to have experienced fatigue with treatment and wished to try shark cartilage, felt weak and did not wish to remain on study, or did not wish/declined further therapy (all these were given as reasons for wishing to come off treatment in the last table).

Late Diarrhea: (Study 0001)

Late diarrhea is defined by the sponsor in the safety analysis as that which occurs >24 hours after the administration of CPT-11. Grade 3 and 4 late diarrhea occurred in 37.5% (18/48) of the patients and in 12.4% (26/210) of the courses. There were no differences based on the demographic characteristics studied.

On May 24, 1993, all study sites were asked to adopt a rigorous standardized approach of intensive loperamide therapy for the treatment of late diarrhea. The new regimen consisted of loperamide, 4 mg orally at the first sign of diarrhea, followed by 2 mg orally every two hours (or 4 mg orally every four hours at night) until complete resolution of diarrhea for at least 12 hours.

Reviewer comment: *According to the sponsor, the incidence of grade 3 or 4 diarrhea was markedly reduced after the introduction of this loperamide regimen, but the information was provided according to the number courses rather than the number of patients effected. The influence of dose reduction on the reduced incidence of diarrhea by course is not clear from the submitted summary data.*

The incidence of late diarrhea for this study is shown in the table below:

Table 41. Frequency of Late Diarrhea*

	No.	No. (%) with Diarrhea	Maximum NCI Grade				No. (%) Grade 3 + 4
			1	2	3	4	
Patients		42 (87.5)	18	6	5	13	18 (37.5)
Courses	210	122 (58.1)	77	19	8	18	26 (12.4)

* Occurred more than 24 hours after administration of CPT-11.
Source: Appendix B, Tables 6.2.3, 6.2.4, 6.4.3, 6.4.4

Overall, 44 (91.7%) of the 48 patients were prescribed loperamide with/without another antidiarrheal agent as treatment for late diarrhea. The CPT-11 dose was reduced in 17.6% (37/210) of the courses because of late diarrhea.

Early Diarrhea: (Study 0001)

Early diarrhea is defined by the sponsor in the safety analysis as that which occurs within 24 hours of CPT-11 administration. Early diarrhea was reported in 60.4% (29/48) of the patients and in 22.4% (47/210) of the courses. Grade 3 or 4 early diarrhea occurred in one (2.1%) patient in one (0.5%) course. Three (6.3%) patients received treatment with atropine for early diarrhea.

Nausea and Vomiting: (Study 0001)

Grade 3 or 4 nausea was reported in 10.4% (5/48) of the patients and in 2.4% (5/210) of the courses, and grade 3 or 4 vomiting was reported in 14.6% (7/48) of the patients and in 3.4% (7/210) of the courses. Various agents, including ondansetron hydrochloride, prochlorperazine, or dexamethasone, were used in a large number of patients as prophylaxis for nausea/vomiting at the discretion of the investigator.

Neutropenia and neutropenic fever: (Study 0001)

Grade 3 or 4 neutropenia occurred in 37.5% (18/48) of the patients and in 17.1% (36/210) of the courses. The CPT-11 dose was reduced in 22.4% (47/210) of the courses because of neutropenia. Neutropenic fever (grade 4 neutropenia and ≥ grade 2 fever) occurred in five of the 48 patients (10.4%) and in 6 of the 210 courses (2.9%). Two of the five patients received the 150-mg/m^2 starting dose. All five patients

received antibiotic therapy and were hospitalized for supportive care. There were no fatal outcomes as a result of neutropenic fever, although one additional patient died with neutropenic sepsis while on study; this patient was afebrile at presentation; however, the death was judged by the medical monitor to be possibly related to treatment with CPT-11 because the patient experienced grade 4 neutropenia and septic shock before death. Four (8.3%) patients received G-CSF at any time as prophylaxis or therapy for neutropenic fever.

Reviewer comment: *As noted previously, the use of grade 4 neutropenia (i.e., <500 cells/mm^3) for neutropenic fever is somewhat liberal but acceptable. Some investigators use fever in the presence of grade 3 neutropenia. Based on an analysis of the electronic data by FDA statistician Tony Koutsoukos, 12.5% of the patients on this study met the criteria for febrile neutropenia defined using the more conservative criteria of grade 3 or 4 neutropenia.*

Simultaneous Neutropenia and Late Diarrhea: (Study 0001)

Grade 3 or 4 neutropenia occurred simultaneously with grade 3 or 4 late diarrhea in 16.7% (8/48) of the patients and in 4.3% (9/210) of the courses. Of the eight patients with simultaneous grade 3 or 4 neutropenia/late diarrhea seven were hospitalized for supportive care (all but no. 418878), and three had received the 150-mg/m^2 starting dose. Five of the eight patients with simultaneous neutropenia and late diarrhea experienced neutropenic fever There were no fatal outcomes in patients who experienced simultaneous grade 3 or 4 neutropenia/late diarrhea.

Hematologic Toxicities Other Than Neutropenia: (Study 0001)

The incidence of grade 3 or 4 leukopenia occurred in 22.9% (11/48) of the patients and in 11.4% (24/210) of the courses. Lymphocytopenia of any grade was observed in 47 (97.9%) patients and was grade 3 or 4 in 36 (75.0%) patients. There were no opportunistic infections specifically attributed to lymphocytopenia. Most of the reductions in hemoglobin were grade 1 or 2. Thrombocytopenia (grade 3) was observed in only one (2.1%) patient.

Median time to the nadir for hematology values ranged from 14 days for platelets to 21 days for neutrophils and hemoglobin.

Liver and Renal Function Tests: (Study 0001)

Grade 3 values for alkaline phosphatase were reported for five (10.4%) of the patients, all of whom had elevated alkaline phosphatase values at baseline. Three patients had grade 3 values for SGOT. Grade 3 or 4 bilirubin values were observed in 7 (14.6%) patients. Five of these patients had normal values for bilirubin at baseline , one had a grade 2 value for bilirubin at baseline (no. and one had a grade 3 value for bilirubin at baseline . In five of these patients bilirubin elevations were not considered to be drug related. In patients with bilirubin abnormalities that were considered to be potentially related to CPT-11 .. elevations were transient, reached a maximum of 2.9 mg/dL, and resolved spontaneously.

One patient had a grade 3 value for creatinine. This patient who had a baseline value within normal limits (0.9 mg/dL), had a value of 5.3 mg/dL in course 8. This decreased to within normal limits with continued treatment.

Other Chemistry Abnormalities: (Study 0001)

These will be discussed in the integrated summary of the three controlled studies or in the package insert.

Diffusion Capacity of the Lung for Carbon Monoxide (DLCO):

A DLCO measurement was obtained at baseline in 46 of the 48 patients; however, follow-up measurements were obtained in only six patients. Four patients had increases and two had decreases (3% and 11%) in DLCO values between baseline and the end of the study.

Concomitant Medications: (Study 0001)

CNS drugs including psychotropic agents (e.g., prochlorperazine) and corticosteroids (eg, dexamethasone) were commonly used primarily administered as antiemetic agents.

8. Conclusions: (Study 0001)

a. Scientific: (Study 0001)

This was an open label Phase II study in 48 patients with metastatic colorectal cancer that recurred or progressed following a 5FU based

chemotherapy regimen. This can be considered an adequate and well controlled (historical) study for the primary endpoint of objective tumor response. This is not an adequate and well controlled study of the secondary endpoints such as time to progression and survival. The study was not adequately designed to adequately evaluate clinical benefit endpoints such as changes in PS, body weight, and disease related symptoms.

There were 10 patients of the 48 entered whose tumors achieved an objective response resulting in a overall response rate of 20.8%. Only one of these was a CR. but that occurred in a patient with a relatively small tumor burden and who did not have disease related symptoms reported at baseline. The median duration of response for the ten patients who obtained an objective response was 6.4 months (range, 2.7 to 13.7 months) according to the sponsor's analysis and approximately 5.6 months (range, 2.7 to 13.7 months) according to the FDA analysis. For all 48 patients, the median time to disease progression was 3.9 months (range, 0.5 to 16.6 months). The median survival time for the 48 patients was 10.4 months (range, 1.0 to 26.7 months).

The most prominent toxicities were diarrhea and neutropenia. The incidence of grade 3 or 4 late diarrhea was 37% in this study. Grade 3 or 4 neutropenia occurred in 37.5% (18/48) of the patients. Lymphocytopenia was also very common; grade 3 or 4 lymphopenia occurred in 75.0% of patients. Opportunistic infections were not reported in associated with lymphopenia.

b. Deficiencies/Problems: (Study 0001)

See Section on OVERALL CONCLUSIONS.

All the patients in this study were treated with the drug product which differs from the Upjohn product proposed for marketing in that it was prepared with sterilization whereas the Upjohn product is prepared without sterilization. The chemists need to evaluate whether the sterilization process effects the quantity of "impurities" particularly that of the potent CPT-11 metabolite SN-38. This may or not be an important issue.

This study was not adequately designed to evaluate clinical benefit. The limited amount of retrospectively collected data is not adequate to draw firm conclusions regarding clinical benefit from treatment with CPT-11.

A2. Protocol M/6475/0003R:

A Phase II Trial of CPT-11 in Patients with Metastatic Colorectal Carcinoma (D92-1108). M/6475/0003R consists of only those patients from this North Central Cancer Treatment Group (NCCTG) study who had disease refractory to previous 5-fluorouracil-based chemotherapy. (The original protocol included patients with previously untreated disease but these patients were to be excluded from NDA study M/6475/0003R; data on those patients are included in the NDA as an uncontrolled study; see report of study 0003N).

Study P.I.: Henry C. Pitot, MD (Study Chair) Mayo Clinic

Protocol dates:

Original:	Enrollment of first patient: May 21, 1993
Amendments:	June 18, 1993, July 2, 1993, September 7, 1993, December 1, 1993, November 3, 1994, November 18, 1993, December 28, April 5, 1994.

A total of 90 previously treated patients were enrolled in this study by 16 P.I.s at 25 different sites. As of the March 31, 1995 NDA data cutoff date, this study was ongoing. However, all patients were enrolled and only two patients remained in the study.

Brief description of Relevant Protocol Amendments: (Study 0003R)

- Addendum 1, dated June 18, 1993, stipulated the following: 1) Toxicity monitoring was to be performed before each dose of CPT-11. 2) Loperamide was not to be used as a premedication or during CPT-11 infusion. 3) Use of metoclopamide was not allowed during the study. 4) At least one lesion in each of the different organ systems must be assessed at the time of each tumor evaluation in patients who had multiple, clearly measurable indicator lesions in different organ systems.

- Addendum 3, dated September 7, 1993 defined further procedures for the management of chemotherapy-induced diarrhea.

- Addendum 5, dated November 3, 1993, stated that CPT-11 should be dissolved and administered in D5W, not in normal saline because since crystals of CPT-11 have been observed in some of the normal saline vials available in Japan.

- Addendum 8, dated April 5, 1994, allowed treatment with the next

course of therapy to begin on day 36, rather than on day 42, in those patients in whom week 4 treatment was withheld because of toxicity and providing all toxicities had returned to a grade of 0 to 1 by day 36. This addendum also allowed the dose of CPT-11 to be increased to 150 mg/m^2 in patients who developed only grade 0 to 1 toxicities throughout an entire course at 125 mg/m^2 dose and changed the dose and nightly administration regimen for loperamide (for treatment of late diarrhea). The sponsor of the study changed from Yakult Honsha Co, Ltd (Tokyo, Japan) to The Upjohn Company.

Reviewer comment: *Not listed above is a change in early February 1994 to accrue an additional 40 previously treated patients to the study to better estimate the 90% confidence intervals for response rate (see below).*

Unless otherwise indicated, the final version of the protocol is described below:

1. Objectives of the study: (Study 0003R)

The objectives of this study were as follows:

- To evaluate the objective response rate of CPT-11 in patients with metastatic colorectal carcinoma that has recurred or progressed following one prior 5-FU-based chemotherapeutic regimen.

- To evaluate the qualitative and quantitative toxicities of CPT-11.

Please note that the original protocol had an additional objective of evaluating response rate in patients who were not previously treated with chemotherapy. Those patients were not to be included this study report but in the report of Study 0003N (see section on Uncontrolled studies).

2. Rationale for the study: (Study 0003R)

The lack of effective treatments for patients with refractory colorectal cancer, combined with its poor prognosis, was the major rationale for conducting a Phase II study in this disease.

3. Experimental Design: (Study 0003R)

This multi center, North Central Cancer Treatment Group (NCCTG) open-label, US phase II study evaluated the antitumor activity and toxicity of irinotecan hydrochloride (CPT-11) in patients with metastatic colorectal

cancer. Patients who had not received previous chemotherapy were enrolled, but data regarding these patients are found in another report (0003N). Only patients with disease that had recurred or progressed following at least one prior 5-fluorouracil (5-FU)-based chemotherapy were to be included in this report. The study used a modified Gehan two-stage accrual design (15 + 30 patients).

a. Patient Population: (Study 0003R)

(I) Clinical characteristics:

Inclusion Criteria: (Study 0003R)

- Known colorectal adenocarcinoma beyond hope of surgical cure.
- Histological or cytological confirmation of metastatic colorectal cancer that had recurred or progressed following one prior 5-FU-based chemotherapeutic regimen. Histological or cytological confirmation was not necessary if the patient had previously had a histologically confirmed primary colorectal carcinoma and a clinical diagnosis of pulmonary metastasis with no other tumor area accessible to biopsy. Under these circumstances, the patient was to have had two or more nodular lesions on chest x-ray that had newly appeared or shown progression, as determined by comparison of the current x-ray with one taken no more than 18 months and no less than one month earlier. Progression was defined as a > 25% increase in the product of perpendicular diameters of any one new lesion and/or the appearance of additional new lesions and was to be documented by providing the measurements of lesions on the chest x-ray that was taken more than one month prior to comparable "on-study" measurements.
- Measurable disease. If the only site of disease was in a previously irradiated site, there must be clear evidence of progressive disease at that site.
- No chemotherapy for at least four weeks or for at least six weeks if previous treatment was with mitomycin-C or nitrosoureas.
- No radiation therapy for at least four weeks before study entry (previous radiotherapy must have been to ≤ 25% of bone marrow).
- Performance status of 0 (asymptomatic) to 2 (symptomatic, in bed less than 50% of day) based on Eastern Cooperative Oncology Group (ECOG) criteria.
- Pretreatment (≤ 14 days prior to study entry) laboratory values within

the following limits: absolute granulocyte count, ≥ 1500/mm^3; platelet count, ≥ 100,000/mm^3; creatinine, ≤ 0.8 mg/dL outside the upper limit of the normal range; bilirubin, < 1.0 mg/dL (regardless of whether liver involvement was secondary to the tumor); and serum glutamic-oxaloacetic transaminase (SGOT; AST), ≤ three times the upper limit of the normal range.

- Ability to understand the study and willingness to sign a written informed consent statement.

Reviewer Comment: *The latter criteria regarding informed consent was not listed as an eligibility in the protocol but was included in the sponsor's NDA study report list.*

Exclusions: (Study 0003R)

- Active uncontrolled infection.
- Psychiatric disorders that would interfere with consent or follow-up.
- History of myocardial infarction within the previous six months or current clinical evidence of congestive heart failure.
- Severe underlying diseases that, in the investigator's judgement, were inappropriate for entry into this study.
- Central nervous system metastasis.
- Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, adequately treated noninvasive carcinomas, or other cancer from which the patient had been disease-free for at least five years.
- Pregnant or lactating women.
- Men or women of reproductive potential, unless they agree to use an effective contraceptive method.
- Treatment with more than one 5-FU-based chemotherapeutic regimen (including treatment with 5-FU as a radiosensitizer).
- Severe pulmonary disease, as defined by a value of < 50% of that predicted for DLCO after correction for hemoglobin or by severe interstitial changes on chest x-ray.
- Abdominal exploration, with or without intestinal resection, within 21 days of study entry.

(iii) Procedure: (Study 0003R)

DRUG ADMINISTRATION (Study 0003R)

Drug supply: (Study 0003R)

The drug was manufactured and supplied by

Reviewer Comment: *All the patients in this study were treated with the drug product which differs from the Upjohn product proposed for marketing. product uses sterilization and the Upjohn product uses an product. According to the CMC information on page 2/1/59 of the NDA, there was a switch to begin using the Upjohn drug product (lot 27,211) but this did not take place until 5/94, and the sponsor's study report does not list any UpJohn lot as being used in the patients included in study 0003R.*

Starting Dose and Schedule (Study 0003R)

The total daily starting dose of CPT-11 was 125 mg/m^2. The appropriate dose of CPT-11 was initially diluted in normal saline. However, an amendment dated November 3, 1993, stated that CPT-11 should be dissolved and administered in 500 mL of 5% D5W, not in normal saline, because crystals of CPT-11 had been observed in some of the normal saline vials available in Japan. The drug was to be infused IV over 90 minutes once weekly for four consecutive weeks, the same as that for studies 0001 and 0006.

Additional Courses of Therapy

Repeat courses of therapy were to be continued until disease progression occurred or until one or more of the criteria for removal from the study was reached. Patients who obtained a partial response or whose disease remained stable could continue to receive treatment with CPT-11 indefinitely, unless unacceptable toxicity occurred. Patients who achieved a complete response were to be given four additional courses of therapy before discontinuation from the study, unless unacceptable toxicity occurred.

Dose Modifications (Study 0003R)

The toxicity of CPT-11 was assessed according to a modification of the NCI Common Toxicity Criteria (Mayo/NCCTG). If multiple toxicities occurred,

subsequent doses were to be decreased from the recommended starting dose of 125 mg/m^2 of CPT-11 based on the greatest dose reduction required for any single toxicities observed. No dose modifications were to be made for alopecia, weight gain, hyperglycemia, or decreases in hemoglobin, hematocrit, or lymphocytes. Dose modifications were to be made for nausea and vomiting only if these events occurred despite maximal antiemetic therapy. If a patient completed an entire course of therapy at the 125-mg/m^2 dose level without experiencing any toxicities of greater than grade 1, the dose of CPT-11 for the next course of therapy could be increased to 150 mg/m^2. Patients who entered the study with grade 2 elevation of SGOT were to receive full doses of CPT-11. Worsening of this toxicity to grade 3 was to necessitate a reduction of 2 dose levels.

Dose Modifications at the Start of Each Course of Therapy (Study 0003R)

Before each new course of therapy was begun, values for hematologic and serum chemistry tests were required to be within the limits specified at study entry or treatment was delayed for up to two weeks to allow for recovery. If values were not within acceptable limits at the end of this two-week period, the patient was to be discontinued from the study.

If the dose of CPT-11 was modified at any time during a course of therapy for any toxicity other than grade 4 diarrhea, the next course of therapy was to be initiated at one dose level below the level of the initial dose from the preceding course. If grade 4 diarrhea occurred, the next course of therapy was to be initiated at two dose levels below the level of the initial dose from the preceding course. If no toxicities of greater than grade 1 occurred during the entire course of treatment at the reduced dose, then the dose for the next course of therapy was to be increased one dose level up to a maximum of 150 mg/m^2. The CPT-11 dose levels are the same as that provided in Study 0001, described previously.

Treatment courses were to be repeated at 42-day intervals. However, if treatment was withheld on week 4, the next course of therapy could begin one week earlier (ie, on day 36 instead of day 42) if all toxicities were of grade of 0 or 1 by that time.

Dose modifications during therapy (Study 0003R)

Dose modifications were to be made during therapy based on hematologic toxicities (granulocyte and platelet counts), the grade of diarrhea at the time of the scheduled administration of drug on week 2, 3, or 4, or the worst grade of other nonhematologic toxicities that had occurred since administration of the last dose of CPT-11. If the CPT-11 dose was reduced

during a course of therapy, the reduced dose was to be administered on each of the remaining weeks of treatment in that course, unless further dose reductions were required.

Dose modifications that were to be made as a result of hematologic toxicity or diarrhea at the time of scheduled treatment on week 2, 3, or 4 were the same as for Study 0001 described previously. Doses were to be reduced based on the worst grade of any other toxicities that had been experienced since the last dose of CPT-11. Treatment with CPT-11 was to be discontinued in any patient whose value for DLCO was < 40% of the predicted value after correction for hemoglobin.

CONCOMITANT MEDICATIONS (Study 0003R)

Antidiarrheal Therapy

Treatment with antidiarrheal agents was allowed and was to be initiated at the earliest sign of diarrhea. The choice of antidiarrheal therapy depended on whether the diarrhea occurred during CPT-11 infusion or between CPT-11 treatments. Diarrhea that occurred during infusion of CPT-11 was to be treated with 0.25 to 0.5 mg of atropine IV. Use of loperamide as premedication or during CPT-11 infusion was not allowed. Initially, diarrhea that occurred between treatments was to be treated with loperamide 4 mg after each bowel movement (not to exceed 16 mg per day) and diphenhydramine 25-50 mg every six hours as needed. These measures were to be initiated at the earliest sign of the onset of diarrhea. On September 7, 1993, the protocol was amended to modify the dosing regimen for treating diarrhea with loperamide and the new instructions were provided to all study sites by September 28, 1993. Diarrhea that occurred between CPT-11 treatments was to be treated with 2 mg of loperamide orally every two hours for 12 hours, day and night, for a total of six doses. If the diarrhea did not recur, administration of loperamide was to be discontinued after the first 12 hours. If the diarrhea recurred, administration of loperamide 2 mg every two hours was recommended for another 12 hours. If the diarrhea was not controlled after three days, administration of loperamide was to be stopped. On April 5, 1994, the protocol was amended to further specify the procedures for managing late diarrhea. All patients were to be treated aggressively with loperamide at the earliest signs of diarrhea (i.e., first poorly formed stool, first episode of 2 or more bowel movements in one day) that occurs more than 12 hours after receiving CPT-11. The initial dose of loperamide was to be 4 mg orally. Furthermore, 2 mg of loperamide was to be given every two hours "around-the-clock" until the patient was free of diarrhea for at least 12 hours. To minimize sleep disruption, 4 mg of loperamide could be taken every four hours during

the night. Loperamide was to be discontinued and, if necessary, supportive care was to be provided if the diarrhea was not controlled after three days of treatment. Hospitalization was to be considered, if necessary, to provide adequate supportive care. Investigators were permitted to prescribe alternative antidiarrheal medications to loperamide.

Antiemetic Therapy: (Study 0003R)

Use of standard antiemetic agents to control nausea and vomiting was permitted during the study. Treatment with metoclopramide was not allowed (in order to avoid possible akathisia).

Other Medications

Use of standard analgesic agents to control pain was permitted during the study. Instructions for concomitant use of granulocyte colony-stimulating factor (G-CSF) were not specifically provided in the protocol.

CLINICAL EVALUATIONS (Study 0003R)

Clinical and laboratory evaluations to be done at baseline and during the study were similar to those for Study 0001. Please refer to the description of study 0001 earlier in this in this report. The major differences were that PK sampling was not included in Study 0003R and the instructions for obtaining tumor measurements were slightly different. In this study, tumor measurements were to be obtained prior to the second and third courses of therapy for all patients and before every other subsequent course in patients who attained a partial or complete response.

Reviewer comment: *Unlike study 0001, Study 0003R makes no reference in the evaluations section to confirming responses with measurements at the next course of therapy.*

To assess survival rate after treatment with CPT-11, patients were to be followed until death.

4. Safety considerations: (Study 0003R)

a. Monitoring for Toxicity:

The appendix of the protocol contained the Mayo Clinic/NCCTG Toxicity

Criteria which is the NCI Common Toxicity Criteria modified and supplemented with Mayo/NCCTG criteria. In Section 10.5 of the protocol lists the toxicities that needed to be graded at each evaluation (alopecia, # stools per day, diarrhea, nausea, stomatitis, vomiting, dyspnea, skin, anorexia) and pretreatment symptoms/conditions (i.e., # stools per day) to be evaluated at baseline per those criteria unless otherwise specified.

A DLCO measurement was to be obtained at screen, every 12 weeks (or more frequently, if clinically indicated) during the study, and at study completion. This measure of pulmonary function was included because of reports of pneumonitis in Japanese phase II studies of CPT-11 in patients with lung cancer (*Fukuoka M, et al. J Clin Oncol 1992;10(1):16-20; Masuda N, et al. J Clin Oncol 1992;10(8):1225-9*).

b. Criteria for Removal from the Study:

The reasons for patients to be discontinued from the study were essentially the same as for study Protocol 0001:

- Progressive disease
- Unacceptable toxicity in the absence of an objective response
- Patient's decision to withdraw
- Intercurrent, noncancer-related reason, which prevented continuation of therapy or regular follow-up
- General or specific changes in the patient's condition, which, in the investigator's judgement, rendered the patiant unacceptable for further treatment.

C. Dose Modifications (see Procedures Section, above)

5. Efficacy considerations: (Study 0003R)

The primary efficacy endpoint was response rate (complete response or a partial response). A standard two-step design was used. As noted previously, the original protocol included two studies (two populations of patients): previously treated and previously untreated. Each study was to have a minimum of 15 patients and a maximum of 30 patients. The protocol was modified in early February 1994 to enroll an additional 40 previously treated patients (for a total of 80 previously treated patients) to the study to better estimate the 90% confidence intervals for response rate.

Reviewer comment: *This change to increase the sample size is not included in the list of protocol amendments. The change is noted in Section 16.8 of the NCCTG protocol. Other than to better estimate the response rate, no explanation is given in the protocol or in the NDA for the change.*

The protocol did not refer to secondary endpoints as such, but did include definitions for time to progression and death (from date of entry to event). Duration of response was defined in the protocol as the time from the date of entry until the last date of regression. The protocol did not define time to response. For the purposes of this NDA submission, the sponsor includes the following definitions: 1) duration of response, defined as the period from date of first objective documentation of response to the date of first objective documentation of disease progression or to the off-study date or data cutoff date, whichever came first; 2) time to response, defined as the period from first dose of CPT-11 to the first objective documentation of response; 3) time to disease progression, defined as the period from the date of initial treatment to the date of first objective documentation of disease progression or to the off-study date or data cutoff date, whichever came first; 4) survival, defined as the period from the date of initial CPT-11 to the last date known alive.

Reviewer comment: *As previously noted, the accuracy of the time-to-event data depends heavily on how carefully patients were monitored and evaluated for those events.*

Tumor Measurements

As noted under the Procedures Section, tumor measurements were to be obtained in all patients at baseline and prior to the second and third courses of therapy and after every other subsequent course of therapy. The protocol provided instructions for the selection of indicator lesions included minimum sizes.

Tumor measurements were performed as follows:

Palpable Hepatomegaly:

Specific instructions for palpable hepatomegaly were: If the liver was enlarged (palpable ≥5 cm below costal margin) because of tumor involvement documented by biopsy or imaging study (e.g., CT scan, MRI, ultrasound), include liver as an indicator. Measure liver in cm below costal margins at midclavicular lines (L,R), and below xiphoid (X); take measurements during quiet respiration; do not use liver span; if

measurements can be obtained by palpation, after initial documentation by imaging study, imaging is not required on subsequent evaluations.

Bidimensional Indicator Lesions:

If the patient had multiple clearly measurable indicator lesions in different organ systems, at least one lesion in each of the different organ systems was to have been assessed at the time of each tumor evaluation. The minimum size of the indicator lesion depended on the method of measurement and was 1.0 cm for discrete lesions that could be measured with calipers either during physical examination or by chest x-ray, 3.0 cm for lesions that were measured by CT or MRI scan, and 5.0 cm for lesions that were measured by radioisotope liver scan.

The same tumor site(s) was (were) to be evaluated throughout the study.

Response Criteria: (Study 0003R)

Complete Response (CR):

Total disappearance of all tumors for at least four weeks and no new lesions.

Partial Response (PR):

Palpable hepatomegaly: ≥ 30% decrease in the sum of the linear measurements below the right and left costal margins in the midclavicular lines and below the xiphoid process for at least four weeks

Bidimensional tumors: ≥ 50% reduction in the sum of the products of the longest perpendicular diameters of indicator lesion(s), which were chosen before therapy, for at least four weeks.

Both palpable hepatomegaly and bidimensional indicator lesions: ≥ 50% decrease in the sum of the products of the largest perpendicular diameters of the indicator lesions that were chosen before therapy for at least four weeks or ≥ 30% decrease in the sum of the linear liver measurements below the right and left costal margins in the midclavicular lines and below the xiphoid process for at least four weeks.

Stable Disease (SD):

Patients were considered to have stable disease if they did not meet the criteria for complete or partial response or for progression.

Progressive Disease (PD):

Progression was defined as the appearance of new lesions, an increase in tumor size, or significant clinical deterioration that could not be attributed to treatment or to other medical conditions, including > 5% loss in body weight, worsening of tumor-related symptoms, or a decline of more than one in performance on the ECOG Performance Status scale. For patients who had a measurable indicator lesion(s) and who achieved a partial response, progression was defined as an increase in the smallest size of the indicator lesion of at least 50% of the decrease in size between the pretreatment measurement(s) and the smallest measurement at the point of maximum tumor reduction. For patients who had a measurable indicator lesion(s) and who achieved a complete response, progression was defined as a measurable tumor mass that met any of the following criteria: 1.0 cm for discrete lesions that could be measured with calipers either during physical examination or by chest x-ray, 3.0 cm for lesions that were measured by CT or MRI scan, and 5.0 cm for lesions that were measured by radioisotope liver scan. For patients who had a measurable indicator lesion(s) and who did not achieve a partial or complete response, progression was defined as a > 25% increase in the measurement(s) of the indicator lesion(s) relative to pretreatment measurements.

Reviewer comment: *These response criteria differ from those of study Protocol 0001; the definition of progressive disease is particularly complex.*

Eastern Cooperative Oncology Group Performance Status

The eligibility criteria were based on ECOG criteria; so, it is assumed that the ECOG Performance Status scale was used to rate the patient's performance throughout the study. The protocol did not further define the ECOG PS scale.

Carcinoembryonic Antigen (CEA)

Levels of CEA were determined in some patients. However, CEA levels were not used to evaluate disease response.

6. Results of statistical consultation

See Biometrics Division review (T. Koutsoukos). The statistical aspects of this submission are mainly descriptive.

7. Results of study (Study 0003R)

Sponsor's Monitoring of the Data (Study 0003R)

NCCTG acted on behalf of in conducting and monitoring this trial. After US development of CPT-11 was licensed to The UpJohn Company in November 1993, certain obligations for the study continued to reside with and the NCCTG. These included study monitoring, investigational medication accountability, review of CRFs, and data clean-up and entry. In addition, had responsibility for submitting study-related information to the IND. Narrative summaries for patients who died while on study, discontinued treatment because of medical events, or were hospitalized were drafted by Responsibility for the analysis of the study results and report writing resided with The Upjohn Company.

An internal audit of scans for patients who attained an objective response to CPT-11 therapy was conducted, according to the NCCTG standard operating procedures for reviews, by members of the NCCTG at the Mayo Clinic. The peer-review panel was composed of four medical oncologists: Henry C. Pitot, MD; Harold E. Windschitl, MD; Richard M. Goldberg, MD; and Joseph Rubin, MD.

Another panel reviewed scans and clinical records to determine whether CPT-11 responders were progressing during or after 5-FU therapy but before receiving CPT-11. The panel was composed of three physicians—one radiologist and two medical oncologists—who were selected based on their expertise in the treatment of gastrointestinal cancers. The members of this independent review committee were as follows: Janet L. Potter, MD (Department of Radiology, The University of Texas Health Center at San Antonio, San Antonio, TX); Kathy Lyn Christman, MD (Department of Hematology-Medical Oncology, Lackland AFB, Texas); and Margaret Ann Tempero, MD (University of Nebraska Medical Center, Omaha, NE).

Protocol Deviations: (Study 0003R)

The following deviations from the protocol were identified by the sponsor:

- The protocol designated that patients must have received one prior 5-FU-based chemotherapy prior to entry into this protocol. As best as can be determined, 23 patients received more than one chemotherapy regimen because investigators interpreted this wording to mean *at least* one prior 5-FU-based regimen.

- In the protocol, patients were designated as evaluable if they had signed a consent form and had begun treatment. In the efficacy analysis, patients who received at least one dose of CPT-11 were included in the intent-to-treat population while those who received at least one course of treatment were considered evaluable. (All patients enrolled were treated with at least one dose of CPT-11)

- The original estimate of total accrual in the protocol was 30 previously treated patients. It was decided in February, 1994 to increase accrual to a total of 80 previously treated patients to better estimate the confidence intervals for response. A total of 90 patients were ultimately accrued.

- 95% confidence intervals were included in the analysis rather than the 90% confidence intervals, as suggested by the protocol.

- The duration of response, which was defined in the protocol as "the time of the date of study entry until the last date regression is documented," was modified to "the period from date of first objective documentation of response to the date of first objective documentation of disease progression or to the off-study date or data cutoff date, whichever came first."

- Secondary endpoints of time to response, response duration, time to disease progression, survival and performance status were evaluated.

- Additional subgroup analyses of efficacy based on age, gender, performance status, prior 5-FU therapy, and prior response to 5-FU were included.

- One patient received a 130-mg/m^2 dose and one patient was given a 25-mg/m^2 dose; these dose levels were not described in the protocol.

- Because SGPT determinations were not performed routinely at all institutions, values for this assay were obtained in only 13 patients.

- Seven patients received metoclopramide during the trial despite instructions in the protocol requesting that this concomitant medication not be given.

Demographics (Study 0003R)

The median age for the 90 patients on this study is 63 years. There were 58 (64.4%) men and 32 (35.6%) women. Eighty-six (95.6%) of the patients were white, the remainder were African-Americans. All of the patients had a PS of 2 or better (37.8%, PS 0; 47.8%, PS 1; 14.4%, PS 2). Please refer to the Integrated Summary for more details on demographic characteristics.

Pretreatment Disease-Related Characteristics: (Study 0003R)

The majority of patients (> 70%) had colon cancer and half of the patients had three or more metastatic sites. The most common sites of metastases were the liver (63.3%) and lung (54.4%). The time from first diagnosis to the first CPT-11 infusion ranged from 3 to 148 months (mean, 32 months; median, 21 months) for the intent-to-treat population.

Prior Therapy: (Study 0003R)

The most common previous 5-FU-based chemotherapeutic regimen was 5-FU + leucovorin; 60.0% of patients had received this combination. Twenty-six (28.9%) patients had previously received radiation therapy to the pelvic/abdominal area. Forty-six (51.1%) of the patients had previously received 5-FU therapy for metastatic disease and had experienced disease progression during or within three months after stopping therapy. The prior therapy of patients on this study is shown in the following table:

Prior Therapy for Colorectal Cancer (Study 0003R)
(Source: Adopted from Table 19 m0003R.txt)

Characteristic	N=90	
	No.	%
Classification of Prior 5-FU Therapy:		
PD ≤ 6 months after adjuvant 5-FU R_x	6	6.7
PD > 6 months after adjuvant 5-FU R_x	14	15.6
PD ≤ 3 months after 5-FU R_x for metastatic disease	46	51.1
PD > 3 months after 5-FU R_x for metastatic disease	13	14.4
Could not be classified	11	12.2

Source: Appendix B, Tables 2.2.1, 2.2.2, 5.1.10, 5.2.3

As shown in the above table, 15.6% of patients had progressed more than

six months after receiving adjuvant chemotherapy. This is in contrast to only 2.1% and 1.1% of patients in studies 0001 and 0006.

TREATMENT ADMINISTRATION (Study 0003R)

Number of Courses Delivered:

As of the cutoff date, a total of 288 courses of therapy were delivered. The median number of courses was 3.0 (range, 1 to 14), for a median of 18 weeks on therapy.

Dose Adjustments: (Study 0003R)

The course starting dose of CPT-11 was 125 mg/m^2, and all 90 patients initially received this dose. Dosage adjustments after the initial starting dose were made for each patient based on individual tolerance.

Twenty-five (27.8%) of the 90 patients required no adjustment in the 125-mg/m^2 starting dose during the study. The dose was adjusted downward (to 100, 75, 50, or 25 mg/m^2) in 61 (67.8%) of the patients and upward (to 130 or 150 mg/m^2) in four (4.4%) of the patients.

The CPT-11 dose was to be adjusted within courses based on the toxicities that were present at the time of scheduled treatment on week 2, 3, or 4. No adjustment in the course starting dose was made within 80 (61.1%) of the 131 courses that were initiated at the 125-mg/m^2 dose. The dose was reduced to 100, 75, or 50 mg/m^2 within 50 (38.2%).

A total of 1023 doses of CPT-11 were administered, and 612 (59.8%) of the doses were administered at a doses of < 125 mg/m^2, primarily at the 75- and 100-mg/m^2 dose levels; 59 doses were omitted during the study.

Disposition by dose: (Study 0003R)

Patients received from 1 to 14 courses of therapy. All 90 of the patients received at least one dose of CPT-11. Two-thirds of the patients received at least part of the second course. The median number of courses was 3.0.

Treatment Modifications for Diarrhea and Neutropenia/Leukopenia: (Study 0003R)

The number of courses that were associated with a decrease in dose because of diarrhea, neutropenia, or leukopenia is summarized in the

following table:

Frequency of Dosage Adjustments due to Late Diarrhea, Neutropenia, or Leukopenia by Course (Study 0003R)

(Source: modified from Table 24 m0003R)

Reason for Dosage Modification	No. & % of Courses with Event N = 288		No. & % of Courses Requiring Dosage Modification for Event N = 288	
	No.	%	No.	%
Diarrhea (late)*	164	56.9	57	19.8
Neutropenia	130	45.1	52	18.1
Leukopenia	151	52.4	14	4.9

*Occurred > 24 hours after administration of CPT-11.

Dose Intensity: (Study 0003R)

The projected dose intensity was 83.3 mg/m^2/week for the 125 mg/m^2 starting dose. The actual median dose intensity for the entire duration of treatment was 56.1 mg/m^2/week. Median dose intensity decreased from 62.5 mg/m^2/week to 54.2 mg/m^2/week between courses 1 and 2 and then remained relatively constant at about 50.0 mg/m^2/week thereafter.

EFFICACY RESULTS (Study 0003R)

Efficacy data were summarized for two patient populations: 1) the intent-to-treat population, which comprised the 90 patients who received at least one dose of CPT-11, and 2) the evaluable population, which comprised the 66 (73.3%) patients who received at least one course of CPT-11. The response information presented in the following sections is based on the results of the peer-review panel's findings. Censored data were used in the duration of response, time to disease progression, and survival analyses.

The reasons for not completing the first course of therapy and for exclusion from the evaluable-patient efficacy analyses are summarized in the table, below.

Study 0003R
Reasons for Not Completing One Course of CPT-11[a]
(Source: Table 16, m0003r.txt)

Pt. No.	Reason for Study Discontinuation	No. of Doses	Total Dose (mg/m^2)
	Disease progression before completing one course	3	375
	Disease progression before completing one course	3	375
	Disease progression before completing one course	3	350
	Disease progression before completing one course	2	225
	Disease progression before completing one course	2	200
	Death due to disease progression	1	125
	Death due to disease progression	3	350
	Personal request (did not wish to receive further therapy due to side effects)	3	325
	Personal request (tired of chemotherapy)	1	125
	Grade 4 diarrhea	3	325
	Disease progression before completing one course	3	325
	Disease progression before completing one course	3	350
	Personal request (did not wish to receive further therapy due to side effects)	1	125
	Disease progression before completing one course	3	350
	Disease progression before completing one course	3	325
	Personal request (did not wish to receive further therapy due to side effects)	2	250
	Disease progression before completing one course	3	375
	Disease progression before completing one course	3	350
	Disease progression before completing one course	2	200
	Disease progression before completing one course	3	350
	Disease progression before completing one course	2	225

Study 0003R
Reasons for Not Completing One Course of CPT-11[a]
(Source: Table 16, m0003r.txt)

Pt. No.	Reason for Study Discontinuation	No. of Doses	Total Dose (mg/m^2)
	Disease progression before completing one course	3	325
	Disease progression before completing one course	2	250
	Personal request (refused further chemotherapy due to abdominal discomfort)	2	250

[a] Each of these patients did not complete one full course of CPT-11. These patients are included in the intent-to-treat efficacy analysis, which is presented alongside the evaluable patient efficacy analysis.
Source: Appendix B, Tables 1.1.4, 4.1.1, 6.6.1

Reviewer comment: *Please note that the proportion of patients who did not complete at least one course of therapy in this study is considerably higher than in Studies 0001 and 0006. Also note that the vast majority of patients (18/24) who were excluded from the intent-to-treat analysis did not complete the first course of CPT-11 because of progressive disease. The response rate in the intent-to-treat population probably better represents the rate expected in the practice of oncology than does the response rated in the evaluable population.*

Response Rate: (Study 0003R)

Twelve patients achieved a partial response to CPT-11 therapy (there were no complete responses), for an overall response rate of 13.3% (12/90) for the intent-to-treat population and 18.2% (12/66) for the evaluable population. Stable disease was achieved in 55.6% of the intent-to-treat population and 71.2% of the evaluable population. Information on the 12 responding patients is included in the table below:

Study 0003R
Demographic and Prior 5-FU Therapy for Responders to CPT-11[a]
(Source: modified from Table 29, m0003R)

Pt. No.	Sex/Age (y)	Response to CPT-11	Classification of Prior 5-FU Therapy[b]
	M/58	PR	PD ≤ 3 months after 5-FU therapy for MD
	M/38	PR	PD ≤ 3 months after 5-FU therapy for MD
	F/71	PR	PD ≤ 3 months after 5-FU therapy for MD
	F/76	PR	PD ≤ 3 months after 5-FU therapy for MD
	M/48	PR	PD > 6 months after adjuvant 5-FU
	M/69	PR	PD ≤ 3 months after 5-FU therapy for MD
	F/61	PR	PD ≤ 3 months after 5-FU therapy for MD
	M/65	PR	PD > 3 months after 5-FU therapy for MD
	M/69	PR	PD ≤ 3 months after 5-FU therapy for MD
	M/70	PR	PD ≤ 3 months after 5-FU therapy for MD
	M/66	PR	PD ≤ 3 months after 5-FU therapy for MD
	F/32	PR	PD ≤ 3 months after 5-FU therapy for MD

[a] MD = metastatic disease, PR = partial response, PD = progressive disease, NA = not available

[b] During data analyses, the sites were asked to provide further information on each patient's prior 5-FU regimen and these data were used to further clarify the status of each patient at entry into this study. Classifications of prior 5-FU therapy for CPT-11 responders were those of the independent review committee. Please note that the number of months after 5-FU refers to the number of months after stopping 5-FU.

According to the information provided by the sponsor in the NDA, among the 11 responders who had received previous 5-FU therapy for metastatic disease, two (18.2%) were reported as having responded and seven (63.6%) as not having responded to their prior 5-FU therapy; the response to 5-FU in two (18.2%) patients was unknown.

Reviewer comment: *Please note that one of the responding patients had progressive disease more than 6 months after stopping adjuvant chemotherapy (actually, 2½ years after stopping adjuvant therapy). Perhaps a good argument can be made for excluding this patient from the response analysis. If*

this patients were excluded from the efficacy intent-to-treat analysis, the overall response rate for this study would merely drop from 13.3% to 12.2%. Also, please note that the details regarding prior therapy and response of prior therapy were obtained retrospectively.

Time to Response: (0003R)

The median time to achieve objective response was 1.5 months (range, 0.9 to 5.5 months). Five responses were observed after the first, four were observed after the second, one was observed after the third, and two were observed after the fourth course.

Duration of Response: (Study 0003R)

The median duration of response for the 12 patients who obtained an objective response to therapy was 5.9 months (range, 2.6 to 15.1 months). Censored information for two patients were used in this analysis; one of these patients was still on study as of the data cutoff date (March 31, 1995).

Reviewer comment:

Reviewer evaluation of the response data:

The information in the CRF's and data listings were reviewed to verify the sponsor's assessment of response. The individual patient data listings for tumor measurements for this study were difficult to follow. The listings for some tumor measurements were in one table (e.g. liver exam measurements) and those for other measurements (CXR, CT) were in another table. The tables have the same number (Table 1.4.3 for both) and almost identical headings. Evidently, the two tables differ in the manner the calculating the tumor measurements (i.e., length + width + thickness versus length x width). The manner in which these data were presented in the NDA was awkward for the reviewer but otherwise acceptable.

This protocol's response criteria for progression is somewhat complicated, making the verification of response duration difficult for the reviewer. The definition of progressive disease includes criteria for worsening of disease-related symptoms or performance status and for weight loss; these are difficult to

confirm from the CRFs because of lack of detailed documentation. In addition, the definition of progressive disease for patients who had a PR is an increase in the smallest size of the indicator lesion of ≥ 50% of the decrease in size between the pretreatment measurement(s) and the smallest measurement at the point of maximum tumor reduction. These criteria are not only more difficult to confirm but are somewhat liberal compared to the standard ≥ 25% increase in the size of the tumors compared to best response.

If the one patient who had progressive disease more than 6 months after adjuvant chemotherapy and achieved a PR on CPT-11 were excluded from the efficacy intent-to-treat analysis, the overall response rate would drop from 13.3% to 12.2%. This patient's only prior chemotherapy was adjuvant 5FU/leucovorin which was administered from 12/11/89 to 10/09/90. He started CPT-11 on 7/06/93 for progression that occurred about 2½ years after adjuvant therapy.

On review of the CRFs and data listings on the patients who according to the sponsor's assessment responded to CPT-11, fairly good concordance was found between the FDA's assessment and the sponsor's assessment of response for most patients. However, discrepancies were noted in three cases The sponsor was notified of these discrepancies on April 23 and April 24, 1996. Discrepancies regarding two of the patients were adequately clarified by the sponsor in a fax dated April 25, 1996. The sponsor's explanation regarding the discrepancies in the other patient were not adequate. This patients tumor did not meet the criteria of response according to the FDA assessment. The response rate should be corrected by omitting the one patient from the numerator.

Discrepancies Between FDA and Sponsor Tumor Response Assessments		
Pat. #	Change in Response Status	Comments
	Change best response status from PR to non-responder.	There were bidimensional measurements by CT scan for two hepatic lesions at baseline and follow-up. According to the patient listings in the CRF, only one was categorized as measurable; the other, for no apparent reason, is categorized as evaluable. Both should have been included in the assessment of response, in which case the criteria for PR is not met. In the sponsor's April 25, 1996 facsimile, the sponsor indicated that the NCCTG peer review committee considered only one of the lesions as measurable. Unfortunately, this assessment was made retrospectively. But it is still unclear why the other lesion was not considered measurable if bidimensional measurements are recorded at baseline and follow-up. If the measurements of both lesions are considered, the greatest decrease in the area of the lesions was 38% on 12/28/93.

Time to Disease Progression: (Study 0003R)

The estimates of time to disease progression include censored data for nine patients; two of these patients were still on study as of the data cutoff date (March 31, 1995). For all 90 patients, the median time to disease progression was 3.5 months (range, 0.3 to 19.9 months).

Reviewer comment: *Please refer to the FDA Statistician's (Tony Koutsoukos, Ph.D.) Review regarding the verification of the time to event data. This was done using the sponsor's electronic data basis.*

Survival: (Study 0003R)

The estimates of survival time include censored data for the 23 patients who were still living as of the data cutoff date. The median survival time for the 90 patients was 8.1 months (range, 0.4 to 22.1 months). As of the data cutoff date for this report, five of the 12 patients who attained an objective response to therapy were still living. The median survival time for the 12 responders was 12.5 months (range, 4.5 to 22.1 months).

Performance Status: (Study 0003R)

Of the 12 responders, seven had a baseline performance status of 0, four had a baseline performance status of 1, and one had a baseline performance status of 2. See the integrated discussion for the results.

Carcinoembryonic Antigen (CEA): (Study 0003R)

Levels of CEA were measured in only three (3.3%) of the patients. Only one patient had both a baseline and on-study values (no. 9016563).

Clinical Benefit: (Study 0003R)

See Integrated Summary of Efficacy for summary data on PS and body weight.

Reviewer comment: *In regards to disease related symptoms, there are a paucity of data. According to the data listings in the NDA, only 3 of the 12 patients (25%) who achieved an objective tumor response (CR or PR) to CPT-11 had what were reported to be disease related symptoms at baseline. Patient had "swelling of the abdomen", patient had decreased appetite, and patient had "pain - unknown". Patients were reported to have improvement of the symptoms on CPT-11 whereas the outcome of the symptoms in patient was reported as unknown. Seventeen of the 51 patients whose best objective tumor response to CPT-11 was stable disease were reported to have had disease related symptoms at baseline. Only 3 of the seventeen patients were reported to have symptoms to improve on CPT-11; in the remainder of the 17 patients, the symptoms were reported not improve or the outcome of the symptoms is reported as unknown.*

***Review comment:** No firm conclusions regarding clinical benefit from CPT-11 can*

be made from these limited respectively collected results.

SAFETY RESULTS: (Study 0003R)

Medical Events: (Study 0003R)

All Medical Events

One or more medical events was reported for each of the 90 patients. The most frequently reported medical events were in the digestive, hemic and lymphatic, body as a whole, skin, metabolic and nutritional, and respiratory systems, with > 50% of patients reporting at least one event in each of these systems.

Drug-Related Medical Events: (Study 0003R)

One or more drug-related medical events (considered by the investigator to be possibly, probably, or definitely related to study medication) were reported for each of the 90 patients. Each of the 90 patients reported at least one drug-related digestive system event; > 50% of the patients reported nausea, late diarrhea (> 24 hours after administration of CPT-11), vomiting, or anorexia. Anemia, leukopenia, neutropenia, asthenia, and alopecia were also frequently reported as drug-related events (reported for > 50% of patients).

Grade 3 and 4 Medical Events: (Study 0003R)

Potentially serious medical events were categorized as grade 3 or 4 events using the NCI Common Toxicity Criteria. Grade 3 or 4 events reported in > 10% of patients were late diarrhea, nausea, vomiting, anorexia, neutropenia, and leukopenia (Please refer to the discussion of the integrated data for the incidence of these events).

Hospitalizations: (Study 0003R)

Thirty-eight (42.2%) of the 90 patients were hospitalized at least once during the study for medical-event reasons. Thirty-two (35.6%) patients were hospitalized for events judged by the investigators to be related to administration of CPT-11.

Discontinuations on Study: (Study 0003R)

As of the cutoff date for this report, 88 (97.8%) of the 90 patients had

discontinued from the study (75 patients due to progression), and two (2.2%) of the 90 patients were still in the study.

On-Study Deaths: (Study 0003R)

On-study deaths were defined as deaths that occurred in the treatment phase of the study or within 30 days of administration of the last dose of CPT-11. Seven (6.7%) of the 90 patients died while on study. Three of these patients were actually discontinued from therapy due to death; two died of disease progression and one of a myocardial infarction None of the seven deaths were attributed to treatment with CPT-11 by the investigators.

Reviewer comment: *These results need to be interpreted with caution. In going over the sponsor's narratives of the patients who died on study, the usual scenario is that the patient is admitted to the hospital with a serious adverse event, the patient is treated for that complication, the patient dies. At the time of death, the patient has evidence of progressive disease, and the cause of death is listed as progressive disease. However, in some cases it may be difficult to rule out an association between the drug-related adverse event and the death of the patient. FDA review of the CRFs of the patients who died on study found evidence that the death of one patient was definitely related to CPT-11; this patient developed grade 3 dehydration and grade 4 neutropenia the day prior to death. The death of another patient was possibly related to CPT-11.*

Discontinuations Due to Medical Events (Study 0003R)

Two (2.2%) patients discontinued treatment due to drug-related medical events [grade 1 dyspnea] and [grade 4 diarrhea, grade 3 leukopenia, grade 1 neutropenia]). An additional patient who experienced diarrhea, vomiting, and fever in course 1, requested removal from treatment for reasons that can reasonably be related to medical events.

Selected Medical Events: (Study 0003R)

Late Diarrhea

Grade 3 and 4 late diarrhea occurred in 33.3% (30/90) of the patients and in

13.2% (38/288) of the courses. In this study, the frequency of grade 3 and 4 late diarrhea was significantly greater in male than in female patients (43.1 versus 15.6%; p=0.01).

On September 28, 1993, all study sites were asked to adopt the more rigorous standardized approach of intensive loperamide therapy for the treatment of late diarrhea described earlier in this report.

Reviewer comment: *The sponsor claims that the incidence of grade 3 and 4 diarrhea was reduced after the institution of aggressive loperamide therapy. However, the summary data in the NDA is provided by course rather than by patient. The influence of dose reduction on the incidence of diarrhea by course is not clear from the submitted summary data.*

The following table summarizes the incidence of late diarrhea on this study.

Frequency of Late Diarrhea[a] (Study 0003R)
(Source: Table 42, m0003R)

	No.	No. (%) with Diarrhea	Maximum NCI Grade				No. (%) Grade 3 + 4
			1	2	3	4	
Patients		76 (84.4)	23	23	11	19	30 (33.3)
Courses	288	164 (56.9)	78	48	17	21	38 (13.2)

[a] Occurred > 24 hours after administration of CPT-11
Source: Appendix B, Tables 6.2.3, 6.2.4, 6.4.3, 6.4.4

Overall, 56 (62.2%) of the 90 patients received loperamide with/without another antidiarrheal as a treatment for late diarrhea. The CPT-11 dose was reduced in 19.8% (57/288) of the courses because of late diarrhea.

Early Diarrhea: (Study 0003R)

Early diarrhea was reported in 44.4% (40/90) of the patients and in 31.9% (92/288) of the courses. Grade 3 or 4 early diarrhea occurred in 33.3% (30/90) of the patients and in 4.2% (12/288) of the courses. Five (5.6%) of the patients received treatment with atropine for early diarrhea.

Nausea and Vomiting: Study 0003R)

Grade 3 or 4 nausea was reported in 23.3% (21/90) of the patients and in 8.7% (25/288) of the courses, and grade 3 or 4 vomiting was reported in 16.7% (15/90) of the patients and in 6.3% (18/288) of the courses.

Treatment with antiemetic agents was allowed. Various agents and regimens were used. Sixty-five (72.2%) of the patients received ondansetron hydrochloride, 54 (60.0%) were given prochlorperazine, and 47 (52.2%) received dexamethasone as prophylaxis for nausea/vomiting.

Dyspnea: (Study 0003R)

Dyspnea was reported for 35.6% (32/90) of the patients and in 16.7% (48/288) of the courses. Grade 3 or 4 dyspnea was reported for 6.7% (6/90) of the patients and in 2.1% (6/288) of the courses. Dyspnea was judged to be related to administration of CPT-11 for 21.1% (19/90) of the patients. Of the 32 patients with dyspnea, 22 had lung metastases, including 11 of the 19 patients whose dyspnea was judged to be potentially related to administration of CPT-11. One patient was removed from protocol treatment for grade 1 dyspnea in conjunction with a decline in DLCO from 61 L/sec to 30 L/sec over four courses of therapy. These events were considered to be potentially related to study medication.

Neutropenia: (Study 0003R)

Grade 3 or 4 neutropenia occurred in 31.1% (28/90) of the patients and in 13.9% (40/288) of the courses. The CPT-11 dose was reduced in 18.1% (52/288) of the courses because of neutropenia.

Simultaneous Neutropenia and Fever: (Study 0003R)

Neutropenic fever, defined as grade 4 neutropenia and ≥ grade 2 fever, occurred in two (2.2%) patients and in two (0.7%) of the courses. Both patients were hospitalized and recovered after receiving antibiotic therapy. Only six (6.7%) of the 90 patients received G-CSF at any time as prophylaxis or therapy for neutropenic fever.

Reviewer comment: *As noted previously, the use of grade 4 neutropenia (i.e., <500 cells/mm^3) for neutropenic fever is somewhat liberal but acceptable. Some investigators use fever in the presence of grade 3 neutropenia. Based on an analysis of the electronic data by FDA statistician Tony Koutsoukos, 4.4% of the patients on this study met the criteria for febrile neutropenia defined using the more conservative criteria of grade 3 or 4 neutropenia.*

Simultaneous Neutropenia and Late Diarrhea: (Study 0003R)

Grade 3 or 4 neutropenia occurred simultaneously with grade 3 or 4 late diarrhea in 10.0% (9/90) of the patients and in 3.1% (9/288) of the courses. Of the nine patients with simultaneous grade 3 or 4 neutropenia/late diarrhea

also had neutropenic fever. There were no fatal outcomes in patients who experienced simultaneous grade 3 or 4 neutropenia/late diarrhea.

Hematologic Toxicities Other Than Neutropenia:

Lymphocytopenia of any grade was observed in all 89 (100%) of the patients who had baseline and at least one follow-up evaluation and was grade 3 or 4 in 77.5% (69/89) of the patients. There were no opportunistic infections specifically attributed to lymphocytopenia, although one patient received amantadine hydrochloride orally as treatment for a viral infection, one patient received acyclovir as treatment for herpes zoster, and another patient was given metronidazole orally as an amebicide.

Thrombocytopenia occurred in 3.4% (3/89) of the patients; there was only one case of grade 3 and only one case of grade 4 thrombocytopenia. The grade 4 thrombocytopenia in this patient was judged to be related to treatment with CPT-11.

Anemia was observed in 97.8% (87/89) of the patients and was grade 3 or 4 ($\leq$ 8 g/dL) in 11.2% (10/90) of the patients. Fourteen (15.6%) patients received blood transfusions for anemia.

Median time to the nadir for hematology values ranged from 14 days for platelets to 21 days for leukocytes, neutrophils, lymphocytes, and hemoglobin.

Liver and Renal Function Tests:

Fewer than 10% of patients had grade 3 or 4 values for liver or renal function tests. Grade 3 or 4 values for bilirubin were reported for 4.8% (4/84) of the patients and in 1.7% (4/233) of the courses. All four patients had bilirubin values within normal limits at baseline. The highest on-study value was 4.0 mg/dL in a patient who had a baseline value of 0.7 mg/dL.

Abnormal values in two patients (nos. 9011591 and 9016590) returned to within normal limits with continued treatment; no follow-up values were available for the remaining two patients.

Grade 3 values for creatinine were reported for 2.4% (2/85) of the patients and in 0.8% (2/237) of the courses. Both patients had normal values at baseline. The highest on-study values in these patients occurred in course 1 and were 5.6 mg/dL and 6.1 mg/dL, respectively. Values in one patient returned to within normal limits with continued treatment; the other patient had a grade 3 value for creatinine at the time treatment was discontinued, and no further follow-up was available.

Other Chemistry Abnormalities:

These will be discussed in the integrated summary of the three controlled studies or in the package insert.

Diffusion Capacity of the Lung for Carbon Monoxide (DLCO):

A DLCO measurement was obtained at baseline and at study completion in 58 of the 90 patients. There was a significant mean decrease in DLCO from 91.5 L/sec to 84.0 L/sec ($p<0.001$) in these patients between baseline and the end of the study. Thirty-six patients had decreases, 19 had increases, and three had no change in DLCO values. Effects did not appear to be related to the CPT-11 dose. In 15 patients who received a total dose of > 2000 mg/m^2 of CPT-11, seven had an increase and seven had a decrease in DLCO between baseline and the end of the study; the remaining patient showed no change. The overall decrease of 7.5 L/sec in DLCO was not considered by the sponsor to be clinically significant given the 20% variability of the test and the lack of adjustment for progressive pulmonary metastases or progressive anemia in some of the patients.

Concomitant Medications:

Central nervous system drugs (primarily analgesics and antiemetic/antivertigo agents) were the most frequently taken followed by gastrointestinal (primarily antidiarrheal agents), hormonal (primarily dexamethasone as prophylaxis for nausea/vomiting), and nutritional agents. Antiemetic/antivertigo agents were taken by 65.6% of patients, and adrenal cortical steroids (primarily dexamethasone as prophylaxis for nausea/vomiting) were taken by 51.1%. None of the 54 patients who received prochlorperazine as prophylaxis for nausea/vomiting in this study experienced akathisia. It is of note that 28.9% of the patients used laxatives

during the study.

8. Conclusions: (Study 0003R)

a. Scientific:

This was an open label expanded Phase II study in 90 patients with metastatic colorectal cancer who had previously received a 5 FU based chemotherapy regimen. This study is similar to study 0001 but enrolled about twice as many previously treated patients and has somewhat more complex response criteria. This can be considered an adequate and well controlled (historical) study for the primary endpoint of objective tumor response. This is not an adequate and well controlled study of the secondary endpoints such as time to progression and survival. The study was not adequately designed to adequately evaluate clinical benefit endpoints such as changes in PS, body weight, and disease related symptoms.

Regarding prior 5FU therapy, as many as 15.6% of patients had progressed more than six months after receiving adjuvant chemotherapy on this study compared to only 2.1% and 1.1% of patients in studies 0001 and 0006. Fortunately, only one of the 12 patients the sponsor classified as a responder to CPT-11 did not receive 5FU for metastatic disease.

Twelve of 90 patients achieved a partial response to CPT-11 therapy (there were no complete responses), for an overall response rate of 13.3% for the intent-to-treat population and 18.2% (12/66) for the evaluable population. According the FDA review of the data listings, the data on only 11 of the 90 patients met the criteria for response resulting in a response rate of 12.2%.

Please note that one of the responding patients who responded to CPT-11 in this study had progressive disease more than 6 months (i.e., 2½ years) after adjuvant chemotherapy. If this patient were excluded from the efficacy intent-to-treat analysis, the overall response rate for this study would drop from 13.3% to 12.2% according to the sponsor's assessment and from 12.2% to 11.1% in the FDA analysis.

The median duration of response according to the sponsor's analysis was 5.9 months (range, 2.6 to 15.1 months). The median time to disease progression for all 90 patients was 3.5 months (range, 0.3 to 19.9 months). The median survival time for the 90 patients was 8.1 months (range, 0.4 to 22.1 months); the significance of these time to event results is not clear without a comparative control not treated with CPT-11.

The most prominent toxicities were diarrhea and neutropenia. The incidence of grade 3 or 4 late diarrhea was 33.3% in this study. In this study, the frequency of grade 3 and 4 late diarrhea was significantly greater in male than in female patients (43.1 versus 15.6%; $p=0.01$). Grade 3 or 4 neutropenia occurred in 31.1% (28/90) of the patients and in 13.9% (40/288) of the courses. Febrile neutropenia was uncommon (2.2% of patients. Lymphocytopenia was also very common; grade 3 or 4 lymphopenia occurred in 75.0% of patients. Opportunistic infections were not reported in associated with lymphopenia.

b. Deficiencies/Problems: (Study 0003R)

See Section on OVERALL CONCLUSIONS.

Based on the information in the NDA, all the patients in this study were treated with the drug product which differs from the UpJohn product proposed for marketing.

As noted above, according to FDA review of the submitted data, tumor measurements on one of the "responding" patients did not meet the criteria for objective response.

This study was not adequately designed to evaluate clinical benefit. The limited amount of retrospectively collected data is not adequate to draw firm conclusions regarding clinical benefit from treatment with CPT-11.

A3. Controlled studies (Study 0006)

Title: Phase II trial of irinotecan hydrochloride (CPT-11) for patients with 5-FU-refractory colorectal cancer.

Nine investigators participated in this multi center open-label multi center Phase II study - See the NDA for a listing of investigators and sites.

Enrollment of first patient: April 6, 1994 (date of 1st dose)
Data cutoff date for this report: March 31, 1995

(As of the March 31, 1995, data cutoff date for this report, 19 (11.4%) of the 166 patients were still receiving CPT-11 therapy: four received a starting dose of 125 mg/m^2 and 15 received a starting dose of 100 mg/m^2.)

Reviewer comment: *Please note that the sponsor submitted an update of the efficacy data on April 15, 1996 which provides additional response information through December 31, 1995 (Data on survival available to UpJohn as of March 12, 1996 (database freeze date) were also included in the update submission. Although the listings of the update may have been used for verifying some of the response data, the summary results included in this NDA review is from the original application. There were some minor changes in the time to event data because fewer data points are censored in the efficacy update, and longer follow-up to confirm one more response (brings the total number of responders in the sponsor's evaluation from 38 to 39 patients. Other than that, the summary data are not substantially changed from the original NDA.*

Protocol Amendments: (Study 0006)

- Amendment 1, dated March 11, 1994, changed the toxicity grading system from SWOG toxicity grading criteria to NCI criteria and specified that patients who attained a partial response would be treated until disease progression.

- Amendment 2, dated May 25, 1994, reduced the starting dose in the first course of therapy from 125 mg/m^2 to 100 mg/m^2 because the toxicity seen at the 125 mg/m^2 dose was perceived to be greater than that seen in previous studies. This amendment also revoked a restriction on the

consumption of caffeine-containing beverages that had been included in the study eligibility criteria.

- Amendment 3, dated July 14, 1994, increased the enrollment goal from 100 patients to 165 patients.

1. Objectives of the study: (Study 0006)

- To assess the antitumor activity of CPT-11 when administered once weekly for four consecutive weeks, followed by a two-week rest, in patients with metastatic colorectal cancer that had progressed within six months of one prior 5-FU-based chemotherapeutic regimen.
- To evaluate the toxicities of CPT-11 in this patient population.
- To ascertain the pharmacokinetics of CPT-11 and the active metabolite SN-38 in this population.

2. Rationale for the study: (Study 0006)

The rationale is not clearly stated in the protocol. Studies 0001 and 0003R were already in progress when this study was initiated. The rationale for this additional phase II study is not clear. Perhaps the sponsor wanted to expand the experience with CPT-11 to the community oncology setting.

3. Experimental Design: (Study 0006)

This was a multi center, open-label, phase II study of the efficacy, toxicity, and pharmacokinetics of CPT-11 in patients with metastatic colorectal carcinoma that progressed within six months of one prior 5-FU-based chemotherapeutic regimen.

a. Patient Population: (Study 0006)

(I) Inclusion criteria. (Study 0006)

- Histologic diagnosis of metastatic colorectal cancer.
- Measurable disease.
- Progressive disease within six months of treatment with one 5-FU-based regimen for metastatic colorectal carcinoma or recurrent disease within six months of treatment with an adjuvant 5-FU-based regimen.
- No chemotherapy for at least 28 days before study entry.

- No prior radiation to the pelvis for colorectal cancer, no radiation therapy delivered to areas other than the pelvis for at least six weeks prior to study entry and measurable lesions outside the radiation field.
- Performance status of 0 (asymptomatic) to 2 (symptomatic; in bed less than 50% of day) based on the Southwest Oncology Group (SWOG) criteria.
- Predicted life expectancy of at least 12 weeks.
- Pretreatment granulocyte count of $\geq$ 1500/mm^3, pretreatment hemoglobin level of $\geq$ 9 g/dL, and pretreatment platelet count of $\geq$ 100,000/mm^3.
- Adequate renal function, as defined by a value of $\leq$ 2 mg/dL for serum creatinine.
- Adequate hepatic function, as defined by a value of $\leq$ 2 mg/dL for serum total bilirubin, regardless of whether liver involvement was secondary to the tumor, and a value of $\leq$ 3 times the upper limit of the normal range for serum glutamic-oxaloacetic transaminase (SGOT; AST), unless the liver was involved with the tumor (in which case the SGOT value must have been $\leq$ 5 times the upper limit of the normal range).
- Ability to understand the study and willingness to sign a written informed consent statement.

(ii) Exclusions: (Study 0006)

- Two or more chemotherapeutic regimens for colorectal cancer (5-FU therapy on two different schedules was considered two regimens, unless the schedule change was for toxicity, not tumor progression).
- Active or uncontrolled infection.
- Concomitant use of coumadin (the original protocol did not allow caffeine but the protocol was amended to lift this restriction.
- Psychiatric disorders that would interfere with the patient's ability to give informed consent or to complete follow-up visits.
- History of myocardial infarction within the previous six months or current clinical evidence of congestive heart failure.
- Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the patient had been disease-free for at least five years.
- Central nervous system metastases.

- Pregnancy or lactation.
- Reproductive potential (male or female), unless an effective contraceptive method was used.
- The presence of severe underlying disease that, in the investigator's judgement, would make candidates inappropriate for entry into this study.

(iii) Procedure: (Study 0006)

DRUG ADMINISTRATION (Study 0006)

Drug supply: (Study 0006)

CPT-11 was supplied by The UpJohn Company as a 20 mg/mL sterile solution (ie, 2 mg of CPT-11 in 0.1 mL of solution) in two vial sizes: 2 mL vials containing 40 mg of CPT-11 and 5 mL vials containing 100 mg of CPT-11. Before 5/94, all of the patients were treated with drug manufactured by

Reviewer Comment: *Only two of seven lots of CPT-11 used in this study were produced by UpJohn, the remainder were produced by using sterilization. The switch to the UpJohn drug product (lot 27,211) did not take place until after 5/94. It is not clear how many patients were treated with the UpJohn product but is probably a small minority.*

Starting Dose and Schedule (Study 0006)

The starting dose was 125 mg/m^2 for the first 64 patients enrolled into the study. For the subsequent 102 patients, the starting dose was reduced to 100 mg/m^2 because the toxicity seen at the 125 mg/m^2 dose was perceived to be greater than that seen in previous studies. The appropriate dose was diluted and mixed in 500 mL of 5% Dextrose Injection (D5W) and administered IV (via a free-flowing catheter) over 90 minutes once weekly for four consecutive weeks followed by a two-week rest.

Additional Courses of Therapy (Study 0006)

Patients who obtained a partial response or whose disease remained stable could receive treatment with CPT-11 indefinitely unless unacceptable toxicity occurred. Patients who achieved a complete response could receive at least

two additional courses of therapy.

Dose Modifications (Study 0006)

Guidelines provided in the protocol for dose reductions and for dose escalations are summarized in Table 1.

Dose Level Reduction/Escalation Guidelines (Study 0006)
(Source: Table 1, 0006.txt)

CPT-11 Starting Dose (mg/m^2)	Dose Level Reduction or Escalation				
	-2	-1	0	+1	+2
100	60	75	100	125	150
125	75	100	125	150	

The dose of CPT-11 could not be escalated in the first course of therapy. If no significant toxicity occurred in patients beginning therapy at 125 mg/m^2, the dose could be increased to 150 mg/m^2 in the subsequent course of therapy. Patients who received CPT-11 at the 100 mg/m^2 dose-level in the first course could have the dose increased to 125 mg/m^2 in the second course and to 150 mg/m^2 in the third course if no toxicities had occurred in the prior course. No further escalation in dose beyond 150 mg/m^2 was allowed. Dose escalations were to be only made at the beginning of a new course of therapy. Dose reductions, as summarized below, were to be made before the start of each course or during a course of therapy depending on the toxicities that occurred.

Dose Modifications at the Start of Each Course of Therapy (Study 0006)

Before each new course of therapy was begun, if values for hematologic and serum chemistry tests were outside acceptable limits specified at study entry, treatment could be delayed for up to two weeks to allow for recovery. If values were not within acceptable limits at the end of this two-week period, the patient was to be discontinued from the study, unless it could be documented that the cause of the abnormal laboratory values was unrelated to treatment with CPT-11 or to the underlying cancer. Dose modifications for the next course of treatment are summarized in the table below.

Dose Modifications for the Next Course of Treatment[a] (Study 0006)

(Source: Table 2, 0006.txt)

Toxicity Grade	Type of Dose Modification	
	Hematologic Toxicity	Non-Hematologic Toxicity
0	↑ 1 Dose Level[b]	↑ 1 Dose Level[b]
1	None	None
2	None	↓ 1 Dose Level[c]
3	↓ 1 Dose Level	↓ 2 Dose Levels[d,e]
4	↓ 2 Dose Levels[e]	↓ 2 Dose Levels[e]
Neutropenic Fever	↓ 2 Dose Levels[e]	

[a] Based on worst toxicity observed during the preceding course.

[b] Dose was not to be escalated in course 1. For the 100 mg/m^2 starting dose, if no toxicity occurred in course 1, the dose was to be increased to 125 mg/m^2 in course 2. If no toxicity was seen in course 2, the dose was to be increased to 150 mg/m^2 in course 3. For the 125 mg/m^2 starting dose, if no toxicity occurred, the dose was to be increased to 150 mg/m^2 beginning in the subsequent course.

[c] Patients who experienced grade 2 diarrhea as their only grade 2 nonhematologic toxicity were to receive the same dose of chemotherapy on the next cycle.

[d] Patients who experienced grade 3 diarrhea as their only grade 3 nonhematologic toxicity were to be treated with one dose level lower (not two) on the next cycle of chemotherapy.

[e] The lowest dose level on the weekly schedule was to be 60 mg/m^2. Patients who experienced toxicity and required dose modification to levels below 60 mg/m^2 were to be taken off study due to toxicity. If there were extenuating factors (ie, intercurrent toxicity believed to be unrelated to CPT-11 therapy), the principal investigator was to be contacted to discuss appropriate dosing for that patient. Three patients at the 100 mg/m^2 starting dose received doses below 60 mg/m^2–one patient received 50 mg/m^2 and two patients received 45 mg/m^2.

Treatment courses were to be repeated at 42-day intervals. However, if treatment was withheld on week 4, the next course of therapy could begin one week earlier (ie, on day 36) if all toxicities were of grade 0 or 1 by that time.

Dose modifications during therapy (Study 0006)

Dose modifications were to be made during therapy (week 2, 3, or 4) based on the hematologic (granulocyte and platelet counts) and nonhematologic toxicities that were present at the time of the scheduled administration of the drug and based on the worst toxicities that occurred since administration of the last dose of CPT-11. Dose modifications as a result of toxicity are summarized in following table.

Dose Modifications during a Course of Therapy (Study 0006)

(Source: Table 3, m0006txt)

Toxicity Grade	Hematologic Toxicity	Non-Hematologic Toxicity
0-1	None[a]	None[a]
2	↓ 1 Dose Level	↓ 1 Dose Level
3	Omit Dose[b]	Omit Dose[b]
4	Omit Dose[c]	Omit Dose[c]
Neutropenic Fever	Omit Dose[c]	

a Dose was to remain stable during the course of therapy. Dose escalations were allowed only at the beginning of a new course of therapy and only if all toxicities during the preceding course of therapy were of grade 0.

b Dose was to be omitted if grade 3 hematologic toxicity or grade 3 diarrhea was present on the scheduled day of treatment. After resolution of toxicity to ≤ grade 2, treatment was to be restarted at one dose level lower and maintained at that level for the remainder of that course.

c Dose was to be omitted if grade 4 hematologic or nonhematologic toxicities occurred or if neutropenic fever was present on the scheduled day of treatment. After resolution of toxicity to ≤ grade 2, treatment was to be restarted at two dose levels lower and maintained at that level for the remainder of that course.

CONCOMITANT MEDICATIONS (Study 0006)

Antidiarrheal Therapy (Study 0006)

Diarrhea or abdominal cramping that occurred during or within one hour of infusion of CPT-11 was to be treated with 1 mg of atropine IV. Diarrhea that occurred later was to be treated with loperamide as follows: 4 mg orally at the first sign of poorly formed or loose stool or after the first episode of two or more bowel movements in one day, then 2 mg orally every two hours around the clock or 2 mg orally every two hours during the day and 4 mg orally every four hours at night until diarrhea-free for at least 12 hours.

Antiemetic Therapy: (Study 0006)

Each patient should have been treated with 10 mg of dexamethasone IV as part of the pretreatment antiemetic regimen, unless the use of steroids was contraindicated for that patient. Other antiemetic agents were permitted except for prochlorperazine, which was not allowed on the day of infusion due to its possible association with akathisia but was permitted on other days within the treatment cycle.

Other Medications (Study 0006)

Concomitant use of G-CSF was allowed. Concomitant use of coumadin was

not allowed.

CLINICAL EVALUATIONS (Study 0006)

Within 21 days prior to administration of CPT-11 the following evaluations were to be performed: medical history; chest x-ray; carcinoembryonic antigen (CEA); contraceptive counseling; and tumor assessment by chest x-ray, scans (including a computed tomography [CT] scan through the liver if the disease was in the lungs), or physical examination. Within seven days prior to drug administration, the following evaluations were to be performed: physical examination; 12-lead electrocardiogram (EKG); complete blood cell (CBC) count with differential, serum chemistries and electrolytes; pregnancy test (if applicable); and SWOG performance status.

At each weekly visit, including the two-week rest period, the following were to be performed: CBC with leukocyte differential, review of systems, and notation and grading of toxicities. Blood specimens for pharmacokinetic determinations were to be obtained after the first and third CPT-11 doses in the first course of therapy.

The following evaluations were to be performed before each new course of CPT-11 was begun: a physical examination; SWOG performance status; assessment of toxicities; review of systems; CBC with leukocyte differential, serum chemistries, and serum electrolytes; and CEA determination for those patients who had elevated values at baseline.

Tumor measurements were to be obtained after every two courses of therapy. All patients who responded to therapy were required to have their response confirmed four to six weeks after the first documentation of response.

At the end of treatment, a final physical examination and tumor measurement were to be performed, and a Study Termination Report was to be completed. Each patient was to be followed to determine the date and cause of death.

Pharmacokinetic evaluations were performed to better define the pharmacokinetic characteristics of CPT-11 (lactone and total) and the active metabolite SN-38 (lactone and total). A second goal was to establish possible correlations between peak plasma concentrations (C_{max}) and the area under the plasma concentration-time curve (AUC_N) for CPT-11 and its metabolites with response and toxicity. Pharmacokinetic sampling in at least 50 patients was planned.

4. Safety considerations: (Study 0006)

Criteria for removing patients from the study

Participation in the study was to be discontinued for any of the following reasons: Progressive disease, unacceptable toxicity, patient's decision to withdraw, intercurrent, noncancer-related reason, which prevented continuation of therapy or regular follow-up.

Medical Events

The NCI Common Toxicity Criteria were used to grade the toxicity of CPT-11. Any medical event that was reported by the patient or observed by the investigator during the study was to be reported on the CRF, regardless of whether the event was considered to be related to CPT-11. All medical events were to be followed until they resolved or until the patient's participation in the study ended.

A CBC with leukocyte differential was to be obtained within seven days prior to administration of the first dose of CPT-11, weekly during the study, and at the end of treatment. Serum chemistries and electrolytes were to be obtained within seven days prior to administration of the first dose of CPT-11, at the beginning of each new course of therapy, and at the end of treatment.

5. Efficacy considerations: (Study 0006)

The primary efficacy parameter was tumor response to treatment, defined as the total percentage of patients who experienced either a complete response or a partial response to CPT-11 therapy. Secondary efficacy parameters were: 1) duration of response, defined as the period from date of first objective documentation of response to the date of first objective documentation of disease progression; 2) Time to treatment failure was defined as the date of initial treatment to the date of progressive disease or to date off treatment due to toxicity; 3) Time to death was defined as the time from initial treatment to date of death.

Reviewer Comment: *The NDA includes time to response (defined as the period from first dose of CPT-11 to the first objective documentation of response) as a secondary endpoint but this was not defined in the protocol. The protocol did not specifically define time to disease progression but implied that the analysis of this endpoint would be performed. In other words, some of the efficacy endpoints used in this*

NDA were retrospectively applied to Study 0006. It is not likely that this represent a significant problem in interpreting the results.

Based on the expected response rate ranging from 23-27%, the planned sample size was 100 patients to estimate with 95% confidence limits of ± 8%.

Reviewer Comment: *As discussed later, the actual patient accrual was much higher than 100 (i.e., 168 total). This apparently occurred to treat more patients at the reduced starting dose.*

Response Criteria: (Study 0006)

Each patient was required to have a bidimensionally measurable lesion that had clearly defined margins on photograph, x-ray, or scan. At least one diameter of the lesion must have been greater than 1 cm on radiographic imaging or 2 cm on physical exam. Bone lesions were not included.

The response criteria were very similar to those of Study 0001, described previously in this review, with exception that unidimensional measurements from physical examination of the liver were not included.

Performance Status (Study 0006)

The SWOG performance scale was used. The SWOG performance scale, with the corresponding scores on the Karnofsky grading scale, are summarized in the table below:

Southwest Oncology Group (SWOG) Performance Scale
Source: Table 5, m0006.txt)

Grade	Scale	Karnofsky Score
0	Fully active; able to carry on all predisease activities without restriction.	90%-100%
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	70%-80%
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	50%-60%
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.	30%-40%
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	10%-20%
5	Dead.	0

Carcinoembryonic Antigen (CEA) (Study 0006)

Levels of CEA were to be determined at baseline in all patients and at the start of each new course of therapy in those patients whose values were elevated at baseline. However, CEA levels were not used to evaluate disease response.

6. Results of statistical consultation (Study 0006)

See Biometrics Division review (T. Koutsoukos). The statistical aspects of this submission are mainly descriptive.

7. Results of study (Study 0006)

Sponsor's Monitoring of data (Study 0006)

The scans of patients who were judged by the investigators to have achieved a partial or complete response to CPT-11 therapy were reviewed for confirmation of CPT-11 response at a central location by an independent panel. This procedure is similar to that described previously for Study 0006.

Since a NDA data cutoff date of March 31, 1995 was established, only therapeutic events occurring before this time were to be included in the database for this report. Reconciliation of data discrepancies was conducted

thereafter, but the database was not altered after December 1, 1995

Reviewer comment: *The data base was actually altered. The sponsor submitted an update of the efficacy data on April 15, 1996; those results are not included in the summary reported in this NDA review although some of the updated listings and case report forms were used for purposes of verification.*

Demographics (Study 0006)

Two study populations were defined based on the extent of exposure to CPT-11:

1) Intent-to-treat, which includes all patients who received at least one dose of CPT-11, and

2) Evaluable, which includes all patients who received at least one course of therapy and had at least one assessment of response.

Protocol Deviations: (Study 0006)

At least 98 protocol deviations were discovered and as described by the sponsor in the NDA. The sponsor judged them not to have had an effect on the outcome of the study or patient safety. The most notable deviations were as follows: Chest X-rays for 13 patients were either not done, done > 21 days before treatment, done after treatment began; CT scans (ie, tumor measurements) were obtained > 21 days (range, 22 to 46 days) before treatment for 14 patients; physical examinations for 16 patients were either not done, not complete, conducted > 7 days before treatment; three patients had values for hepatic and renal function outside the defined range: six patients received coumadin as a concomitant medication (no bleeding or adverse drug interactions were noted); secondary endpoints of time to response, response duration, time to disease progression, survival time, and performance status were defined and evaluated retrospectively.

Disposition of Patients by Course

A total of 167 patients consented and were enrolled in the study. One patient was screened and assigned a patient number but died at home of unknown causes prior to receiving CPT-11. This patient's data are not included in the safety or efficacy analyses. A total of 166 patients received at least one infusion of CPT-11. Of the 166 patients, the first 64 patients enrolled received a starting dose of 125 mg/m^2 and the 102

subsequently enrolled patients received a starting dose of 100 mg/m^2. The median number of courses administered was about 2.

This study enrolled 82 males and 84 females. There was approximately equal distribution of males and females enrolled among the two starting dose levels. The majority (87.3%) of patients were white. Patients ranged in age from 25 to 84 years, with 42.2% of the patients aged ≥ 65 years.

Pretreatment Disease-Related Characteristics: (Study 0003R)

Over half of the patients (57.8%) had metastatic disease (Duke's classification D) at time of initial diagnosis. Pretreatment demographic characteristics are also summarized in the integrated summary of efficacy results later in this review.

Prior Therapy: (Study 0003R)

The most common previous 5-FU-based chemotherapeutic regimen was 5-FU + leucovorin (69.3% of patients). None of the patients had prior radiation to the pelvic/abdominal area; five (3.0%) patients had prior radiation therapy to other areas of the body. Of the 166 patients, 116 (69.9%) had previously received treatment with 5-FU for metastatic disease. The majority of these patients (92.2%; 107/116) had experienced disease progression during or within three months after prior 5-FU. See the Integrated Efficacy Results section below for additional details.

TREATMENT ADMINISTRATION (Study 0006)

Number of Courses Delivered (Study 0006)

As of the cutoff date, 562 courses of therapy were delivered. The median number of courses was three (range, 1 to 9) or a median of 18 weeks on therapy.

Dose Adjustments of CPT-11 from First Dose to Last Dose within Patients

The starting dose for the first course of CPT-11 was 125 mg/m^2 for the first 64 patients enrolled. The remaining 102 patients were enrolled at the 100 mg/m^2 starting dose. Dosage adjustments after the initial starting dose were made for each patient based on individual tolerance.

Dose Adjustments of CPT-11 Within Courses (Study 0006)

For example, 93 (69.9%) of the 133 courses initiated at the 125 mg/m^2

dose did not require a dosage adjustment within a course, while 40 (30.1%) courses did require a decrease in dose to 100, 75, or 60 mg/m^2 within a course. Of the 257 courses initiated at the 100 mg/m^2 dose, 157 (61.1%) did not require a dosage adjustment within a course, while 99 (38.5%) courses did require a decrease in dose to 75 or 60 mg/m^2 within a course.

Distribution of Doses (Study 0006)

A total of 2013 doses of CPT-11 were administered. For patients treated at the beginning dose level of 125 mg/m^2, 347/812 (42.7%) of doses were administered at 125 mg/m^2 of CPT-11; 619/1201 doses (51.5%) were given at 100 mg/m^2 among patients starting at the 100 mg/m^2 dose level. Of the 2013 total doses, 748 (37.2%) were < 100 mg/m^2. Only 114 doses were omitted during the study.

Treatment Modifications for Diarrhea and Neutropenia/Leukopenia (Study 0006)

The most common reasons for dose modification were late diarrhea, neutropenia, and leukopenia. Patients starting with the 125 mg/m^2 dose had somewhat more dose modifications for late diarrhea than did patients starting with the 100 mg/m^2 dose (14.9% vs 8.1%) but fewer dose modifications for neutropenia (2.2% vs 4.8%) and leukopenia (1.3% vs 4.5%). The number of courses that were associated with a decrease in dose because of late diarrhea, neutropenia, or leukopenia are summarized in the table below.

Courses with Dosage Adjustments due to Late Diarrhea, Neutropenia and Leukopenia[a] (Study 0006)
(Source: Table 23, m0006.txt)

Reason for Dosage Modification	No. (%) of Courses with Event	No. (%) of Courses Requiring Dosage Modification for Event		
		All Courses N=562	By Starting Dose	
			125 mg/m^2 N=228	100 mg/m^2 N=334
Late Diarrhea[b]	399 (71.0)	61 (10.9)	34 (14.9)	27 (8.1)
Neutropenia	170 (30.2)	21 (3.7)	5 (2.2)	16 (4.8)
Leukopenia	231 (41.1)	18 (3.2)	3 (1.3)	15 (4.5)

[a] Appendix B, Table 4.1.8, lists all of the medical event reasons for dosage modifications.

[b] Occurring more than 24 hours after administration of CPT-11.

Source: Appendix B, Table 4.1.9.

Dose Intensity (Study 0006)

Dose intensity was calculated by dividing the total dose administered during a course by six. The projected dose intensity was 83.3 mg/m^2/week for the 125 mg/m^2 starting dose and 66.7 mg/m^2/week for the 100 mg/m^2 starting dose. The actual median dose intensity for the entire duration of treatment was 61.0 mg/m^2/week for the patients beginning treatment with the 125 mg/m^2 dose and 53.5 mg/m^2/week for patients treated with the 100 mg/m^2 starting dose. There was discernable difference in median dose intensity by age (< 65 y vs. ≥ 65 y), sex, baseline performance status, or radiation therapy was apparent within a dosing group. There was a suggestion that the dose intensity was slightly higher in patients with a PS of 0 vs. PS >0.

EFFICACY RESULTS (Study 0006)

Of the 166 patients enrolled in the study, 152 (91.6%) completed at least the first course of therapy and were included in the evaluable-patient efficacy analysis (59 patients who received a starting dose of 125 mg/m^2 and 93 patients who received a starting dose of 100 mg/m^2). The reasons for not completing one course of therapy and for exclusion from the evaluable-patient efficacy analysis were: disease progression (7), patient desired no further treatment (2), medical events (4), death (1).
As noted previously, 19 patients who were still on the study as of the data cutoff date were included in both sets of analyses. The response information presented in the following sections is based on the independent review committee's findings. Censored data were used in the duration of response, time to disease progression, and survival analyses (see page 27 for description of data censoring for these variables).

Reviewer comment: *On April 15, 1996, the sponsor submitted an update of the efficacy data as an amendment to the NDA. Those data are not included in this NDA review. Because there are less censored data, the time to event results differ slightly from those in the original NDA. In addition, one more patient had confirmation of response, so there is one more responder in the update than in the original NDA (i.e., 17 instead of 16).*

Response Rate (Study 0006)

The investigators reported an overall objective response to CPT-11 therapy in

19 of the 166 intent-to-treat patients, 18 of whom achieved partial responses and one of whom achieved a complete response. The independent review committee confirmed 16 responses: one complete response and 15 partial responses. Therefore, according to the independent review committee analysis, the response rate in the intent-to-treat population by starting dose was 12.5% (8/64) for those beginning with the 125 mg/m^2 dose and 7.8% (8/102) for patients starting with the 100 mg/m^2 dose. For evaluable patients, the response rate was 13.6% (8/59) among those initiating treatment at 125 mg/m^2 of CPT-11 compared with 8.6% (8/102) for those beginning study drug at the 100 mg/m^2 dose. The percentage of patients with stable disease was also higher in the 125 mg/m^2 starting dose group (45.3% at 125 mg/m^2 vs 39.2% at 100 mg/m^2), while the percentage of patients with progressive disease was higher in those starting with the 100 mg/m^2 dose (28.1% at 125 mg/m^2 vs 44.1% at 100 mg/m^2). Response results are summarized in the table below.

Study 0006

Response to CPT-11 Therapy Based on Independent Review Committee Findings

Source: Adapted from Table 26, m0006.txt.

	No. (%) Patients					
	Intent-to-Treat Population			Evaluable Population		
		Starting Dose			Starting Dose	
Response	All Pts. N=166	125 mg/m^2 N=64	100 mg/m^2 N=102	All Patients N=152	125 mg/m^2 N=59	100 mg/m^2 N=93
Complete Response	1 (0.6)	1 (1.6)	0	1 (0.7)	1 (1.7)	0
Partial Response	15 (9.0)	7 (10.9)	8 (7.8)	15 (9.9)	7 (11.9)	8 (8.6)
Stable Disease	69 (41.6)	29 (45.3)	40 (39.2)	69 (45.4)	29 (49.2)	40 (43.0)
Progressive Disease	63 (38.0)	18 (28.1)	45 (44.1)	60 (39.5)	18 (30.5)	42 (45.2)
No Follow-up Scan[a]	18 (10.8)	9 (14.1)	9 (8.8)	7 (4.6)	4 (6.8)	3 (3.2)
Overall Response[b] [95% CI][c]	16 (9.6) [5.1-14.1]	8 (12.5) [4.4-20.6]	8 (7.8) [2.6-13.1]	16 (10.5) [5.6-15.4]	8 (13.6) [4.8-22.3]	8 (8.6) [2.9-14.3]

[a] As of 3/31/95
[b] Complete response + partial response
[c] Confidence interval based on the normal approximation to the binomial distribution

Source: Appendix 6, Table 5.1.1

Of the 16 responders, eight were < 65 years of age and eight were ≥ 65 years of age.. Nine responders were female and seven were male. Fourteen

(87.5%) of the 16 responders had received prior therapy with 5-FU for metastatic disease and eleven (68.8%) had experienced progression of their disease during or within three months of stopping 5-FU therapy. No differences in response rate were noted by age, sex, number of tumor sites, baseline performance status, or prior 5-FU therapy. (See the Integrated Summary of Efficacy for additional demographical information on responders).

The following is a list of patients reported in the NDA by the sponsor as responding to CPT-11 in Study 0006.

Response to CPT-11 by Prior 5-FU Therapy for Responders to CPT-11 (Study 0006)
(Source: modification of Table 28, m0006.txt)

Pt. No.	Starting Dose (mg/m^2)	Response to CPT-11	Classification of Prior 5-FU Therapy[a]
	125	CR	PD ≤ 6 mo after adjuvant 5-FU R_x[b]
	125	PR	PD ≤ 3 mo after 5-FU R_x for MD
	125	PR	PD > 3 mo after 5-FU R_x for MD
	125	PR	PD > 3 mo after 5-FU R_x for MD
	125	PR	PD ≤ 3 mo after 5-FU R_x for MD
	125	PR	PD ≤ 3 mo after 5-FU R_x for MD
	125	PR	PD ≤ 3 mo after 5-FU R_x for MD
	125	PR	PD ≤ 3 mo after 5-FU R_x for MD
	100	PR	PD ≤ 6 mo after adjuvant 5-FU R_x
	100	PR	PD ≤ 3 mo after 5-FU R_x for MD
	100	PR	PD ≤ 3 mo after 5-FU R_x for MD
	100	PR	PD > 3 mo after 5-FU R_x for MD
	100	PR	PD ≤ 3 mo after 5-FU R_x for MD
	100	PR	PD ≤ 3 mo after 5-FU R_x for MD
	100	PR	PD ≤ 3 mo after 5-FU R_x for MD
	100	PR	PD ≤ 3 mo after 5-FU R_x for MD

[a] During data analysis, the sites were asked to provide further information on each patient's prior 5-FU regimen, and these data were used to further clarify the status of each patient at entry into this study. Classifications of prior 5-FU therapy for CPT-11 responders were those of the independent review committee.

[b] Refers to the number of months after stopping 5-FU.

Source: Appendix B, Tables 2.1.2, 4.1.1, 5.1.5, 5.2.3

Information regarding the patient's response to prior 5-FU was collected on the CRF as either "never responded" or "responded then progressed." Therefore, this information regarding response to the last 5-FU regimen does not differentiate between patients with confirmed objective responses and patients with stable disease, minor responses, changes in CEA, subjective improvements, etc.

Time to Response (Study 0006)

The median time to achieve objective response was 2.7 months (range, 1.3 to 5.2 months) for the 16 patients who achieved an objective response to therapy. Because the protocol specified that the first scan for response was to be obtained after the second course of treatment, most scans were done between 11 and 12 weeks (or 2.7 months) after the first dose, accounting for the general lack of variability between patient groups in median time to response.

Duration of Response (Study 0006)

The median duration of response for the 16 patients who obtained an objective response to therapy was 5.2 months (range, 2.9 to 8.8 months). Durations were slightly longer for responders starting with the 125 mg/m^2 dose (5.6 months; range 2.9 to 8.8 months) than for responders starting with the 100 mg/m^2 dose (5.2 months; range, 3.0 to 6.1 months); however, some of these data are currently censored because of the data cutoff date of March 31, 1995.

Reviewer comment: *Using the information in the data listings and CRFs of the patients who the sponsor listed as responding to CPT-11, discrepancies were identified for the data from five patients, as shown in the table below. We asked the sponsor to clarify these discrepancies and are awaiting a response. The discrepancy regarding patient was clarified from the information in the April 15, 1996 efficacy update.*

Discrepancies Between FDA and Sponsor Tumor Response Assessments			
Pat. #	Discrepancy in Response Status	Comments	Sponsor's Clarification[b]
	Criteria for objective PR not met on 8/4/94 (only 48% decrease in tumor area). Criteria first met on 9/15/94 (61% decrease).	Shorter response duration (by 5 weeks).	Based on the Independent panel review, the tumor decreased by 52.9% on 8/4/94
	Recorded date of progression was 6/27/95; but there was no evidence in the listing or CRF of progression until 9/21/95.	Longer duration of response (by about 11 weeks).	6/27/95 date was used because that was the date the investigator took the patients off study date (based on the plan outlined in the April 15 update, the off study date would be used in the analysis (censored)
	There was only a 45% decrease on 9/7/94 (date recorded as PR); did not meet criteria for PR until 10/7/94.	Shorter duration of resp[illegible]nd longer time to [illegible]e (by 4 weeks).	Based on the Independent panel review, the tumor decreased by 75.5% on 9/7/94.
	The date of progression should be 4/24/95 (instead of 7/24/95) because the lesion area increased from 20.2 to 99 cm^2.	[illegible]r duration of resp[illegible]se (by 12 weeks).	The sponsor agrees that the date of progression should be 4/24/95.
	Tumor area decreased by only 35% on 6/1/94, recorded as date of response; response criteria met on 7/5/94.	Shorter the duration of response and longer time to response (by 4 weeks).	Based on the Independent panel review, [illegible]e tumor decreased by 60.4% on 6/1/94.
	First date of PR reported as 8/8/94, but there was a 53% decrease in the total area of the lesions as of 6/23/94.	Longer response duration (by about 6 weeks).	Based on the Independent panel review, the tumor decreased by only 42.1% on 6/23/94.

[a] Pt [illegible] was added as an additional responder in the sponsor's efficacy update submitted April 15, 1996.

[b] Additional information clarifying discrepancies in the original NDA are found in the sponsor's efficacy update submitted April 15, 1996 and in a May 8, 1996 facsimile responding to FDA request to clarify discrepancies.

Reviewer comment: *There were no discrepancies in the number of patients who achieved a response. Each of the discrepancies involve the time to event data, particularly the duration of response. On May 8, 1996 we received a facsimile from the sponsor clarifying the discrepancies. Apparently, the measurements in the CRFs and data listings were not used for the sponsor's assessment of response. The sponsor used the measurements made by the independent panel for assessing response. Most of the discrepancies were clarified using that information. That is probably acceptable, with the caveat that the review panel did not review all of the scans, only those to confirm response and the date of progression, and the panel had not examined the patient. In any event, correcting the duration of response using the FDA data would only result in a minor change in the response duration: median duration of response 5.8 months (FDA) versus 6.0 months (sponsor). The sponsor's analysis of response and response duration for this study can be used in the labeling.*

Time to Progression: (Study 0006)

The estimates of time to disease progression includes censored data for 46 patients. Nineteen patients were still on study as of the data cutoff date (March 31, 1995). Patients starting with the 125 mg/m^2 dose had a slightly longer median time to disease progression than patients starting with the 100 mg/m^2 dose (3.2 months vs 2.8 months).

A baseline performance status of 0 tended to be associated with a longer median time to disease progression than did a baseline performance status of $\geq$ 1. Median time to disease progression did not differ significantly by sex or age.

Survival: (Study 0006)

Of the 166 patients, 74 (44.6%) were still living as of the data cutoff date for this report. The median survival time for the 166 patients was 8.0 months (range, 0.3 to 15.2 months). The median survival time was somewhat longer in the patients who attained an objective response to therapy (9.9 months) than in those who had stable disease (8.6 months) or progressive disease (7.0 months) as their best response to therapy. For

evaluated patients starting with the 125 mg/m^2 dose, median survival times were longer than for those starting with the 100 mg/m^2 dose (10.0 months [range, 0.3-15.2] versus 7.8 months [range, 0.6-13.3]. However, these differences must be interpreted with caution because of the large number of censored data points and the longer follow-up time among patients enrolled at the higher dose level.

Median survival time did not differ significantly by age or sex. Patients with a baseline performance status of 0 had a significantly longer survival time than those with a performance status of $\geq$ 1 (8.7 months [range, 0.9-15.2] versus 7.5 months [range, 0.3-13.4]; p =0.0001). The difference was also statistically significant when the patients treated at the 125 mg/m^2 starting dose and the 100 mg/m^2 starting dose are considered separately.

The median survival time for the 16 responders was 9.9 months (range, 7.4 to 12.4 months). As of the data cutoff date for this report, 13 of the 16 patients who responded to therapy were still living at the data cut-off date of March 31, 1995.

Reviewer comment: *See the sponsor's efficacy update submitted April 15,1996; there are minor differences from these results.*

Performance Status (Study 0006)

The majority of all 166 patients had a baseline PS of 0 (50.0%) or 1 (44.0%); only ten (6.0%) patients had a baseline PS of 2.

Ten of the responders had a baseline PS of 0, five had a baseline PS of 1, and the remaining other responder had a baseline PS of 2. Please see the Integrated Efficacy Results for a discussion of PS changes on CPT-11.

Carcinoembryonic Antigen (CEA) (Study 0006)

Levels of CEA were determined for 139 (83.7%) of the 166 patients. Of the 139 patients, 90 (64.7%) had a decrease and 49 (35.2%) patients had an increase in CEA sometime during treatment with CPT-11. CEA values for each of the patients can be found in Table 8.7.1 of the electronic submission in section m0006).

Clinical Benefit (Study 0006)

Please refer to the Integrated Summary of the Efficacy Results for a summary of the PS and body weight clinical benefit results.

Disease related symptoms (Study 0006)

Please refer to the Integrated Summary of Efficacy Results for the types of symptoms present at baseline and reported to improve in the CPT-11 responders.

Reviewer comments: *According to data listings, only six of the 16 patients (37.5%) who achieved an objective response to CPT-11 had disease-related symptoms reported at baseline. For the remaining responding patients, disease related symptoms were not present or were not recorded as such. Five of these six patients were reported to have improvement of the disease related symptoms on CPT-11 treatment.*

Of the patients whose objective response on CPT-11 was stable disease, 33 patients (47.8%) were reported to have disease related symptoms at present at baseline. Of these 33 patients with disease related symptoms reported to be present at baseline, 13 (39.4%) were reported to have improvement in symptoms on CPT-11.

No firm conclusions regarding clinical benefit from CPT-11 can be made from these limited retrospectively collected and analyzed results.

Pharmacokinetics (Study 0006)

Please refer to the Biopharmacology Review (Gene Williams, M.D.).

SAFETY RESULTS (Study 0006)

Discontinuation of Study Medication (Study 0006)

Discontinuations Due to Death (Study 0006)

Seven (4.2%) of the 166 patients died while on study; five received a starting dose of 125 mg/m^2 and two received a starting dose of 100 mg/m^2. None of these seven deaths were related to CPT-11 therapy by the investigators. However, one of these patients who died after a cerebral event, was described as having CPT-11 discontinued due to death. According to the sponsor's narrative summary of this case, an association with the study drug could not be excluded in this case. In the other cases,

the sponsor listed the cause of death to be disease progression.

Reviewer comment: *These results need to be interpreted with caution. In going over the sponsor's narratives of the patients who died on study, the usual scenario is that the patient is admitted to the hospital with a serious adverse event, the patient is treated for that complication, the patient dies. At the time of death, the patient has evidence of progressive disease, and the cause of death is listed as progressive disease. However, in some cases it may be difficult to rule out an association between the drug-related adverse event and the death of the patient. FDA review of the CRFs of the patients who died on study found evidence that the deaths in three patients were possibly or probably related to CPT-11.*

Discontinuations Due to Medical Events (Study 0006)

Ten (6.8%) of the 147 patients who discontinued treatment did so because of medical events; 4/60 (6.7%) received a starting dose of 125 mg/m^2 and 6/87 (6.9%) patients received a starting dose of 100 mg/m^2. Events for eight of the ten patients were considered drug-related and two patients discontinued treatment for personal reasons that may have been influenced by medical events.

Discontinuations Due to Disease Progression (Study 0006)

Of the 147 patients who discontinued treatment, 125 (85.0%) patients discontinued due to disease progression after one to eight courses of therapy; 50 of the patients (40%) received a starting dose of 125 mg/m^2 and 75 of the patients (60%) were treated at a starting dose of 100 mg/m^2.

Discontinuations for Other Reasons (Study 0006)

Eleven (7.5%) of the 147 patients withdrew from the study for personal reasons. One patient discontinued while she was still a responder; she chose to withdraw from the study because of the distance she had to travel each week for therapy.

Medical Events (Study 0006)

The following is a synopsis of the results of this study. Please refer to the Integrated Safety Results section for a more detailed listing of the adverse events occurring on the controlled CPT-11 studies.

All Medical Events

One or more medical events were reported for each of the 166 patients during the study.

The most frequently reported medical events were in the digestive (e.g., diarrhea, nausea, vomiting), body as a whole (e.g., asthenia, abdominal pain), hemic and lymphatic (e.g., leukopenia), skin (e.g., alopecia), and nervous (e.g., insomnia) systems with > 50% of patients reporting one or more event in each of these systems.

Drug-Related Medical Events (Study 0006)

Digestive system-related events—primarily late (> 24 hours after administration of CPT-11) diarrhea, nausea, and vomiting were the most frequently reported drug-related medical events (reported by > 50% of the patients) with each of the 166 patients reporting one or more such drug-related event. Drug-related events were also frequently reported (by > 50% of the patients) in the body as a whole (ie, asthenia, abdominal pain), hemic and lymphatic (ie, leukopenia), and skin (ie, alopecia) systems. There did not appear to be any marked dose-related effect on drug-related medical events overall, with the possible exception of vomiting. No fatal drug-related events were reported during the study.

Grade 3 and 4 Medical Events (Study 0006)

Grade 3 or 4 events reported in > 10% of patients were leukopenia (30.1%), late diarrhea (27.1%), neutropenia (20.5%), abdominal pain (21.1%), asthenia (16.3%), and nausea (15.1%). There was a somewhat greater incidence of grade 3 and 4 diarrhea (32.8% vs. 23.5%), nausea (21.9% vs. 10.8%), vomiting (21.9% vs. 2.0%), abdominal pain (25.0% vs. 18.6%) and early diarrhea (10.9% vs. 5.9%) associated with the 125 mg/m^2 starting dose. According to the sponsor's analysis, the only significant difference between the dose groups was the greater occurrence of grade 3 vomiting ($p < 0.001$) in patients starting at the 125 mg/m^2 dose. The NDA contains narrative summaries for the patients who experienced grade 3 or 4 medical events that led to hospitalization.

Hospitalizations (Study 0006)

Sixty-two (37.3%) of the 166 patients were hospitalized for medical events during the study with a total of 82 hospitalizations. Forty (24.1%) of the patients were hospitalized for events that were judged by the investigators to be related to the administration of CPT-11. The primary reasons for

drug-related hospitalizations were diarrhea (14.5%; 24/166) and nausea and/or vomiting (7.8%; 13/166).

Reviewer comment: *Some of the patients who were hospitalized for a drug-related, died relatively shortly after admission to the hospital or discontinued therapy relatively shortly after admission to the hospital. However, in many of those cases, the cause of death or discontinuation is listed as due to progressive disease or some other event not attributed to the drug. As discussed above, these data need to interpreted. It is often difficult in these to rule out an association between the drug-related adverse event and the death of the patient.*

Selected Medical Events (Study 0006)

Late Diarrhea

Late diarrhea occurred in 89.8% of the patients and in 71.0% of the courses. Grade 3 and 4 late diarrhea occurred in 27.1% (45/166) of the patients and in 10.9% (61/562) of the courses. The frequency of grade 3 and 4 late diarrhea by age was significantly greater ($p = 0.0076$) in patients $\geq$ 65 years. There were no significant differences in the frequency of late diarrhea by sex, baseline performance status, and previous radiation. There was a tendency for a higher frequency of late diarrhea in the group of patients receiving the higher starting dose of CPT-11. The frequency of late diarrhea according to selected characteristics is shown in the table below:

Frequency of Late Diarrhea[a] (Study 0006)
Selected Demographic and Disease-Related Characteristics
(Source: adapted from Table 43, m0006.txt)

Subgroup	No. of Pts	No. (%) of Pts with Event	Maximum NCI Grade				No. (%) Grade 3 + 4	p-value[b]
			1	2	3	4		
Sex:								
Male	82	72 (87.8)	31	21	16	4	20 (24.4)	0.4271
Female	84	77 (91.7)	26	26	18	7	25 (29.8)	
Age:								
< 65 y	96	86 (89.6)	37	31	11	7	18 (18.7)	0.0076
≥ 65 y	70	63 (90.0)	20	16	23	4	27 (38.6)	
Baseline PS:								
0	83	76 (91.6)	28	23	22	3	25 (30.1)	0.4852
≥ 1	83	73 (88.0)	29	24	12	8	20 (24.1)	
Starting Dose:								
100 mg/m^2	102	89 (87.3)	39	26	18	6	24 (23.5)	0.2120
125 mg/m^2	64	60 (93.8)	18	21	16	5	21 (32.8)	

[a] Occurred more than 24 hours after administration of CPT-11.
[b] For comparison of proportion of patients with grade 3 + 4.
Source: Appendix B, Table 6.7.1

The frequency of grade 3 and 4 late diarrhea remained relatively constant (12% to 13%) as the first dose of CPT-11 in a course was decreased from 125 mg/m^2 to 75 mg/m^2. Only grade 1 diarrhea was reported in six of the seven courses in which the first dose was escalated from 125 mg/m^2 to 150 mg/m^2.

Reviewer comment: *Note that these data with dose-escalation to 150 mg/m^2 too limited to draw any firm conclusions.*

Early Diarrhea (Study 0006)

Thirteen of the 166 patients (7.8%) had grade 3 or 4 early diarrhea. Eighteen (10.8%) patients were given atropine as treatment for early diarrhea (10 patients at 125 mg/m^2 CPT-11 dose, 8 at the 100 mg/m^2 dose). There was a somewhat greater incidence of grade 3 and 4 early diarrhea (10.9% vs. 5.9%) associated with the 125 mg/m^2 starting dose.

Nausea and Vomiting (Study 0006)

Grade 3 or 4 nausea was reported in 15.1% (25/166) of the patients and in 5.2% (29/562) of the courses, and grade 3 or 4 vomiting was reported in 9.6% (16/166) of the patients and in 3.0% (17/562) of the courses. There was a somewhat greater incidence of grade 3 and 4 nausea (21.9% vs. 10.8%) and vomiting (21.9% vs. 2.0%) associated with the 125 mg/m^2 starting dose. According to the sponsor's analysis, the only significant

difference between the dose groups was the greater occurrence of grade 3 vomiting ($p < 0.001$) in patients starting at the 125 mg/m^2 dose. Antiemetic agents were routinely used as a pretreatment in this study, but the regimen varied. The most frequently used antiemetic agents were daxamethasone (97.0%) and ondansetron (61.4%).

Dehydration (Study 0006)

Of the 166 patients, 37 (22.3%) experienced dehydration, with grade 3 or 4 dehydration in 11 (6.6%) patients (there were no differences between the two starting doses of CPT-11).

Dyspnea (Study 0006)

Dyspnea was reported for 15.1% (25/166) of the patients and in 5.9% (33/562) of the courses. Of these 25 patients, 12 were reported to have documented lung metastases. Grade 3 or 4 dyspnea was reported for 2.4% (4/166) of the patients and in 0.9% (5/562) of the courses. Dyspnea was judged to be related to administration of CPT-11 for 1.2% (2/166) of the patients and in 0.4% (2/562) of the courses. The two incidents of potentially drug-related dyspnea were only grade 1 and grade 2 events.

Neutropenia

The frequency of neutropenia is summarized by patient, course, and maximum grade for all patients and by starting dose in table below. Grade 3 or 4 neutropenia occurred in 20.5% (34/166) of the patients and in 9.4% (53/562) of the courses.

Frequency of Neutropenia (Study 0006)
(Source: Table 46, m0006.txt)

	No.	No. (%) with Neutropenia	Maximum NCI Grade				No. (%) Grade 3 + 4
			1	2	3	4	
ALL PATIENTS							
Patients	166	72 (43.4)	12	26	19	15	34 (20.5)
Courses	562	170 (30.2)	47	70	36	17	53 (9.4)
STARTING DOSE = 125 mg/m^2							
Patients	64	27 (42.2)	2	13	7	5	12 (18.8)
Courses	228	54 (23.7)	14	23	12	5	17 (7.5)
STARTING DOSE = 100 mg/m^2							
Patients	102	45 (44.1)	10	13	12	10	22 (21.6)
Courses	334	116 (34.7)	33	47	24	12	36 (10.8)

Source: Appendix B, Tables 6.2.3 and 6.2.4

There were no notable significant differences in the frequency of grade 3 and 4 neutropenia by sex, age, previous radiation, number of involved disease sites, or CPT-11 starting dose. There a tendency for the frequency of grade 3 and 4 neutropenia to be somewhat less in the patients with a baseline performance status of 0 compared to those with a PS of ≥ 1 but the differences were not statistically significant (15.7% vs. 25.3%; p = 0.1777).

Neutropenic Fever (Study 0006)

Neutropenic fever, defined as grade 4 neutropenia and ≥ grade 2 fever, was reported in only 1.2% (2/166) of the patients and in 0.4% (2/562) of the courses. Both patients (nos. 319 and 719) had started treatment at the 100 mg/m^2 dose level. They were hospitalized and recovered after receiving antibiotic therapy. Only seven (4.2%) of the 166 patients received G-CSF at any time as prophylaxis or therapy for neutropenic fever.

Reviewer comment: *As noted previously, the use of grade 4 neutropenia (i.e., < 500 cells/mm^3) for neutropenic fever is somewhat liberal but acceptable. Some investigators use fever in the presence of grade 3 neutropenia. Based on an analysis of the electronic data by FDA statistician Tony Koutsoukos, 4.2% of the patients on this study met the*

criteria for febrile neutropenia defined using the more conservative criteria of grade 3 or 4 neutropenia.

Simultaneous Neutropenia and Late Diarrhea (Study 0006)

Grade 3 or 4 neutropenia occurred simultaneously with grade 3 or 4 late diarrhea in only 3.0% (5/166) of the patients and in 7.1% (4/562) of the courses. Of the five patients with grade 3 or 4 neutropenia/late diarrhea, two were hospitalized for supportive care There were no fatal outcomes in patients who experienced simultaneous grade 3 or 4 neutropenia/late diarrhea.

Hematologic Abnormalities Other Than Neutropenia (Study 0006)

Lymphocytopenia occurred in 163 (98.8%) of 165 patients for whom laboratory assays were performed and was grade 3 or 4 in 102 (61.8%) patients. Despite its high frequency of occurrence based on laboratory findings, lymphocytopenia was not consistently reported as a medical event. There were no systemic opportunistic infections reported as a result of the lymphocytopenia based on antibiotic (antifungal/antiviral) use and infection occurrence during lymphocytopenia.

Seven (4.2%) patients had abnormal platelet counts; only one patient (no. had a platelet count as low as grade 3. This patient had grade 3 thrombocytopenia in the third course that was judged by the investigator to be related to treatment with CPT-11 and was discontinued from the study.

Anemia was reported for 42.2% (70/166) of the patients and was grade 3 or worse (< 8 gm/dL) in only 4.8% (8/166) of the patients. Ten (6.0%) patients received blood transfusions.

Nadir for Hematology Assays (Study 0006)

Median time to the nadir for hematology values ranged from 14 days for platelets to 21 days for neutrophils and hemoglobin

Chemistry Assays (Study 0006)

Approximately 25% of the patients had abnormalities in serum chemistry assays. However, grade 3 or 4 toxicities occurred in fewer than 5% of the patients, and the abnormalities were noted only for the bilirubin assay and SGOT assay. No patients had grade 3 or 4 creatinine toxicity.

Eleven (7.2%) patients had grade 3 or 4 elevations in nonfasting blood glucose values. Six of these patients had a history of diabetes, three had elevated glucose values at screen, and two received dexamethasone as prophylaxis for nausea and vomiting.

Concomitant Medications (Study 0006)

Hormonal drugs (primarily adrenalcortical steroids) were the most frequently taken, followed by gastrointestinal drugs (primarily antidiarrheal agents), and central nervous system drugs (primarily antiemetic/antivertigo agents and analgesics). Psychotropic agents (specifically prochlorperazine), and hormonal agents (primarily dexamethasone), were administered as antiemetic agents.

8. Conclusions: (Study 0006)

a. Scientific: (Study 0006)

This is an open label phase II study of CPT-11 in previously treated patients with colorectal cancer. The actual patient accrual of 168 patients was much higher than 100 patients planned in the original protocol. After the first 100 patients were treated at 125 mg/m^2 starting dose, the starting dose was reduced to 100 mg/m^2 because of the perceived excessive toxicity resulting in hospitalization. The sample size was apparently increased to better estimate the response rate and tolerance at the lower starting dose.

This can be considered an adequate and well controlled (historical) study for the primary endpoint of objective tumor response. This is not an adequate and well controlled study of the secondary endpoints such as time to progression and survival. The study was not adequately designed to adequately evaluate clinical benefit endpoints such as changes in PS, body weight, and disease related symptoms.

The response rate in the intent-to-treat population by starting dose was 12.5% (8/64) for those beginning with the 125 mg/m^2 dose and 7.8% (8/102) for patients starting with the 100 mg/m^2 dose. The median duration of response was 5.2 months (range, 2.9 to 8.8 months). Durations were slightly longer for responders starting with the 125 mg/m^2 dose (5.6 months; range 2.9 to 8.8 months) than for responders starting with the 100 mg/m^2 dose (5.2 months; range, 3.0 to 6.1 months).

Grade 3 and 4 late diarrhea occurred in 27.1% (45/166) of the patients and in 10.9% (61/562) of the courses. The frequency of grade 3 and 4 late

diarrhea by age was significantly greater ($p = 0.0076$) in patients ≥ 65 years. Grade 3 or 4 neutropenia occurred in 20.5% (34/166) of the patients and in 9.4% (53/562) of the courses.

b. Deficiencies/Problems (Study 0006)

Only two of seven lots of CPT-11 used in this study were produced by UpJohn, the remainder were produced by using sterilization. The switch to the UpJohn drug product (lot 27,211) did not take place until after 5/94. It is not clear how many patients were treated with the UpJohn product but is probably a small minority.

More of the time to event data on this study were censored than on the other two studies. The sponsor submitted an efficacy update on April 15, 1996 which provides less censored data on the existing patients. Based on a preliminary review of that submission, there are some minor changes in the time to event results, and one additional PR was confirmed.

This study was well controlled to evaluate objective tumor response. However, it was not adequately designed to evaluate clinical benefit. Some of the secondary endpoints were retrospectively defined.

B. INTEGRATED SUMMARY OF CONTROLLED STUDIES

The following summary integrates selected results from the controlled Phase II studies. Depending on the variables, the results are either combined, provided according to study or according to starting dose.

1. Summary of Efficacy Results

Disposition of Patients (ISE)

A total of 304 patients were enrolled in the three pivotal studies. As of the NDA data cutoff date (March 31, 1995), 283 (93.1%) of the patients were off study, and 21 (6.9%) of the patients were still on study (ie, still receiving treatment with CPT-11). The 21 patients who were still on study included 2 (2.2%) of the 90 patients who were enrolled in protocol 0003R and 19 (11.4%) of the 166 patients who were enrolled in protocol 0006.

Pretreatment Demographic Characteristics (ISE)

The pretreatment demographic characteristics for the three controlled Phase II studies is shown in the table below:

Pretreatment Demographic Characteristics by Study: Controlled Studies in Previously Treated Colorectal Cancer

(Source: modified from Table 8.F-5 section 8f.txt).

Protocol No.:	0001	0003R	0006	
Starting Dose (mg/m^2):	150[a]/125	125	125	100
Patient Population:	ITT[b] N=48	ITT N=90	ITT N=64	ITT N=102
Age (y):				
Mean	59	62	61	59
Median	63	63	61	64
Range				
Distribution (No. & %):				
< 35	2 (4.2)	3 (3.3)	0 (0.0)	8 (7.8)
35-49	11 (22.9)	12 (13.3)	6 (9.4)	14 (13.7)
50-64	13 (27.1)	34 (37.8)	35 (54.7)	33 (32.4)
≥ 65	22 (45.8)	41 (45.6)	23 (35.9)	47 (46.1)
Sex (No. & %):				
Male	26 (54.2)	58 (64.4)	32 (50.0)	50 (49.0)
Female	22 (45.8)	32 (35.6)	32 (50.0)	52 (51.0)
Ethnic Origin (No. & %):				
White	38 (79.2)	86 (95.6)	52 (81.3)	93 (91.2)
African American	6 (12.5)	4 (4.4)	7 (10.9)	5 (4.9)
Hispanic	4 (8.3)	0 (0.0)	5 (7.8)	2 (2.0)
Oriental/Asiar	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)
Performance Status (No. & %):				
0	29 (60.4)	34 (37.8)	38 (59.4)	45 (44.1)
1	18 (37.5)	43 (47.8)	21 (32.8)	52 (51.0)
2	1 (2.1)	13 (14.4)	5 (7.8)	5 (4.9)

[a] 9/48 patients received the 150-mg/m^2 starting dose.

[b] Intent to treat

Source: References 93-95 (Appendix B, Table 2.1.1)

Pretreatment Disease-Related Characteristics (ISE)

The pretreatment disease related characteristics for the 3 phase II studies combined are shown in the following table:

Pretreatment Disease-Related Characteristics Pivotal Studies in Patients with Previously Treated Colorectal Cancer[a] (Source: adapted from Table 8.F-8 section 8f.txt)

	All Studies	
Patient Population:	**ITT N=304**	**Evaluable N=261**
Primary Tumor (No. & %)		
Colon	258 (84.9)	221 (84.7)
Rectum	41 (13.5)	35 (13.4)
Data Unavailable	5 (1.6)	5 (1.9)
No. of Metastatic Sites (No. & %)		
1	59 (19.4)	50 (19.2)
2	83 (27.3)	70 (26.8)
≥ 3	162 (53.3)	141 (54.0)
Sites of Metastases (No. & %)		
Liver	213 (70.1)	187 (71.6)
Lung	114 (37.5)	96 (36.8)
Lymph Node	58 (19.1)	52 (91.9)
Abdomen	28 (9.2)	22 (8.4)
Soft Tissue	27 (8.9)	26 (10.0)
Pelvis	20 (6.6)	19 (7.3)
Bone	18 (5.9)	11 (4.2)
Colon/Rectum	14 (4.6)	13 (5.0)
Adrenal	4 (1.3)	4 (1.5)
Brain	2 (0.7)	0 (0.0)
Other	8 (3.1)	5 (2.0)
Baseline Tumor Size (area in cm^2)[c]		
< 20	130 (42.8)	114 (43.7)
20- < 40	64 (21.1)	50 (19.2)
40- < 60	34 (11.2)	29 (11.1)
60- < 80	28 (9.2)	26 (10.0)
≥ 80	48 (15.8)	42 (16.1)
Largest Single Tumor Size (area in cm^2)[d]		
< 5	49 (16.1)	43 (16.5)
5-10	54 (17.8)	48 (18.4)
10- < 20	62 (20.4)	52 (19.9)
20- < 40	62 (20.4)	53 (20.3)
≥ 40	74 (24.3)	64 (24.5)
Unknown	3 (1.0)	1 (0.4)

a Pooled data from protocols 0001, 0003R & 0006.
b Intent to treat.
c Figures are based on the sum of the perpendicular products of all measured lesions. Data were taken from the case report forms, not reanalysis by the independent review committees [105, 115].
d Based on the perpendicular product of the largest tumor.

Source: Section 7, Table 1.2.2.

Prior Therapy for Colorectal Cancer (ISE)

The classification of prior 5-FU therapy (e.g., progressive disease during or within 6 months after stopping adjuvant 5-FU therapy, progressive disease during or within 3 months after stopping 5-FU therapy for metastatic disease, etc) was not prospectively collected on the case report forms. Rather, this information was collected during data analysis to further classify the prior 5-FU status of each patient at study entry. The type of prior 5-FU therapy could not be classified for 15 (4.9%) of the 304 patients. Of the 304 patients in the three pivotal studies, 249 (81.9%) had experienced disease progression during or within 3 months after stopping 5-FU therapy for metastatic disease (62.8%; 191/304) or disease recurrence during or within 6 months after stopping adjuvant 5-FU therapy (19.1%; 58/304). The most common previous 5-FU therapy—received by 207 (68.1%) of the patients—was 5-FU/leucovorin. Prior therapy by study is outlined in the table below.

Prior Therapy for Colorectal Cancer by Study
Pivotal Studies In Patients with Previously Treated Colorectal Cancer
(Source modified from Table 8.F-9 Section 8f.txt)

Protocol No.:	0001	0003R	0006	
Starting Dose (mg/m^2):	150[b]/125	125	125	100
Prior Radiation Therapy (No. & %)				
Pelvis/Abdomen	1 (2.1)	26 (28.9)	0 (0.0)	0 (0.0)
Other	3 (6.3)	8 (8.9)	1 (1.5)	4 (3.9)
None	44 (91.7)	56 (62.2)	63 (98.4)	98 (96.1)
Last 5-FU Regimen No. & %)				
5-FU + Leucovorin	35 (72.9)	54 (60.0)	46 (71.7)	72 (70.6)
5-FU + Leucovorin + Levamisole	4 (8.3)	15 (16.7)	2 (3.1)	2 (2.0)
5-FU + Levamisole	4 (8.3)	11 (12.2)	12 (18.8)	15 (14.7)
Other 5-FU or 5-FU + Leucovorin regimen	5 (10.5)	10 (11.0	4 (6.3)	13 (12.8)
Classification of Prior 5-FU Therapy (No. & %)				
PD ≤ 6 mo of adjuvant 5-FU R_x	7 (14.6)	6 (6.7)	17 (26.6)	28 (27.5)
PD > 6 mo after adjuvant 5-FU R_x	1 (2.1)	14 (15.6)	0 (0.0)	2 (2.0)
PD ≤ 3 mo after 5-FU R_x for metastatic disease	38 (79.2)	46 (51.1)	45 (70.3)	62 (60.8)
PD > 3 mo after 5-FU R_x for metastatic disease	1 (2.1)	13 (14.4)	2 (3.1)	7 (6.9)
Classification Unknown	1 (2.1)	11 (12.2)	0 (0.0)	3 (2.9)
Responded to Last 5-FU Regimen[a,b] (No. & %)				
Yes	3 (7.5)	19 (21.1)	30 (63.8)	39 (58.2)
No	35 (89.7)	34 (57.6)	17 (36.2)	28 (41.8)
Unknown	1 (2.5)	6 (10.2)	0 (0.0)	2 (2.9)

[a] Only includes the patients who received treatment with 5-FU for metastatic disease.
[b] Yes = complete or partial response, and no = stable or progressive disease for protocols 0001 & 0003R. Yes = responded, then progressed, and no = never responded for protocol 0006; this information does not differentiate between patients with confirmed objective responses and those with stable disease, minor responses, changes in carcinoembryonic antigen (CEA) or subjective improvements.

Source References 93-95 (Appendix B, Tables 2.2.1, 2.2.2 & 5.2.3)

Number of Courses Delivered & Dose Intensity (ISE)

The median number of courses delivered per patient for each of the controlled studies is shown in the table below.

Number of Courses Delivered & Dose Intensity by Study
Pivotal Studies in Patients with Previously Treated Colorectal Cancer
(Source: Table 8.F-11 Section 8f.txt)

Protocol No.:	0001	0003P	0006	
Starting Dose (mg/m^2):	150[a]/125	125	125	100
Patient Population:	ITT[b] N=48	ITT N=90	ITT N=84	ITT N=102
No. of Courses Delivered[c]:				
Median	3.5	3.0	3.0	3.0
Range	1-13	1-14[e]	1-9[f]	1-7[g]
Dose Intensity (mg/m^2/wk)[d]:				
Median	62.0	56.1	61.0	53.5
Range	31.3-85.4	20.8-94.4	20.8-94.4	16.7-86.9

[a] 9/48 patients received the 150-mg/m^2 starting dose.
[b] Intent to treat.
[c] Each course constituted 5 weeks: once-weekly treatment with CPT-11 for 4 weeks, followed by 2-week rest.
[d] Total dose administered in a course ÷ 6 (number of weeks in a course). Projected dose intensities for a full course of therapy were 100 mg/m^2/wk for the 150-mg/m^2 starting dose, 83.3 mg/m^2/wk for the 125-mg/m^2 starting dose, and 66.6 mg/m^2/wk for the 100-mg/m^2 starting dose.
[e] Includes 2 patients who were still on study as of the data cutoff date (03/31/95); each of these patients had received 8 courses as of that date.
[f] Includes 4 patients who were still on study as of the data cutoff date; 3 patients had received 8 courses and 1 had received 9 courses as of that date.
[g] Includes 15 patients who were still on study as of the data cutoff date; 6 patients had received 6 courses and 9 patients had received 7 courses as of that date.

Source: References 93-95 (Appendix B, Table 4.1.2)

For the 304 patients in the three pivotal studies, the median number of courses delivered per patient was 3.0 (range, 1 to 14), for a median of 18 weeks on therapy.

Response to Therapy: (ISE)

According to the sponsor's analysis, there were 2 complete and 36 partial responses in the three pivotal studies combined, for an overall response rate of 12.5% (38/304) based on the intent-to-treat population and 14.6% (38/261) based on the evaluable population. The sponsor's statistical comparison for the difference between the 14.5% (95% CI, 9.5% to 19.5%) response rate observed with the 125-mg/m^2 starting dose and the 7.8%

(95% CI, 2.6% to 13.1%) response rate observed with the 100-mg/m^2 starting dose yielded a p-value of 0.096 (Chi-square test).

Reviewer comment: *Firm conclusions should not be drawn from this difference in response between the two dosing groups because the groups were not randomized. The results do suggest that there may be a true dose-response relationship. Further study may be warranted.*

Response rate for all 304 patients based on the FDA assessment is 12.2 (37/304; 95% C.I., 9% to 16%).

Objective response data for the three controlled Phase II studies according to the sponsor's assessment, by study and by starting dose, are shown in the next two tables.

Response to CPT-11 Therapy by Study: Pivotal Studies In Previously Treated Colorectal Cancer [a]
(Source: Table 8.F-13 Section 8f.txt)

Protocol No.:	0001		0003R		0006			
Starting Dose (mg/m^2):	150[b]/125		125		125		100	
Patient Population:	ITT[c] N=48	Evaluable N=43	ITT N=90	Evaluable N=66	ITT N=64	Evaluable N=59	ITT N=102	Evaluable N=93
Complete Response	1 (2.1)	1 (2.3)	0 (0.0)	0 (0.0)	1 (1.6)[e]	1 (1.7)[e]	0 (0.0)	0 (0.0)
Partial Response	9 (18.8)	9 (20.9)	12 (13.3)[e]	12 (18.2)[e]	7 (10.9)[e]	7 (11.9)[e]	8 (7.8)[g]	8 (8.6)[g]
Stable Disease	30 (62.5)	30 (69.8)	50 (55.6)[e]	47 (71.2)[e]	29 (45.3)[f]	29 (49.2)[f]	40 (39.2)[h]	40 (43.0)[h]
Progressive Disease	4 (8.3)	3 (7.0)	24 (26.7)	7 (10.6)	18 (28.1)	18 (30.5)	45 (44.1)[e]	42 (45.2)[e]
No Follow-up Scan	4 (8.3)	0 (0.0)	4 (4.4)	0 (0.0)	9 (14.1)	4 (6.8)	9 (8.8)	3 (3.2)
Overall Response[d]	10 (20.8) [9.3-32.3]	10 (23.3) [10.6-35.9]	12 (13.3) [6.3-20.4]	12 (18.2) [8.9-27.5]	8 (12.5) [4.4-20.6]	8 (13.6) [4.8-22.3]	8 (7.8) [2.6-13.1]	8 (8.6) [2.9-14.3]

[a] Based on the independent review committee (protocols 0001 & 0006)/peer review panel (protocol 0003R) results [105].
[b] 9/48 patients received the 150-mg/m^2 starting dose.
[c] Intent to treat.
[d] Complete response + partial response; no. (%) of patients [95% confidence interval (%)]. The confidence interval is based on the normal approximation to the binomial distribution.
[e] Includes 1 patient who were still on study as of the data cutoff date (03/31/95).
[f] Includes 2 patients who were still on study as of the data cutoff date.
[g] Includes 5 patients who were still on study as of the data cutoff date.
[h] Includes 9 patients who were still on study as of the data cutoff date.

Source: *References 93-95 (Appendix 8 Tables 1.1.4, 5.1.1 & 5.1.5).*

Response to CPT-11 Therapy by Starting Dose: Pivotal Studies In Previously Treated Colorectal Cancer[a]
(Source: Table 8.F-14 Section 8f.txt)

Starting Dose (mg/m^2):	100		125		150		All Doses	
Patient Population:	ITT[b] N=102	Evaluable N=93	ITT N=193	Evaluable N=160	ITT N=9	Evaluable N=8	ITT N=304	Evaluable N=261
Complete Response	0 (0.0)	0 (0.0)	2 (1.0)[f]	2 (1.2)[f]	0 (0.0)	0 (0.0)	2 (0.7)[f]	2 (0.8)[f]
Partial Response	8 (7.8)[d]	8 (8.6)[d]	26 (13.5)[g]	26 (16.2)[g]	2 (22.2)	2 (25.0)	36 (11.8)[i]	36 (13.8)[i]
Stable Disease	40 (39.2)[e]	40 (43.0)[e]	104 (53.9)[h]	101 (63.1)[h]	5 (55.6)	5 (62.5)	149 (49.0)[j]	146 (55.9)[j]
Progressive Disease	45 (44.1)[f]	42 (45.2)[f]	45 (23.3)	27 (16.9)	1 (11.1)	1 (12.5)	91 (29.9)[f]	70 (26.8)[f]
No Follow-up Scan	9 (8.8)	3 (3.2)	16 (8.3)	4 (2.5)	1 (11.1)	0 (0.0)	26 (8.6)	7 (2.7)
Overall Response[c]	8 (7.8) [2.6-13.1]	8 (8.6) [2.9-14.3]	28 (14.5) [9.5-19.5]	28 (17.5) [11.6-23.4]	2 (22.2) [0.0-49.4]	2 (25.0) [0.0-55.0]	38 (12.5) [8.8-16.	38 (14.6) [10.3-18.8]

[a] Pooled data from protocols 0001, 0003R & 0006. Results are based on the independent review committee (protocols 0001 & 0006)/peer review panel (protocol 0003R) results [105].
[b] Intent to treat.
[c] Complete response + partial response; no. (%) of patients [95% confidence interval (%)]. The confidence interval is based on the normal approximation to the binomial distribution.
[d] Includes 5 patients who were still on study as of the data cutoff date (03/31/95).
[e] Includes 9 patients who were still on study as of the data cutoff date.
[f] Includes 1 patient who were still on study as of the data cutoff date.
[g] Includes 2 patients who were still on study as of the data cutoff date.
[h] Includes 3 patients who were still on study as of the data cutoff date.
[i] Includes 7 patients who were still on study as of the data cutoff date.
[j] Includes 12 patients who were still on study as of the data cutoff date.

Source: Section 7, Tables 1.4.1 & 1.4.4 & References 93-95 (Appendix B, Table 1.1.4).

Response by Demographic and Pretreatment Characteristics: (ISE)

Response by demographic and pretreatment characteristics are shown in the table below. In the sponsor's univariate analysis, response rate was significantly greater in patients who had a baseline performance status of 0 than in those who had a baseline performance status of ≥ 1 ($p = 0.009$). Forward stepwise logistic regression confirmed that a better performance status was a prognostic factor for response to CPT-11 ($p = 0.0146$) and indicated that primary involvement of the rectum tended to be predictive of response to CPT-11 ($p = 0.0519$). Response rate did not differ significantly by other demographic or disease-related characteristics.

Response to CPT-11 by Demographic & Other Disease-Related Characteristics: Pivotal Studies in Patients with Previously Treated Colorectal Cancer[a]

(Source: Table 8.F-15, Section 8f.txt)

Subgroup	No. of Pts	Responders		p-value[b]
		No.	%	
Sex:				
Female	138	16	11.6	0.729
Male	166	22	13.3	
Age:				
< 65 y	171	20	11.7	0.727
≥ 65 y	133	18	13.5	
Ethnic Origin:				
White	269	36	13.4	0.191
African American	22	0	0.0	
Hispanic	11	2	18.2	
Oriental/Asian	2	0	0.0	
Baseline Performance Status:				
0	146	26	17.8	0.009
≥ 1	158	12	7.6	
Site of Primary Tumor:				
Colon	258	29	11.2	0.230
Rectum	41	8	19.5	
Data Unavailable	5	1	20.0	
No. of Metastatic Sites				
1	59	5	8.5	0.101
2	83	16	19.3	
≥ 3	162	17	10.5	
Organ Involvement:				
Liver Only	110	16	14.5	0.373
Lung Only	30	3	10.0	
Liver & Lung	37	7	18.9	
Other	127	12	9.4	
Previous Pelvic/Abdominal Radiation:				
Yes	27	4	14.8	0.759
No	277	34	12.3	
Classification of Prior 5-FU Therapy[c]:				
PD ≤ 6 mo of adjuvant 5-FU R_x	58	3	5.2	0.158
PD > 6 mo after adjuvant 5-FU R_x	17	1	5.9	
PD ≤ 3 mo after 5-FU R_x for metastatic disease	191	28	14.7	
PD > 3 mo after 5-FU R_x for metastatic disease	23	5	21.7	
Classification Unknown	15	1	6.7	

[a] Pooled data from protocols 0001, 0003R & 0006.
[b] Fisher's exact test.
[c] PD = progressive disease, R_x = therapy. These data were collected during data analysis to further clarify the status of each patient at study entry. Classifications for the responders were those of the independent review committee [115].

Source: Section 7, Table 1.4.2.

Time to Response: (ISE)

The majority of responses in each study were observed within the first two courses of therapy, and all of the responses to therapy had occurred by the fourth course of CPT-11 therapy. The median time to response for the three controlled studies is shown in the table below. The median time to response may have been affected by the timing of the first scan.

Time to Response by Study: Pivotal Studies in Patients with Previously Treated Colorectal Cancer
(Source: modified from Table 8.F-18, Section 81.txt)

Protocol No.:	0001	0003R	0006	
Starting Dose (mg/m^2):	150[a]/125	125	125	100
No. of Responders:	10	12	8	8
Time to Response (mo)				
Median	2.6	1.5	2.7	2.7
Range	1.1-2.9	0.9-5.5	1.3-5.1	2.5-5.2

[a] 2/10 responders received the 150-mg/m^2 starting dose.
Source: References 93-95 (Appendix B, Tables 5.1.5 & 5.1.6).

For all 38 patients who responded to CPT-11 in the pivotal studies, the median time to response was 2.6 months (range, 0.9 to 5.5 months).

Duration of Response: (ISE)

The estimates of duration of response include censored data for eight patients without documented evidence of disease progression as of the March 31, 1995 data cutoff date. These results are shown in the table below:

Duration of Response by Study
Based on UpJohn's Assessment of Response
(Source: Table 8.F-21, Section 8f.txt)

Protocol No.:	0001	0003R	0006	
Starting Dose (mg/m^2):	150[a]/125	125[b]	125[c]	100[d]
No. of Responders:	10	12	8	8
Duration of Response (mo)				
Median	6.4	5.9	5.6	5.2
Range	2.7-13.7	2.6-15.1	2.8-8.8	3.0-6.1+

[a] 2/10 responders received the 150-mg/m^2 starting dose.
[b] Includes censored data for 2 patients, 1 of whom was still on study and 1 of whom had discontinued therapy as of the data cutoff date (03/31/95).
[c] Includes censored data for 1 patient who was still on study as of the data cutoff date.
[d] Includes censored data for 5 patients who were still on study as of the data cutoff date.

Source: References 93-95 (Appendix B, Tables 5.1.5 & 5.1.6).

The median duration of response for the all 38 responders in the three pivotal studies was 5.8 months (range, 2.6 to 15.1 months). The sponsor provided data on response duration by demographic characteristics. These are not shown in this review because there were too few patients to adequately assess for differences.

Reviewer comment: *The sponsor's efficacy update submitted April 15, 1996 contains less censored data. The results of that analysis are not included in this NDA review. They will be presented at the June 13, 1996 ODAC meeting. There were minor changes in the time to event results. Briefly, the median duration of response for the 39 responders (includes an additional responder) in the three pivotal studies was 6.0 months (range, 2.6 to 15.1 months). Median duration of response was 6.2 months (range, 3.0 to 9.9 months) for the 8 responders who received the 100-mg/m^2 dose, 5.8 months (range, 2.6 to 15.1 months) for the 29 responders who received the 125-mg/m^2 starting dose, and 11.6 months (range, 9.5 to 13.7 months) for the 2 responders who received the 150-mg/m^2 starting dose.*

Time to Disease Progression: (ISE)

The estimates of time to disease progression include censored data for 64 patients without documented evidence of disease progression as of the March 31, 1995 data cutoff date. For the 304 patients in the pivotal studies, the median time to disease progression was 3.2 months (range, 0.1 to 19.9 months).

Reviewer comment: *The efficacy update submitted on April 15, 1996 contains less censored data. Those analyses are not included in this NDA review. There were minor differences in the time to event results. Briefly, for the 304 patients in the pivotal studies, the median time to disease progression was 4.0 months (range, 0.1 to 19.9 months). Median time to disease progression was 4.2 months for patients treated with the 125-mg/m^2 starting dose and 3.3 months for those who were treated with the 100-mg/m^2 starting dose.*

Based on univariate analysis performed by the sponsor, median time to disease progression was significantly longer in patients who had a better baseline performance status ($p = 0.0001$). The forward stepwise log rank test performed by the sponsor confirmed baseline performance status as a prognostic factor for time to disease progression ($p = 0.0004$); as expected, this analysis showed that response to CPT-11 was a prognostic factor for time to disease progression ($p = 0.0001$). Other demographic and/or disease-related characteristics were not predictive of time to disease progression.

Survival Time (ISE)

As of the time of last follow-up, 10 (20.8%) of the 48 patients in protocol 0001, 23 (25.6%) of the 90 patients in protocol 0003R, and 74 (44.6%) of the 166 patients in protocol 0006 were still alive. The estimates of survival time in the original NDA include censored data for patients who were still alive as of the data cutoff date. The date used in the analysis for these patients was the last date the patient was known to be alive.

Based on available data, the median survival time was 10.4 months (range, 1.0 to 26.7 months) in protocol 0001 and 8.1 months (range, 0.4 to 22.1 months) in protocol 0003R. In protocol 0006, the median survival time was 10.0 months (range, 0.3 to 15.2 months) for the 64 patients who received the 125-mg/m^2 starting dose and 7.8 months (range, 0.6 to 13.3 months) for the 102 patients who received the 100-mg/m^2 starting dose. However, differences between starting doses in this study must be

interpreted cautiously because of the number of censored observations for each starting dose and because of the study design: this was not a randomized study; there was a longer follow-up time for patients who began therapy at the 125-mg/m^2 starting dose than for those who began therapy at the 100-mg/m^2 starting dose.

For the 304 patients in the pivotal studies, the median survival time was 8.3 months (range, 0.3 to 26.7 months). As may be expected, the median survival time was longer for patients who responded to CPT-11 (11.3 months; range, 4.5 to 25.9 months) than for those whose best response to CPT-11 was stable (9.0 months; range, 1.6 to 26.7 months) or progressive disease (6.1 months; range, 0.6 to 11.6 months).

Reviewer comment: *The usual caveats of responder versus non-responder comparisons of survival hold. The efficacy update submitted on April 15, 1996 contains less censored data. Those analyses are not included in this NDA review. There were minor differences in the time to event results. Briefly, the median survival time was 10.4 months (range, 1.0 to 35.8 months) in protocol 0001 and 8.1 months (range, 0.4 to 30.7 months) in protocol 0003R (Table 30). In protocol 0006, the median survival time was 10.7 months (range, 0.3 to 22.5 months) for the 64 patients who received the 125-mg/m^2 starting dose and 9.3 months (range, 0.6 to 20.0 months) for the 102 patients who received the 100-mg/m^2 starting dose. For the 304 patients in the pivotal studies, the median survival time was 9.0 months (range, 0.3 to 35.8 months).*

Based on univariate analysis by the sponsor, median survival time was significantly longer in patients who had a better baseline performance status ($p = 0.0001$). The forward stepwise log rank test confirmed that a better baseline performance status was a prognostic factor for survival ($p = 0.0001$); not surprisingly, this analysis indicated that response to CPT-11 was predictive of survival ($p = 0.0003$). Other demographic and/or disease-related characteristics were not predictive of survival.

Clinical Benefit: (ISE)

Review comment: *Although some of the data (body weight, PS) may have been prospectively collected, the phase II studies were not prospectively designed to evaluate clinical benefit (weight gain,*

improvement of PS, improvement in disease related symptoms). Although the studies may be considered adequate and well-controlled for evaluating objective tumor response, they are not adequate and well controlled for the evaluation of clinical benefit. The sponsor has performed numerous different analyses with the data which are included in the NDA. Only selected summary tables will be included in this NDA review.

Summary of Clinical Benefit Information
(Source: Table 8.1-2, Iss.txt)

Clinical Benefit Parameter	% of Responders (CR & PR)[a]	% of Stable Disease Patients	% of All Patients
Weight (Average versus Baseline)			
Increased (≥ 3%)	13.2%	8.2%	9.3%
Stable	63.2%	48.6%	50.6%
Decreased (< 3%)	23.7%	43.2%	40.1%
Performance Status (Modal)[b]			
Improved	15.8%	11.0%	12.6%
Maintained	76.3%	74.5%	72.8%
Declined	7.9%	14.4%	14.7%
Median Time to Decline in Performance Status	6.4	4.0	2.8
(Range in Months)	(1.4-16.3)	(1.0-12.4)	(0.1-16.3)
Decrease in Tumor Signs/Symptoms	81.8%	31.1%	39.2%
Decrease in Pain	85.7%	21.0%	31.0%
Time to Tumor Progression[c]			
CPT-11 > First-Line 5-FU Regimen	48.5% (16/33)	28.9% (24/83)	23.5% (43/183)

a CR = complete response, PR = partial response
b Most frequent value
c Includes only patients progressing after treatment with 5-FU that was given for metastatic disease

Reviewer comment: *The presence of edema could confound the evaluation of the weight findings in these patients. Also, the majority of patients in these studies had a very good PS at baseline.*

Tumor-Related Signs and Symptoms: (ISE)

Information on tumor-related signs and symptoms was collected retrospectively by the investigators or other study personnel on the prestudy worksheets. The patients who reported such symptoms were evaluated to determine if they experienced improvement in these symptoms during CPT-11 therapy.

Reviewer comment: *Keep in mind that some of this retrospectively collected data was based on recollection and that the questionnaire specifically stated that the purpose was to determine the clinical benefit of CPT-11. Therefore, bias is these assessments cannot be excluded.*

Only eleven (28.9%) of the 38 patients who responded to CPT-11 were retrospectively reported by the investigators or other study personnel to have tumor-related signs and symptoms at study entry. Of these 11 symptomatic patients, 9 (81.8%) experienced improvement in their signs/symptoms during CPT-11 therapy. The sponsor's assessment of clinical benefit in these 11 patients is shown in the table, below.

Prestudy Tumor-Related Signs and Symptoms in Patients Who Responded to CPT-11 in the Pivotal Studies in Previously Treated Colorectal Cancer[a]
(Source: Table 8.F-40, 8f.txt)

Protocol	Patient No.	Signs and Symptoms Present at Baseline	Improved on CPT-11
M/6475/0001		Back pain	Yes
		Hot flashes	Yes
		Constipation	Yes
M/6475/0003R		Swelling in abdomen (Ascites)	Yes
		Decreased appetite	Yes
		Pain	Unknown
M/6475/0006		Sacral pain	Yes
		Fatigue	No[c]
		Left flank pain due to urinary obstruction by tumor[d]	Yes
		Left subcostal pain due to urinary obstruction by tumor[d]	Yes
		Urinary frequency	Yes
		Dysuria	Yes
		Right upper quadrant abdominal pain	Yes
		Left lower quadrant abdominal pain	Yes
		Right upper quadrant abdominal pain	Yes
		Right shoulder pain	Yes
		Swelling in abdomen (ascites)	Yes
		Lower abdominal pain	Yes

[a] 11/38 responders had tumor-related signs or symptoms at baseline.
[b] Patient had pleural and bony metastases. The investigator summary did not comment on a change in the degree of pain for this patient. However, the Expert Panel found definite documentation of a decrease in pain.
[c] Patient had fatigue which was not felt by the research staff to have improved.
[d] Patient had a mass in the prostate which resulted in left hydroureter, left hydronephrosis and likely caused flank pain. His symptoms of urinary frequency and dysuria were due to bladder invasion by tumor.

Source: Reference 96 (Appendix C, Table 3.1.1).

Review comment: *Please refer to the Reviewer comments in the appropriate previous sections of this report for assessments of results for a discussion of the clinical benefit data for the individual studies.*

Time to Tumor Progression (CPT-11 versus Prior Treatment): (ISE)

The time to tumor progression on CPT-11 (which was determined from information prospectively collected on the study case report forms) was compared with that on 5-FU (which was determined from information retrospectively collected on the prestudy worksheets) for the 38 patients who responded to CPT-11, for the 149 patients who had stable disease during CPT-11 therapy, and for all 304 patients who were enrolled in the three pivotal studies. Where scans or reports were available (for 32 of the 38 responders), progressive disease following prior 5-FU therapy was verified by the sponsor's independent review panel for all but one responder (one responder in protocol 0001 appeared to have stable disease on 5-FU therapy).

Reviewer comment: *Evidently, scans were not reviewed for patients other than those who responded to CPT-11.*

Of the 38 patients who responded to CPT-11, 33 had received prior 5-FU therapy for metastatic disease. Of these 33 patients, 16 (48.5%) had a longer time to tumor progression on CPT-11 than on 5-FU. The time to tumor progression for some of these patients was considerably longer during CPT-11 therapy than during prior 5-FU therapy.

Reviewer comments: *There are several problems with these data besides the retrospective nature of the data collection and analysis. Comparing time to progression in the subset of patients who responded to CPT-11 to time to progression on prior therapy must be interpreted with caution because of selection bias. Furthermore, the documentation for disease progression on prior therapy (in the form of tumor measurements and CRFs) is not included in the NDA.*

2. Summary of Safety Results (ISS)

The following summary contains selected information from the three controlled phase II studies. Much of the information is integrated according to starting dose.

Treatment Modifications for Diarrhea and Neutropenia/Leukopenia (ISS)

The three most common reasons for dose modification were late diarrhea, neutropenia, and leukopenia. Among all patients enrolled, 37.5% (114/304) had a dose modification associated with late diarrhea: 23.5% (24/102) of those who received the 100-mg/m^2 starting dose, 43.5% (84/193) of those who received the 125-mg/m^2 starting dose, and 66.7% (6/9) of those who received the 150-mg/m^2 starting dose. Of the 267 patients who experienced late diarrhea, 42.7% (114/267) required an adjustment in their dose during treatment. Only 4 (1.3%) of the 304 patients were reported to discontinue treatment because of late diarrhea.

Among all patients enrolled, 23.4% (71/304) had a dose modification associated with neutropenia: 11.8% (12/102) of those who received a starting dose of 100 mg/m^2, 28.5% (55/193) of those who received a starting dose of 125 mg/m^2, and 44.4% (4/9) of those who received a starting dose of 150 mg/m^2. The CPT-11 dose was modified for 43.8% (71/162) of the patients who experienced neutropenia. Among all 304 patients, 17 (5.6%) received granulocyte colony-stimulating factor (G-CSF) at any time for neutropenia. Neutropenia was listed as a reason for discontinuing treatment for 5 (1.6%) of the 304 patients.

Adverse Experiences: (ISS)

All Medical Events (ISS)

One or more medical events were reported for each of the 304 patients. The medical events that were reported by > 10% of the patients are summarized by body system and by starting dose in the table below. The most frequently reported medical events were in the digestive (ie, diarrhea, nausea, vomiting, anorexia), body as a whole (ie, asthenia, abdominal pain), hemic and lymphatic (ie, leukopenia, anemia, neutropenia), and skin (ie, alopecia) systems, with > 50% of patients reporting one or more of these events

Medical Events Reported by > 10% of Patients[a,b]

Controlled Phase II Studies in Patients with Previously Treated Colorectal Cancer[c]

(Source: Table 8.G-25, ISS)

Body System[d]/Event[e]	Starting Dose (mg/m²) 100 N=102	125 N=193	150 N=9	All Patients N=304
DIGESTIVE	102 (100.0)	193 (100.0)	9 (100.0)	304 (100.0)
Diarrhea (late)[f]	89 (87.3)	171 (88.6)	7 (77.8)	267 (87.8)
Nausea	86 (84.3)	167 (86.5)	9 (100.0)	262 (86.2)
Vomiting	53 (52.0)	139 (72.0)	9 (100.0)	201 (66.1)
Anorexia	43 (42.2)	117 (60.6)	6 (66.7)	166 (54.6)
Diarrhea (early)[g]	49 (48.0)	98 (50.8)	6 (66.7)	153 (50.3)
Constipation	34 (33.3)	51 (26.4)	4 (44.4)	89 (29.3)
Flatulence	15 (14.7)	20 (10.4)	2 (22.2)	37 (12.2)
Stomatitis	7 (6.9)	27 (14.0)	0 (0.0)	34 (11.2)
Dyspepsia	11 (10.8)	19 (9.8)	2 (22.2)	32 (10.5)
BODY	96 (94.1)	182 (94.3)	8 (88.9)	286 (94.1)
Asthenia	84 (82.4)	140 (72.5)	6 (66.7)	230 (75.7)
Abdominal Pain	62 (60.8)	104 (53.9)	7 (77.8)	173 (56.9)
Fever	35 (34.3)	95 (49.2)	7 (77.8)	137 (45.1)
Pain	29 (28.4)	40 (20.7)	2 (22.2)	71 (23.4)
Headache	23 (22.5)	27 (14.0)	1 (11.1)	51 (16.8)
Back Pain	17 (16.7)	25 (13.0)	2 (22.2)	44 (14.5)
Chills	12 (11.8)	29 (15.0)	1 (11.1)	42 (13.8)
Infection	20 (19.6)	19 (9.8)	3 (33.3)	42 (13.8)
General Edema	8 (7.8)	27 (14.0)	3 (33.3)	38 (12.5)
HEMIC & LYMPHATIC[h]	81 (79.4)	158 (81.9)	9 (100.0)	248 (81.6)
Leukopenia	62 (60.8)	123 (63.7)	6 (66.7)	191 (62.8)
Anemia	48 (47.1)	127 (65.8)	9 (100.0)	184 (60.5)
Neutropenia	45 (44.1)	111 (57.5)	6 (66.7)	162 (53.3)

continued

Medical Events Reported by > 10% of Patients[a,b]
Controlled Phase II Studies in Patients with Previously Treated Colorectal Cancer[c]
(Source: Table 8.G-25, ISS)

Body System[d]/Event[e]	Starting Dose (mg/m²) 100 N=102	125 N=193	150 N=9	All Patients N=304
SKIN	69 (67.6)	144 (74.6)	8 (88.9)	221 (72.7)
Alopecia	57 (55.9)	119 (61.7)	8 (88.9)	184 (60.5)
Sweating	21 (20.6)	27 (14.0)	1 (11.1)	49 (16.1)
Rash	4 (3.9)	30 (15.5)	3 (33.3)	37 (12.2)
METABOLIC & NUTRITIONAL	47 (46.1)	119 (61.7)	7 (77.8)	173 (56.9)
↓ Weight	24 (23.5)	61 (31.6)	7 (77.8)	92 (30.3)
Dehydration	19 (18.6)	24 (12.4)	1 (11.1)	44 (14.5)
↑ Alkaline Phosphatase	3 (2.9)	34 (17.6)	3 (33.3)	40 (13.2)
↑ SGOT	1 (1.0)	28 (14.5)	3 (33.3)	32 (10.5)
RESPIRATORY	49 (48.0)	105 (54.4)	6 (66.7)	160 (52.6)
Dyspnea	17 (16.7)	48 (24.9)	2 (22.2)	67 (22.0)
↑ Coughing	19 (18.6)	33 (17.1)	1 (11.1)	53 (17.4)
Rhinitis	18 (17.6)	27 (14.0)	2 (22.2)	47 (15.5)
NERVOUS	57 (55.9)	82 (42.5)	4 (44.4)	143 (47.0)
Insomnia	29 (28.4)	30 (15.5)	0 (0.0)	59 (19.4)
Dizziness	14 (13.7)	30 (15.5)	1 (11.1)	45 (14.8)
CARDIOVASCULAR	34 (33.3)	51 (26.4)	5 (55.6)	90 (29.6)
Vasodilation	17 (16.7)	15 (7.8)	2 (22.2)	34 (11.2)

[a] Reported for ≥ 30/304 patients; all medical events that were reported are listed in Section 18, Table 1.3.3 and includes maximum NCI grade, 1 grade 1 event was uncoded.

[b] Events in the urogenital, special senses, and musculo-skeletal systems were reported for < 10% of the patients.

[c] Protocols 0001, 0003R, 0006.

[d] COSTART body system. Information represents the no. (%) of patients reporting at least 1 event in the body system; patients reporting > 1 event in a body system are counted only once in the body system.

[e] COSTART term. Information represents the no. (%) of patients reporting each event within body system; patients who reported the same event more than once are counted once for that event.

[f] Occurred > 24 h after administration of CPT-11.

[g] Occurred ≤ 24 h after administration of CPT-11.

[h] Lymphocytopenia was identified as a laboratory abnormality for 99.0% (299/302) of the patients (Section 18, Table 1.9.3); it was not consistently reported as a medical event.

Source: Section 18, Tables 1.3.1 & 1.3.3.

Drug-Related Medical Events (ISS)

The occurrence of digestive system-related drug-related events in the 304 patients in the controlled phase II studies were primarily late diarrhea (87.8%), nausea (81.6%), vomiting (61.5%), early diarrhea (49.0%), and anorexia (48.7%). Drug-related neutropenia and anemia occurred in 52.6% and 53.6%, respectively. Drug-related alopecia occurred in 59.9% of patients. Of the 304 patients, only 1 (0.3%) fatal drug-related event was reported protocol 0001) by the sponsor. This patient experienced neutropenia and septic shock before death, which in the medical monitor's judgement could have been related to administration of CPT-11.

Reviewer comment: *As noted previously, according to FDA review of the CRFs, at least four additional deaths were possibly or probably related to CPT-11 (see the individual study reports).*

Grade 3 and 4 Medical Events (ISS)

Grade 3 or 4 events reported in > 10% of patients were late diarrhea (30.6%; 93/304), leukopenia (27.6%; 84/304), neutropenia (26.3%; 80/304), nausea (16.8%; 51/304), abdominal pain (15.8%; 48/304), vomiting (12.5%; 38/304), and asthenia (12.2%; 37/304). Grade 3 or 4 medical events reported to have occurred in >5% of all patients and according to starting dose are listed in the following table.

Frequency of Grade 3 & 4 Medical Events
Pivotal Studies in Patients with Previously Treated Colorectal Cancer
(Source: modified from Table 8.G-27, 8g.txt)

	Starting Dose (mg/m²)					
	100 (N=102)	125 (N=193)	150 (N=9)	All Patients (N=304)		
					Maximum NCI Grade[a]	
Body System/Event	No. (%)	No. (%)	No. (%)	No. (%)	3	4
DIGESTIVE	40 (39.2)	111 (57.5)	6 (66.7)	157 (51.6)	99	58
Diarrhea (late)	24 (23.5)	65 (33.7)	4 (44.4)	93 (30.6)	50	43
Nausea	11 (10.8)	38 (19.7)	2 (22.2)	51 (16.8)	50	1
Vomiting	2 (2.0)	33 (17.1)	3 (33.3)	38 (12.5)	30	8
Diarrhea (early)	6 (5.9)	18 (9.3)	0 (0.0)	24 (7.9)	17	7
Anorexia	2 (2.0)	16 (8.3)	0 (0.0)	18 (5.9)	17	1
HEMIC & LYMPHATIC	45 (44.1)	72 (37.3)	5 (55.6)	122 (40.1)	77	45
Leukopenia[a]	34 (33.3)	47 (24.4)	3 (33.3)	84 (27.6)	63	21
Neutropenia	22 (21.6)	54 (28.0)	4 (44.4)	80 (26.3)	45	35
Anemia	5 (4.9)	14 (7.3)	2 (22.2)	21 (6.9)	19	2
BODY	33 (32.4)	64 (33.2)	1 (11.1)	98 (32.2)	92	6[b]
Abdominal Pain	19 (18.6)	29 (15.0)	0 (0.0)	48 (15.8)	47	1
Asthenia	17 (16.7)	20 (10.4)	0 (0.0)	37 (12.2)	37	0
METABOLIC & NUTRITIONAL[c]	14 (13.7)	34 (17.6)	3 (33.3)	51 (16.8)	41	10

[a] Lymphocytopenia was identified as a grade 3 or 4 laboratory abnormality for 68.5% (207/302) of the patients (Section 18, Table 1.9.3); it was not consistently reported as a grade 3 or 4 medical event.
[b] Grade 5 events (deaths) were included with grade 4 events: one each of cerebral ischemia, 100 mg/m²; sepsis, 125 mg/m²; heart failure, 125 mg/m²; aspiration pneumonia, 125 mg/m²; respiratory disorder, 125 mg/m².
[c] Was rated grade 3 by investigator using World Health Organization (WHO) classification, which is equal to grade 2 NCI classification.
[d] No individual metabolic & nutritional event was occurred in ≥5% of patients.

Source: Section 18, Tables 1.5.1 & 1.5.3

Hospitalizations: (ISS)

One hundred and nineteen (39.1%) of the 304 patients were hospitalized a total of 156 times because of medical events. Eighty-one (26.6%) patients were hospitalized for events judged by the investigators to be related to administration of CPT-11. The primary reasons for drug-related hospitalizations were diarrhea, with or without nausea and/or vomiting (18.4%; 56/304), neutropenia/leukopenia, with or without diarrhea and/or fever (8.2%; 25/304), and nausea and/or vomiting (4.9%; 15/304).

Discontinuations Due to Medical Events: (ISS)

Thirteen 13 (4.3%) of the 304 patients discontinued treatment because of medical events. Twenty-seven patients (8.9%) discontinued treatment due to personal (3) or other reasons.

Discontinuations Due to Disease Progression: (ISS)

Of the 304 patients, 237 (78.0%) discontinued therapy after 1 to 14 courses due to disease progression.

Discontinuations Due to Death and/or On-Study Deaths:

On-study deaths were defined as deaths that occurred ≤ 30 days after administration of the last dose of CPT-11.

Reviewer comment: *See the review of the individual study report for comments.*

Analysis of Selected Medical Events :

Late Diarrhea

The table, below, summarizes the frequency of late diarrhea by patient, course, and maximum grade for all patients and by starting dose.

Frequency of Late Diarrhea[a]
Pivotal Studies in Patients with Previously Treated Colorectal Cancer[b]
(Source: Table 8.G-32, 8g.txt)

	No.	No. (%) with Diarrhea	Maximum NCI Grade				No. (%) Grade 3 + 4
			1	2	3	4	
ALL PATIENTS							
Patients	304	267 (87.8)	98	76	50	43	93 (30.6)
Courses	1060	685 (64.6)	401	159	75	50	125 (11.8)
STARTING DOSE = 100 mg/m^2							
Patients	102	89 (87.3)	39	26	18	6	24 (23.5)
Courses	334	242 (72.5)	160	53	23	6	29 (8.7)
STARTING DOSE = 125 mg/m^2							
Patients	193	171 (86.6)	58	48	32	33	65 (33.7)
Courses	671	415 (61.8)	229	100	49	37	86 (12.8)
STARTING DOSE = 150 mg/m^2							
Patients	9	7 (77.8)	1	2	0	4	4 (44.4)
Courses	55	28 (50.9)	12	6	3	7	10 (18.2)

[a] Occurred > 24 h after administration of CPT-11.
[b] Protocols 0001, 0003R & 0006.
Source: Section 18, Tables 1.3.3, 1.3.4, 1.5.3 & 1.5.4

Grade 3 and 4 late diarrhea was significantly greater (39.8% vs. 23.4%; $p = 0.0025$) in patients ≥ 65 years. No significant differences were observed in the frequency of late diarrhea by sex, ethnic origin, baseline performance status, previous radiation, or number of involved disease sites. A table (Table 8.G-33) summarizing this information can be found in the sponsor's ISS.

Reviewer comment: ***Please note that in one of the studies (0003R), the incidence of grade 3 and 4 late diarrhea was significantly higher in male patients compared to female patients (43.1% versus 15.6%; p = 0.010), but there were no gender differences in the other two controlled phase II studies (0006 and 0001) or in the uncontrolled NCCTG phase II study in patients who did not receive prior chemotherapy.***

The median time to the onset of late diarrhea was 11 to 12 days following CPT-11 administration for patients in the controlled phase II studies. The table below shows the duration and number of days that patients experienced late diarrhea.

Duration of Late Diarrhea[a]
Studies in Previously Treated Colorectal Cancer[b]
(Source: Modified from Table 8.G-35, 8g.txt)

NCI Grades	N[c]	Duration (d)			% of Days on Study With Late Diarrhea
		Median	Min	Max	
ALL PATIENTS					
1 - 4	1369	2	1	205	16.4
3 + 4	134	8	1	97	3.0
STARTING DOSE = 100 mg/m^2					
1 - 4	494	2	1	93	17.1
3 + 4	28	9	1	70	2.9
STARTING DOSE = 125 mg/m^2					
1 - 4	823	3	1	205	16.2
3 + 4	96	7	1	97	3.0
STARTING DOSE = 150 mg/m^2					
1 - 4	52	6	1	24	14.0
3 + 4	10	8	2	15	3.1

[a] Occurred > 24 h after administration of CPT-11.
[b] Protocols 0001, 0003R & 0006.
[c] N = Number of events.
Source: Section 18, Table 1.6.8.

The table below summarizes the number of courses of late diarrhea before and after intensive loperamide therapy was incorporated for protocols 0001 and 0003R. (This approach was used at the onset of protocol 0006 and, therefore, protocol 0006 patients are not included in the table). Overall, 30 (24.0%) of the 125 courses administered before institution of intensive loperamide therapy, compared with 34 (9.1%) of the 373 courses administered after institution of intensive loperamide therapy, were associated with grade 3 or 4 late diarrhea.

Frequency of Late Diarrhea[a] Before & After Institution of Intensive Loperamide Therapy Protocols 0001 & 0003R (Source: Table 8.G-36, 8g.txt)

Time of Course	No. of Courses	No. (%) of Courses with Event	Maximum NCI Grade				No. (%) Grade 3 + 4
			1	2	3	4	
Before standardized loperamide therapy	125	90 (72.0)	47	13	10	20	30 (24.0)
After standardized loperamide therapy	373	196 (52.5)	108	54	15	19	34 (9.1)

[a] Occurred > 24 h after administration of CPT-11.
Source: *Section 18, Table 1.6.6*

Reviewer comment: *The information in the above table is provided by course; it is unclear what effect CPT-11 dose (reduction) may have had on the change in incidence of severe diarrhea.*

Neutropenia: (ISS)

The table below summarizes the frequency of neutropenia by patient, course, and maximum grade for all patients and by starting dose. Among all patients enrolled, 23.4% (71/304) had a dose modification associated with neutropenia.

Frequency of Neutropenia
Pivotal Studies In Patients with Previously Treated Colorectal Cancer[a]
(Source: Table 8.G-40, 8g.txt)

	No.	No. (%) with Neutropenia	Maximum NCI Grade				No. (%) Grade 3 + 4
			1	2	3	4	
ALL PATIENTS							
Patients	304	152 (53.3)	31	51	45	35	80 (26.3)
Courses	1060	425 (40.1)	160	136	87	42	129 (12.2)
STARTING DOSE = 100 mg/m²							
Patients	102	45 (44.1)	10	13	12	10	22 (21.6)
Courses	334	116 (34.7)	33	47	24	12	36 (10.8)
STARTING DOSE = 125 mg/m²							
Patients	193	111 (57.5)	21	36	32	22	54 (28.0)
Courses	671	267 (39.8)	110	78	56	23	79 (11.8)
STARTING DOSE = 150 mg/m²							
Patients	9	6 (66.7)	0	2	1	3	4 (44.4)
Courses	55	42 (76.4)	17	11	7	7	14 (25.5)

[a] Protocols 0001, 0003R & 0006

Source: Section 18, Tables 1.3.3, 1.3.4, 1.5.3 & 1.5.4.

As might be expected, patients with previous radiation tended to have more grade 3 and 4 neutropenia (48.1% vs. 24.1%, p = 0.0358). There was no significant differences in the frequency of grade 3 and 4 neutropenia by age, sex, ethnic origin, baseline performance status, or number of involved disease sites.

Median time to nadir for neutrophils was 21 days (range, -1 to 38 days) among all 302 patients assessed.

Simultaneous Neutropenia and Fever:

Neutropenic fever, defined as grade 4 neutropenia and ≥ grade 2 fever, was reported in 3.0% (9/304) of the patients and in 0.9% (10/1060) of the courses. Neutropenic fever occurred in 2/102 (2.0%) of the patients receiving the 100-mg/m² starting dose, 5/193 (2.6%) of the patients receiving the 125-mg/m² starting dose, and 2/9 (22.2%) of the patients

receiving the 150-mg/m^2 starting dose. All nine patients with neutropenic fever were hospitalized and but recovered after receiving antibiotic therapy. There were no fatal outcomes in these nine patients. One patient (no. . protocol 0001) died of potentially drug-related neutropenic sepsis, but was afebrile at the time of this event.

Simultaneous Neutropenia and Late Diarrhea: (ISS)

Grade 3 or 4 neutropenia occurred simultaneously with grade 3 or 4 late diarrhea in 7.2% (22/304) of the patients and in 2.1% (22/1060) of the courses. Simultaneous grade 3 or 4 neutropenia/late diarrhea occurred in 2/102 (2.0%) patients receiving the 100-mg/m^2 starting dose, 17/193 (8.8%) patients receiving the 125-mg/m^2 starting dose, and 3/9 (33.3%) patients receiving the 150-mg/m^2 starting dose. Sixteen of the 22 patients were hospitalized for supportive care. There were no fatal outcomes reported by the sponsor in the patients who experienced simultaneous grade 3 or 4 neutropenia/late diarrhea.

Hematologic Toxicities Other Than Neutropenia or Leukopenia: (ISS)

The table below summarizes hematologic assays for lymphocytes, hemoglobin, and platelets by maximum NCI grade for all patients.

Hematologic Assays by Maximum Toxicity Grade
Pivotal Studies in Patients with Previously Treated Colorectal Cancer[a]
(Source: adapted from Table 8.G-47, 8g.txt)

Assay	No. of Pts[b]	No. (%) Abnormal	Maximum NCI Grade 1	2	3	4	No. (%) Grade 3 + 4
ALL PATIENTS							
Lymphocytes	302	299 (99.0)	14	78	130	77	207 (68.5)
Hemoglobin	302	293 (97.0)	168	102	21	2	23 (7.6)
Platelets	302	9 (3.0)	0	5	3	1	4 (1.3)

[a] Protocols 0001, 0003R & 0006
[b] No. of pts with assessment.
Source: Section 18, 1.9.3.

Serum Chemistries:

Liver and Renal Function Tests:

Overall, grade 3 or 4 toxicities occurred in < 8% of patients. Many of the increases in hepatic abnormalities were reported to coincide with progression of liver metastases. Grade 3 or 4 creatinine elevations occurred in only 3 of 285 patients (1.1%).

Flushing:

Grade 1 or 2 vasodilation (flushing) was reported for 34 (11.2%) of 304 patients and was judged to be related to administration of CPT-11 in 29 (9.5%) patients.

Extravasation:

Extravasation necrosis of the skin was not reported in the pivotal studies.

Diffusion Capacity of the Lung for Carbon Monoxide:

Protocols 0001 and 0003R, but not protocol 0006, incorporated DLCO measurements. Sixty-four (21.0%) of the 304 patients had at least two DLCO measurements obtained during the study. The mean baseline DLCO value was 90.3 L/sec and the mean last DLCO value was 83.9 L/sec. The mean decrease in DLCO of 6.4 L/sec from baseline to the last DLCO measurement was statistically significant. However, this decrease was not considered to be clinically significant, given the 20% error rate inherent in the test and the variability in DLCO changes; 38 patients had decreases, 23 had increases, and 3 had no change in DLCO values between baseline and the last measurement. No correlation between cumulative dose and changes in DLCO was seen.

Concomitant Medications:

Please refer to the NDA for the list of concomitant medications.

C. UNCONTROLLED STUDIES

The uncontrolled studies were not reviewed with the same detail as the controlled phase II studies described above. Only summary data is provided in this review. Study 0003N represents Phase II experience in patients with metastatic colorectal cancer who did not receive prior chemotherapy. The were treated under the same NCCTG protocol as Study 0003R in previously treated patients. Study 0001 was a similar phase II study in previously untreated patients with metastatic colorectal cancer. Brief descriptions of these studies and their results are provided below. Both studies provide supportive safety and efficacy information. Other relevant studies are also summarized below.

1. Study 0003N:

Title: A Multi center, Phase II Study of Irinotecan Hydrochloride (CPT-11) in Metastatic Colorectal Carcinoma Not Previously Treated with Systemic Chemotherapy (Protocol M/6475/0003N)

This multi center, NCCTG open-label, US phase II study evaluated the antitumor activity and toxicity of CPT-11 in patients with metastatic colorectal cancer who had not previously received systemic chemotherapy. This study is essentially the same as 0003R except it represents the previously untreated cohort of patients. A total of 31 patients received at least one dose of CPT-11 and were included in the intent-to-treat efficacy and safety analyses. Eight of the 31 patients had a partial response to CPT-11 therapy, for an overall response rate of 25.8% (95% CI, 10.4%-41.2%) based on the intent-to-treat population and 30.8% (8/26; 95% CI, 13.0%-48.5%) for the evaluable population. The median duration of response was 4.4 months (range, 2.3-8.1 months). Current information indicates that median survival time for all patients was 11.7 months (range, 2.2-21.3 months). Grade 3 or 4 late diarrhea (occurring > 24 hours after administration of CPT-11) was reported for 25.8% (8/31) of the patients and in 8.7% (9/103) of the courses. There were two (6.5%) cases of neutropenic fever.

2. Protocol 0010

Title: A Phase II, Open-Label Study of Irinotecan Hydrochloride (CPT-11) in Patients with Metastatic Colorectal Cancer Not Previously Treated with Chemotherapy or Radiotherapy.

This multicenter, open-label, US phase II study was sponsored under IND by the National Cancer Institute (NCI). The trial evaluated the

antitumor activity and toxicity of irinotecan hydrochloride (CPT-11) in patients with metastatic colorectal cancer who had not previously been treated with chemotherapy or radiotherapy. The starting dose of CPT-11 was 125 mg/m^2, given intravenously over 90 minutes administered weekly for four weeks, followed by a two-week rest. Forty-one patients received at least one dose of CPT-11 and were included in intent-to-treat efficacy and safety analyses. Of the 41 patients, 40 (97.6%) completed at least one course of CPT-11 and were included in the evaluable-patient analysis. Two (4.9%) of the 41 patients were still in the study as of the data cutoff date (March 31, 1993). Thirteen patients had a partial response to CPT-11 therapy for an overall response rate of 31.7% (95% CI, 17.5%-46.0%) for the intent-to-treat population and 32.5% (95% CI, 18.0%-47.0%) for the evaluable population. The median duration of response was 4.9 months (range, 1.7-12.6 months). The median survival time for all patients was 10.9 months (range, 2.2-22.1 months). The most common grade 3 and 4 drug-related medical events were late diarrhea in 26.8% (11/41) of the patients, neutropenia in 19.5% of the patients (8/41), and leukopenia in 12.2% of the patients (5/41). There were no cases of neutropenic fever reported in this study. No deaths occurred during CPT-11 therapy or within 30 days of study discontinuation.

3. The NDA also contains results from two US Phase I studies using the weekly x 4, 2-wk rest schedule (Study 0008 and Study 0027). Study 0027 involved thirty-two patients with advanced cancer. Diarrhea was identified as the DLT at the 180 mg/m^2 dose level. Two partial responses were reported.

   One of the objectives of Study 0008 was to determine the impact of antidiarrheal therapy and administration of G-CSF on CPT-11-induced diarrhea and dose-limiting neutropenia. There were 17 men and 9 women, ranging in age from 24 to 69 years. Twenty patients had received prior chemotherapy, 7 had received prior radiation therapy, and 6 had received no prior treatment. The most frequent medical events were diarrhea, nausea, and neutropenia. Six patients were hospitalized; four hospitalizations were for neutropenic fevers, and neutropenic fever proved to be the dose-limiting toxicity. The MTD of CPT-11 was 120 mg/m^2 without G-CSF and 145 mg/m^2 with G-CSF. Two patients died while on study (both reported in the NDA as due to progressive disease). Pharmacokinetic results suggest a potential correlation between higher biliary concentrations of unglucuronidated SN-38 and severe diarrhea; it was postulated that an increase in the rate of SN-38 glucuronidation might represent a means to decrease bowel toxicity resulting from exposure to unmetabolized biliary SN-38. Two patients, one with colon cancer and one with gastric cancer, achieved partial responses to therapy that lasted 5.1 and 5.6 months, respectively.

4. The NDA contains summary results of numerous ongoing US Phase I and II studies including those involving other schedules of CPT-11 administration and various types of malignancies; these studies are summarized in the tables below:

Ongoing Phase I Studies of CPT-11

Protocol No. Investigator(s)	Study Design	Drug	Regimen	
M/6475/0007 Saltz 06/0 94-ongoing	Open-label dose-escalating study to determine the maximum-tolerated dose (MTD), dose-limiting toxicity (DLT) & pharmacokinetics of combination therapy of CPT-11, 5-fluorouracil (5-FU) & leucovorin in patients with various malignancies.	CPT-11	100, 125, or 150 mg/m^2 intravenously	1X/wk for 4 wk followed by 2-wk rest
		5-FU	210, 265, 340, 425 or 500 mg/m^2 IV	
		Leucovorin	20 mg/m^2 IV	
M/6475/0008 (Amendment) Vokes 04/20/94-ongoing	Open-label, multiple-dose study at the MTD to evaluate the effects of gender & race on pharmacokinetics in 24 patients with various solid tumors or lymphomas.	CPT-11	145 mg/m^2 IV 1X/wk for 4 wk, followed by 2-wk rest	
M/6475/0009 Parnes 11/17/93-ongoing	Open-label dose-escalating study to determine the MTD, DLT & pharmacokinetics of combination therapy with CPT-11, 5-FU & leucovorin in patients with various malignancies.	CPT-11	Escalating doses, 25, 50, ... mg/m^2 IV on wk 1 & 4	
		5-FU	500 mg/m^2 IV 1X/wk (day 3) for 4 wk, followed by 2-wk rest	
		Leucovorin	500 mg/m^2 IV 1X/wk (day 3) for 4 wk, followed by 2-wk rest	
		CPT-11	100 mg/m^2 IV 1X/wk (day 1) for 4 wk, followed by 2-wk rest	
		5-FU	Escalating doses, 250, 300, 350, ... mg/m^2/d IV x 4 d (days 2-5) q 6 wk	
		Leucovorin	20 mg/m^2/d IV x 4 d (days 2-5) q 6 wk	
		CPT-11	100 mg/m^2 IV 1X/wk (day 1) q 2 wk (wk 1, 3 & 5)	
		5-FU	Escalating doses, 250, 300, 350, ... mg/m^2/d IV x 4 d (days 2-5) q 4 wk	
		Leucovorin	20 mg/m^2/d IV x 4 d (days 2-5) q 4 wk	
M/6475/0013 Rothenberg 02/20/95-ongoing	Open-label dose-escalating study to determine the MTD, DLT & pharmacokinetics of CPT-11 when administered every 2 wk to patients with refractory colorectal cancer.	CPT-11	125-350 mg/m^2 IV every other wk	

Ongoing Phase I Studies of CPT-11

Protocol No. Investigator(s)	Study Design	Drug	Regimen
M/6475/0028 Saltz 12/22/94-ongoing	Open-label, non-comparative, dose-escalating study to determine the MTD, DLT & pharmacokinetics of combination therapy with CPT-11 & cisplatin in patients with various malignancies.	Cisplatin	30 mg/m^2 IV 1X/wk for 4 wk, followed by a 2-wk rest.
		CPT-11	Immediately after cisplatin, 65, 85, 110, 125, or 145 mg/m^2 IV 1X/wk for 4 wk, followed by a 2-wk rest.
M/6475/0032 Drengler 02/01/05-ongoing	Open-label, non-comparative, dose-escalating study to determine the MTD, DLT & pharmacokinetics of oral CPT-11 in patients with various malignancies.	CPT-11	20, 40, 66, 100, or 140 mg/m^2 orally 1X/d for 5 days, repeated q 3 wk.

Ongoing US Phase II Studies of CPT-11

Protocol No. Investigator(s)	Study Design	Drug	Regimen	
COLORECTAL CANCER				
M/6475/0014 Alberts.,et al 01/27/95-ongoing	Multi center, open-label study of alternating cycles of CPT-11 & 5-fluorouracil (5-FU) + leucovorin in patients with untreated metastatic colorectal cancer	CPT-11	100 mg/m^2 IV 1X/wk for 4 wk, followed by a 2-wk rest.	
		5-FU	425 mg/m^2	Daily for 5 d, followed by 3-wk rest.
		Leucovorin	20 mg/m^2	
CERVICAL CANCER				
M/6475/0004 Kavanagh, et al 02/01/93-ongoing	Multi center, open-label study in patients with refractory cervical cancer.	CPT-11	125 mg/m^2 intravenously (IV) 1X/wk for 4 wk, followed by a 2-wk rest.	
M/6475/0019 Look 02/06/95-ongoing	Open-label study in patients with cervical cancer & no prior chemotherapy.	CPT-11	125 mg/m^2 IV 1X/wk for 4 wk, followed by a 2-wk rest.	
LUNG CANCER				
M/6475/0015 Crawford, et al 11/17/94 -ongoing	Multi center, open-label study in patients with stage IIIB or IV non-small-cell lung cancer & no prior chemotherapy.	CPT-11	60 mg/m^2 IV 1X/wk for 4 wk, followed by a 1-wk rest	
		Cisplatin	80 mg/m^2 IV 1X/wk for 1 wk (administered [illegible] after CPT-11 dose), followed by a 3-wk rest.	
M/6475/0016 Baker, et al 10/26/94- ongoing	Open-label study in patients with stage IIIB or IV non-small-cell lung cancer & no prior chemotherapy.	CPT-11	100 mg/m^2 1X/wk for 4 wk, followed by a 2-wk rest.	
M/6475/0029 Blanke, et al 03/14/95-ongoing	Open-label study in patients with small-cell lung cancer refractory to one prior chemotherapeutic regimen.	CPT-11	125 mg/m^2 IV 1X/wk for 4 wk, followed by a 2-wk rest.	

5. There are two open studies to for patients who do not quite fit the eligibility criteria for the Phase II studies (0002 and 0036). These are sought of compassionate exceptions with defined entry criteria.

6. Results of non-US studies were included in the NDA. A discussion of those studies is not included in this NDA review.

VI. REGULATORY CONCLUSIONS

A. Accounting for Investigators

DSI audit pending. Audits were requested at the sites that treated the greatest number of patients. In addition to a routine inspection, the DSI audit team was asked to verify selective NDA data on responding patients including the comparison of tumor measurements with those found in the medical record.

B. Need for Postmarketing Clinical Studies

1. Under the Accelerated Approval regulations, the sponsor must conduct a Phase IV study to verify that the surrogate endpoint (in this case objective tumor response, i.e., tumor shrinkage, essentially partial response) is associated with clinically meaningful patient benefit. The sponsor has submitted a Phase III study comparing CPT-11 alone versus 5-FU plus leucovorin versus CPT-11 in combination with 5-FU plus leucovorin in patients with colorectal cancer who have not previously received chemotherapy. The design of that study will be discussed at the June 13, 1996.

2. In study 0003R, the frequency of grade 3 and 4 late diarrhea was significantly greater in male than in female patients (43.1 versus 15.6%; $p = 0.01$). A difference based on gender was not observed in Study 0001 or Study 0006 nor was it observed in the uncontrolled NCCTG phase II study in patients who did not receive prior chemotherapy. Based on the integrated analysis of the data in patients receiving approximately the same regimen of CPT-11, no differences could be found based on gender. Because gender differences in glucuronidation (of acetominophen) have been described, Mark Ratain and Colleagues conducted a prospective study in a cohort of patients receiving CPT-11 on a weekly x 4 schedule (Proc. ASCO. Abs #1491, 1996); no significant differences in PK and PD based on gender were found but the number of patients was too small to draw firm conclusions. The sponsor may need to conduct postmarketing studies of PK and PD to exclude gender as a risk factor toxicity including grade 3 or 4 diarrhea.

3. In Study 0006, the frequency of grade 3 and 4 late diarrhea was significantly greater ($p = 0.0076$) in patients $\geq$ 65 years. Based on the sponsor's integrated analysis of the safety data, Grade 3 and 4 late diarrhea was

significantly greater (39.8% vs. 23.4%; p = 0.0025) in patients ≥ 65 years. Postmarketing studies should be conducted to further evaluate the PK and PD factors contributing to the higher risk for severe late diarrhea in elderly patient population, and to determine whether specific dosing recommendations can be made based on age.

4. Postmarketing studies should be done to determine the optimal dose and schedule of CPT-11 administration. A randomized controlled trial comparing the 125 mg/m^2 to the 100 mg/m^2 starting dose given on the weekly x 4 schedule should be considered. Also, consideration should be given to conducting a randomized controlled trial comparing the weekly x 4 every 6 week regimen to the once every 3 week regimen (350 mg/m^2). The latter regimen seems to more popular in Europe.

C. Labeling Review

The review of the submitted proposed labeling is pending.

VII. OVERALL EVALUATION AND CONCLUSIONS

The submitted controlled phase II studies of CPT-11 in patients with previously treated carcinoma of the colorectum (0001, 0003R, and 0006) can be considered adequate and well-controlled historical trials in regards to the evaluation of objective tumor response. The vast majority of the patients who responded to CPT-11 had metastatic disease that progressed within 3 months of receiving a 5 FU based regimen. Objective response to CPT-11 in this patient population is a clear demonstration of antitumor activity. The comparator in this case is the known natural history of this disease: tumors do not shrink without treatment (i.e., individual patient control).

Objective tumor response was fairly well documented in 12.5% (95% C.I, [8.8-16.2]) of the 304 patients treated with CPT-11 in the three controlled phase II studies (intent-to-treat analysis). The median duration of response for the all 38 responders in the three pivotal studies was 5.8 months (range, 2.6 to 15.1 months). The intent-to-treat analysis of response rate better approximates the response rate expected in the general oncology community. As defined in the NDA, the evaluable population excludes patients who fail treatment early because of intolerance to therapy or progressive disease. For example, 24 of 90 of patients (73.3%) in Study 0003R did not complete a course of CPT-11, and 18 of these 24 patients (75%) did not complete a course of treatment because of progressive disease. Considering the very limited treatment options available for patients whose disease has failed 5-FU, the 12.5% objective response rate suggests a notable level of antitumor activity.

In regards to the secondary endpoints, particularly time to progression and survival, and clinical benefit, the studies were not adequately controlled. Randomized controlled trials would be required to adequately assess the effects of CPT-11 on survival and time to progression. Relatively few of the patients in the submitted controlled phase II studies were reported to have disease related symptoms at baseline and most of the patients had a relatively good performance status. The study of body weight was not adequately controlled to account for confounding factors. The effect of CPT-11 on disease related symptoms would require prospectively designed studies in patients whose symptoms are well characterized at baseline and response to treatment carefully evaluated periodically during the study.

The phase II studies provided sufficient information to assess the potential toxicities of CPT-11 administered at the dose and schedule proposed for marketing. The grade 3 or 4 events reported for all 304 patients were late diarrhea (30.6%), leukopenia (27.6%), neutropenia (26.3%), nausea (16.8%), abdominal pain (15.8%), vomiting (12.5%), and asthenia (12.2%).

Eighty-one (26.6%) patients were hospitalized for events judged by the investigators to be related to administration of CPT-11. The incidence of neutropenic fever, defined as grade 4 neutropenia and ≥ grade 2 fever, was not particularly excessive, reported in 3.0% (9/304) of the patients. Grade 3 or 4 neutropenia occurred simultaneously with grade 3 or 4 late diarrhea in 7.2% (22/304) of the patients, which is also not particularly excessive. The results of the phase I study 0008, suggest that the addition of G-CSF does not substantially increase the MTD (145 mg/m^2).

In study 0003R, the frequency of grade 3 and 4 late diarrhea was significantly greater in male than in female patients. A difference based on gender was not observed in Study 0001 or Study 0006 or in the uncontrolled NCCTG phase II study in patients who did not receive prior chemotherapy. Based on the integrated analysis of the data in patients receiving approximately the same regimen of CPT-11, no differences could be found based on gender. There is no clear explanation for the gender differences observered in Study 0003R; additional PK/PD studies may be required to rule out differences based on gender.

In Study 0006, the frequency of grade 3 and 4 late diarrhea by age was significantly greater ($p = 0.0076$) in patients ≥ 65 years. Based on the sponsor's integrated analysis of the safety data, Grade 3 and 4 late diarrhea was significantly greater (39.8% vs. 23.4%; $p = 0.0025$) in patients ≥ 65 years. Postmarketing studies are required to further evaluate the PK and/or PD factors contributing to the higher risk of severe diarrhea in elderly patients, and to determine whether specific dosing recommendations can be made based on age.

The incidence of grade 3 or 4 diarrhea was higher in patients who received 125 mg/m^2 starting dose compared to the 120 mg/m^2 starting dose (33.7% versus 23.5%). There is suggestion that the response rate may be higher in patients who received the 125 mg/m^2 starting dose compared to those who received the 100 mg/m^2 starting dose, but patients were not randomized to starting dose so firm conclusions can not be made from these data. The incidence of life-threatening (grade 4) delayed diarrhea appears to be reduced with aggressive loperamide therapy. Loperamide, in and of itself, may be associated with serious complications; at least one case of toxic megacolon associated with loperamide therapy has been reported. Dose reduction in subsequent courses of treatment also plays a role in reducing the occurrence of severe diarrhea.

VIII. RECOMMENDATIONS

The submitted Phase 2 studies of CPT-11 in previously treated patients with metastatic colorectal cancer should be considered adequate and well-controlled studies of objective tumor response. However, the submitted studies were not adequately designed and controlled to evaluate the effects of CPT-11 treatment on efficacy parameters other than objective tumor response. Although objective tumor response (i.e., tumor shrinkage) is reasonably likely to be associated with clinically meaningful patient benefit in some patients, this association requires verification. Considering the very limited available treatment options for patients whose disease has failed a 5-FU based regimen, and the established overall objective tumor response rate of 12.5% (95% C.I, [8.8-16.2]), CPT-11 should be considered for approval under the Accelerated Approval mechanism (21 CRF 314.500) providing the sponsor agrees to conduct an adequate and well-controlled trial to evaluate the effects of CPT-11 on survival and/or quality of life.

Isagani Chico, M.D.
NCI/FDA Fellow

Anthony J. Murgo, M.D., M.S.
Medical Officer
Division of Oncology Drug Products
HFD-150

John R Johnson, MD
5-23-96

cc:
Orig. NDA #20571
HFD-150/Division File
HFD-150/A.J. Murgo, M.D.
HFD-150/I. Chico, M.D.
HFD-151/L. Vaccari (CSO)

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JUN 6 1996

MEDICAL OFFICER REVIEW NDA SAFETY UPDATE

NDA #: 20-571

Drug Name: CAMPTOSAR™ (irinotecan)

Applicant: Upjohn **Date Submitted**: 3/29/96

Comments regarding safety update:

As of March 31, 1995 cutoff date for the original NDA, all patients had been enrolled but 2 patients in protocol 0003R and 19 patients in protocol 0006 were being actively treated. This safety update provides additional safety data up to December 31, 1995; an additional 31 courses of therapy were given.

As of December 31, 1995, a total of 1091 courses were delivered in the 304 patients enrolled in the three controlled phase 2 studies; the median number of courses per patient was 3.0 (range 1 to 14 courses) and the median duration of therapy was 18 weeks. Overall, the medical events reported by >50% of the patients are diarrhea, nausea, vomiting, anorexia, leukopenia, neutropenia, anemia, and alopecia. Late diarrhea, leukopenia and neutropenia were still the most common events associated with dose modifications. There were no additional unexpected or severe events, hospitalizations or treatment related deaths.

Generally, the safety data do not significantly differ from those of the original NDA. The types and frequencies of adverse events for the CPT-11 studies are similar to those provided in the original NDA.

Comments regarding the sponsor's facsimile dated 6/5/96:

The sponsor disagrees with FDA assessment that the deaths of three patients were potentially related to CPT-11. These cases were re-reviewed. We agree with the sponsor that the death of patient is probably not related to CPT-11. It was originally felt that we could not exclude the possibility that the pneumonia may have been due to aspiration secondary to vomiting associated with CPT-11, but we can not support this very well. However, based on re-review of the submitted information, the deaths of the other two patients were potentially related to CPT-11. (See following tables summarizing the information on the patients who died on study).

SPONSOR EVALUATION					FDA EVALUATION					
Protocol, Pt No.	Sex/ Age (y)	Starting Dose (mg/m^2)	Cause of Death	Relationship to CPT-11*	Event prior to death (Grade)	last treatment Date	Date of adverse event	Date of Death	Cause of Death	Relationship to CPT-11*
0001	F 74	125	disease progression	related	neutropenia (4) leukopenia (4) septic shock (4)	4 27 93	5 3 93	5 3 93	septic shock	related
0001	M 53	125	disease progression	unrelated	bilirubin (4)	5 20 93	5 27 93	6 11 93	liver failure probably related to PD	unrelated[1]
0001	M 71	125	cardiopulmonary arrest of unknown etiology	unrelated	catheter infection	11 4 93	11 13 93	11 25 93	cardiopulmonary arrest of unknown etiology	possibly related
0003R	F 71	125	disease progression	unrelated	nausea (3) vomiting (3) leukopenia (1)	9 30 93	10 1 93 10 2 93 10 6 93	one week after 10/8	No evidence of disease progression	Probably related
0003R	M/68	125	disease progression	unrelated	dehydration (3) weakness (3) neutropenia (4)	6/3/94	6/12/94 6/12/94	6/13/94	no documentation of PD	related

[1]Re-review of this case supports the FDA assessment that the death is potentially related to CPT-11 (see sponsor's facsimile dated 6/5/96).

Protocol, Pt No.	Sex/ Age (y)	Starting Dose (mg/m²)	Cause of Death	Relationship to CPT-11*	Event prior to death (Grade)	last treatment Date	Date of adverse event	Date of Death	Cause of Death	Relationship to CPT-11*
0003R	M/81	125	disease progression	unrelated	diarrhea (4) N/V (1) dehydration (2) N/V (1) cough,dyspnea	6/23/93	6/23/93 7/13/93	8/1/93	probable PD but no objective documentation of PD, pneumonia, aortic valve disease	probably unrelated
0003R	M/69	125	acute myocardial infarction	unrelated	belching (4)	12/13/94	12/17/94	12/24/95	acute MI	unrelated
0003R,	M/58	125	disease progression	unrelated	weakness (2) short of breath (2) anorexia (3) confusion (3)	5/30/94	6/3/94	6/24/94	hepatic failure	unrelated
0003R,	M/63	125	disease progression	unrelated	diarrhea (1) anorexia (1)	5/31/94	5/10/94	6/18/94	progressive disease	unrelated
0003R,	F/59	125	disease progression	unrelated	-----	7/20/94	----	8/18/94	progressive disease	unrelated

Protocol, Pt No.	Sex/ Age (y)	Starting Dose (mg/m²)	Cause of Death	Relationship to CPT-11[1]	Event prior to death (Grade)	last treatment Date	Date of adverse event	Date of Death	Cause of Death	Relationship to CPT-11[1]
0006,	F/57	125	disease progression	unrelated	vomiting (3)	6/16/94	6/17/94	7/9/94	aspiration pneumonia ?	Probably[2] Related
0006,	M/62	100	disease progression	unrelated	bowel obstruction	6/22/94	6/29/94	7/9/94	tumor progression ?	unrelated
0006,	M/58	125	disease progression	unrelated	bowel obstruction	5/20/94	5/27/94	6/8/94	progressive disease	unrelated
0006,	F/43	125	disease progression	unrelated	respiratory distress (4)	5/26/94	6/11/94	6/20/94	progressive disease	unrelated
0006,	M/76	100	cerebral dysfunction	unrelated	confusion (3) to coma diarrhea (3) neutropenia (3) anemia (2) Jaundice	7/21/94	7/24/94	8/2/94	metabolic encephalopathy	related[3]

[2]Re-review of this case supports the sponsor's contention that the death is probable not related to CPT-11 (see the sponsor's facsimile dated 6/5/96.

[3]Re-review of this case supports the FDA assessment that the death is potentially related to CPT-11 (see sponsor's facsimile dated 6/5/96).

Protocol, Pt No.	Sex/ Age (y)	Starting Dose (mg/m^2)	Cause of Death	Relationship to CPT-11[a]	Event prior to death (Grade)	last treatment Date	Date of adverse event	Date of Death	Cause of Death	Relationship to CPT-11[c]
0006,	M/63	125	disease progression	unrelated	Candida esophagitis bowel obstruction aspiration pneumonia ARDS	5/4/94	5/12/94	5/22/94	pneumonia/ ARDS	unrelated
0006,	F/54	125	disease progression	unrelated	leukopenia (3) neutropenia (4) septic shock (4) GI bleeding (4)	5/13/94	5/19/94 5/21/94	5/22/94	sepsis ischemic bowel	related

Isagani Chico, M.D.
NCI/FDA Fellow

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Medical Officer
Division of Oncology Drug Products
HFD-150
June 6, 1996

JK Johnson, MD
6-6-96

cc:
Orig. NDA #20571
HFD-150/Division File
HFD-150/A.J. Murgo, M.D.
HFD-150/I. Chico, M.D.
HFD-151/L. Vaccari (CSO)

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Patent Info
Exclusivity Summ.

ITEMS 13 AND 14

PATENT INFORMATION, PATENT CERTIFICATION, AND EXCLUSIVITY INFORMATION

1)	Active Ingredient(s)	irinotecan hydrochloride
2)	Strength(s)	20 mg/mL
3)	Tradename	CAMPTOSAR™ Injection
4)	Dosage Form Route of Administration	Injection Intravenous
5)	Applicant Firm Name	The Upjohn Company
6)	NDA Number	20-571
7)	Approval Date	To be determined (no previous applications)
8)	Exclusivity-date first ANDA could be approved length of exclusivity period.	Five (5) years after date of approval, 5 July 2004, or the date of any patent extension, whichever occurs last.
9)	Applicable patent numbers and expiration date of each.	4,604,463 (5 July 2004)

Hendrick J. DeKoning Gans, M.D.
Director
Worldwide Pharmaceutical Regulatory Affairs

EXCLUSIVITY SUMMARY for NDA # 20-571 **SUPPL #** _____

Trade Name CAMPTOSAR Injection **Generic Name** irinotecan hydrochloride

Applicant Name Pfizer **HFD-** 150

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /✓/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____ _____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain. _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

Investigation #2

YES /___/ Explain _____ | NO /___/ Explain _____

_____ | _____

_____ | _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

Justin Vaccaro
Signature

Title: Project Manager

5-28-96
Date

Robert J. Lesko
Signature of Division Director

6/3/96
Date

cc: Original NDA 20-571 Division File HFD-85 HFD-85 Mary Ann Holovac

NDA 20-571
CAMPTOSAR™ Injection
(irinotecan hydrochloride injection)

REQUEST FOR EXCLUSIVITY

The Upjohn Company requests five (5) years of exclusivity for CAMPTOSAR™ Injection. The following is provided to assist FDA in the eligibility determination. This summary information follows the format contained in the letter of April 28, 1988, from Dr. Carl Peck to All NDA or ANDA Holders or Applicants.

1. Whether any active moiety in the drug product for which approval is sought has ever been approved in another drug product in the United States either as a single entity or as part of a combination product.

   Reply

   The active moiety in the drug product for which approval is being sought has not been approved in another drug product in the United States either as a single entity or as part of a combination product.

2. If not, whether any active moiety of the drug product has been previously marketed in the United States, and under what brand name.

   Reply

   The active moiety in the drug product has not been previously marketed in the United States.

DEBARMENT CERTIFICATION FOR NDA 20-571

Irinotecan Hydrochloride Injection

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, to the best of its knowledge and belief, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.

Ann L. Buckley
Executive Director,
Worldwide Regulatory Compliance

20 Dec. 95
Date

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-571 Trade (generic) names Camptosar (Irinotecan Hydrochloride)

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Colorectal cancer is rare in the pediatric population. The potential for use of irinotecan in other types of malignancies that may occur in pediatric patients has not been fully evaluated.

Leslie Vaccaro, Project Manager 5-29-96
Signature of Preparer Date

cc: Orig NDA 20-571
HFD-150/Div File
HFA Action Package

Concurrence: Anthony Murgo 6/3/96

FEB 12 1996

Division of Oncology and Pulmonary Drug Products

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

45 Day Review

NDA: 20-571

Date of Submission: NDA Dated 12/28/95
Received by CDER 12/28/95

Summary of Camptosar NDA Submission					
Topic	# submitted	previously reviewed	# done on 2/9/96	# left to review	# not planned for review
Pharmacology	106	21	2	?	?
Pharmacokinetics	67	11	33	0	23
Toxicology	27	22	0	5	0
Reproductive toxicity	6	6	0	0	0
Genetic toxicity	3	3	0	0	0
Carcinogenicity	(1)	1	0	0	0

In particular, the following key studies using the i.v. route were included:

Safety Pharmacology: CNS, respiratory/cardiovascular, GI, blood compatibility, antigenicity, isolated organs

Pharmacokinetics: "many" ADME studies by i.v. route

Toxicology:

Single dose in mice, rats, and dogs
Single dose of metabolites and degradation products in mice
Two weeks in dogs
Four weeks in rats and dogs
Four weeks of SN-38 in rats
Thirteen weeks in dogs
Twenty-six weeks in rats and dogs

Reproductive toxicity:

Stage A-B in rats
Stage C-D in rats and rabbits
Stage E-F in rats

Genetic toxicity:

Ames test
Clastogenicity in CHO cells
Clastogenicity in vivo in mice

Carcinogenicity: A non-traditional carcinogenicity study in which only 13 doses were administered

Recommendation: The application is fileable.

Paul A. Andrews, Ph D
Pharmacologist/Toxicologist

2/12/96
Date

cc
IND ORIG and Div File
HFD-150
JJDeGeorge
AMurgo
[redacted]
PAAndrews

Pharm/Tox

MAY 24 1996

Division of Oncology and Pulmonary Drug Products

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original NDA Review

NDA: 20-571

Date of Submission: NDA Dated 12/28/95
Received by CDER 12/28/95

Information to be conveyed to the sponsor: Yes (X) No ( )

Reviewer: Paul A. Andrews, Ph.D.

Date Review completed: 5/24/96

Sponsor: The Upjohn Company
Kalamazoo, MI

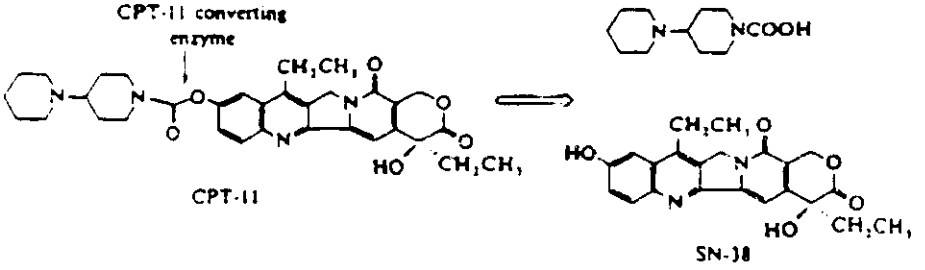
Manufacturer:

Drug Name: Primary: Camptosar
Other: CPT-11, irinotecan, DQ-2805, or U-101440

Chemical Name: (4*S*)-4,11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino)carbonyloxy]-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)-dione hydrochloride trihydrate

CAS Number: 100286-90-6

Structure(s):



Molecular Weight and Formula: 677.2 $C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$

Related INDs, NDAs:

Class: Antineoplastic, topoisomerase I inhibitor

Indication: Carcinoma of the colon or rectum in patients whose disease has progressed following prior 5FU-based chemotherapy

Clinical Formulation:

Format	Ingredient	Amount
vial	Camptosar	mg
	sorbitol	mg
	lactic acid USP	mg
	water	ml (pH 3-4)

Route of administration and dosage form: i.v.

Proposed Dosage: 125 mg/m² (90 min i.v. infusion) administered once weekly for 4 weeks followed by 2 weeks rest

OVERALL SUMMARY AND EVALUATION

CPT-11 is a semi-synthetic derivative of camptothecin and an inhibitor of topoisomerase I, a constitutively expressed enzyme that modulates torsional stress in DNA by inducing and resealing single strand breaks. Camptothecins block the ligation step of topo I without affecting the cleavage reaction. When the replication machinery collides with the topo I-DNA adduct, the single strand beaks are converted to lethal double-strand breaks. CPT-11 is thus preferentially toxic to S-phase cells. CPT-11 is converted *in vivo* by carboxylesterases to SN-38 which is a fold more potent inhibitor of topoisomerase I. Only the closed lactone ring of CPT-11 and SN-38 possess activity. The major toxicities in humans have been myelosuppression (leukopenia) and variable diarrhea. The $t_{1/2}$ of CPT-11 is 5-7 hr and for SN-38 is 11-18 hr; SN-38 is present in plasma at 2-5% of the concentration of CPT-11. The MTD in Japan was 125 mg/m²/week or 250 mg/m² (7.4 mg/kg) as a single bolus. The recommended starting dose in Europe for Phase II trials is 150 mg/m²/week x 4. The recommended dose for the marketed product in the U.S. is 125 mg/m² weekly x 4, repeated every 6 weeks.

Pharmacology. CPT-11 has significant activity *in vivo* against human tumor xenografts in mice, including colon cancer. The relative *in vitro* potency of CPT-11 compared to SN-38 against tumor cell lines varies widely fold). The lowest ratios tended to have high IC_{50}s for SN-38 suggesting that these cells have either low topo I levels or mutant topo I with a lower affinity to SN-38. This indicates that in some tumors CPT-11 may contribute significantly to the antitumor effect, perhaps by a mechanism independent from topo I inhibition. The concentrations of CPT-11 achievable in human plasma (3 μM) exceed the IC_{50} for only ⅛ of the cell lines; whereas the C_{max} of SN-38 in plasma (67 nM) was greater than the IC_{50} for ⅜s of the cell lines.

Safety Pharmacology. A general safety pharmacology screen examined effects of CPT-11 on the central nervous system (mice, cats), respiratory and cardiovascular system (dogs), gastrointestinal system (mice, rats, dogs), and neuromuscular junction (rabbits). The prominent effects produced by *i.v.* CPT-11 were the acceleration of gastrointestinal motility and potentiation of skeletal neuromuscular junctional transmission. CPT-11 induced contraction of isolated guinea pig ileal and tracheal preparations, which was completely inhibited by atropine. CPT-11 potentiated the responses to acetylcholine, nicotine, serotonin, and $BaCl_2$. These results suggest that CPT-11 may contract the smooth muscle preparations by inhibiting cholinesterase. CPT-11 inhibited the spontaneous movement in the uteri (estrus and diestrus stage) and spontaneous chronotropic and inotropic actions in the atrium. CPT-11 decreased the resting tension of the isolated thoracic unrubbed aorta of the rabbit but not of the mechanically rubbed aorta. Contractions induced by norepinephrine or prostaglandin F2a were not affected by CPT-11. The K_i of SN-38 for inhibition of acetyl cholinesterase activity was ~2000 times greater than CPT-11 (~0.25 μM) and the concentration of SN-38 needed to inhibit binding of a model substrate to acetyl cholinesterase was >20 times that of CPT-11. These data show that the cholinergic properties of CPT-11 are due to the piperdinopiperdine side chain. The cholinergic properties of piperdinopiperdine do not appear to have been investigated.

In rabbits, CPT-11 is a mild eye irritant, but is not a skin irritant. It produces a marked necrotic, degenerative inflammation when injected intramuscularly. CPT-11 is antigenic in Guinea pigs (passive cutaneous assay (PCA) and active systemic anaphylaxis assay (ASA)) and rabbits (PCA). The piperdinopiperdine side chain appeared to be the antigenic site since it was antigenic by itself (PCA, ASA), but SN-38 was not (PCA, ASA). CPT-11, SN-38, and piperdinopiperdine are not antigenic in mice (PCA test in rats).

Pharmacokinetics. CPT-11 C_{max} generally correlated with mg/m² dose in mice, rats, and dogs. Inter-species differences were noted, however, in the CPT-11 AUC. Mice and dogs had similar AUCs at a given mg/m² dose and these were approximately double the rat AUC. Clear differences were seen in SN-38

C_{max} and AUC between mice, rats, and dogs. The mouse C_{max} and AUC were fold and fold higher, respectively, than in rats. SN-38 production was very low in the dog representing either low carboxylesterase activity or rapid elimination. Note that all the pharmacokinetic studies were done at doses well below the lethal doses (300-400 mg/m² in rodents and 750 mg/m² in dogs). The rodent toxicity thus correlated best with CPT-11 C_{max}, whereas the lesser sensitivity of the dog to CPT-11 administration correlated best with the absence of SN-38 production. It is also possible that the greater sensitivity of the rodents is due to saturation of elimination pathways as the dose is raised, *e.g.* saturation of glucuronidation. This would lead to greater than expected systemic exposures compared to the dog.

The drug is distributed primarily to the liver and GI tract early after drug administration consistent with predominantly biliary/fecal excretion and entero-hepatic re-circulation. High concentrations were also found in adrenals, thyroid, pancreas, spleen, and bone marrow. The presence in the latter two organs was consistent with the myelosuppresion induced by CPT-11. In general, however, there was not a good correlation of end-organ toxicities with the tissue distribution. The V_d in rodents was much greater than total plasma volume and total body water indicating extensive tissue distribution/binding (V_d in dogs was only 2x total body water).

CPT-11 is primarily eliminated in the bile and 70% can be recovered in the feces. The remainder appears in the urine. In addition to CPT-11 and SN-38, the glucuronide of SN-38 can be found in the bile and accounts for 20% of the excreted dose; ~15% of the biliary excretion are unknown metabolites. Some of the dose may be excreted directly by the intestines. Approximately 20% of the dose excreted in the bile undergoes entero-hepatic re-circulation. CPT-11 is hydrolyzed to SN-38 by a carboxylesterase. In rodents this appears to transpire predominantly in the serum, but in humans the liver appears to be major site of cleavage. The released side chain rapidly decomposes to form piperdinopiperdine and CO_2. CPT-11 is not significantly metabolized by P450 enzymes and does not cause significant induction of them. When the piperdinopiperidine side chain (which is released upon conversion to SN-38) was labeled, the $t_{½}$s tripled, the urinary excretion doubled, and the RBC binding kinetics were altered. Non-fluorescent metabolites not previously detected either by HPLC (with fluorescent detection) or when the radiolabel was on the ethyl side-chain also appeared in the urine and these were attributed to metabolites of piperdinopiperdine. The metabolism of piperdinopiperdine, however, has not been fully studied. The clearance was saturable in rodents but not dogs.

A comparison of the pharmacokinetics in animals and humans at similar levels of toxicity is shown in the following table. The human CPT-11 and SN-38 AUC_{0-24}s after a 125 mg/m² dose were 10.2 ± 3.3 and 0.23 ± 0.11 µg•hr/ml respectively. The only study conducted on a similar schedule in animals was 7219-94-105 in which the rats were dosed weekly x 13. The highest dose administered was 150 mg/m² and this produced only minor toxicities. As a single dose, the MTD in humans is ~350 mg/m² and this produces estimated AUC_{0-24}s of 22.5 and 0.54 µg•hr/ml for CPT-11 and SN-38 respectively. The rat AUCs provided a good surrogate for a maximal single dose in man. The dog SN-38AUC also may provide a reasonable surrogate for pharmacokinetic guidance of dose escalation in humans.

Inter-species Pharmacokinetic Comparisons

Species	Dose[a,b]	CPT-11 AUC[c]	SN-38 AUC[c]
Weekly			
human	125 mg/m² weekly x 4	10.2	0.23
rat	150 mg/m² weekly x 13	13.6	0.44
Single Dose			
human	350 mg/m²	22.5	0.54
mouse	350 mg/m²	73	~3
rat	350 mg/m²	34	~1
dog	750 mg/m²	174	0.36

[a] the weekly human dose is the recommended starting dose and the single dose is an approximate MTD (varied between study locations); [b] the rodent doses are an approximate LD_{10} and the dog dose is the highest non-lethal dose; [c] µg•hr/ml, extraploated from regressions of pooled data (except weekly human data)

Toxicology. The toxicologic effects of CPT-11 were primarily confined to rapidly dividing tissues. Single *i.v.* doses induced increases in thymus and spleen weights in mice and rats, variable effects on platelets, and indications of hepatotoxicity in rats (vacuolar degeneration and congestion). Mice and rats had similar sensitivity to the lethal effects of CPT-11 (LD_{10}=300-400 mg/m²), but the lethal dose on a mg/m² basis was at least 2 times greater in dogs. Dogs exhibited vomiting and diarrhea after single *i.v.* doses of CPT-11.

Daily dosing produced more pronounced effects on hematopoiesis and the GI tract than single doses. The major effects of multiple daily dosing with CPT-11 were anemia (↓RBCs, Hct, Hgb); ↓WBCs; hypocellularity of bone marrow, spleen, thymus, and lymph nodes; vomiting; and diarrhea. Occasional signs of hepatotoxicity (↑AST, LDH, AP, atrophy) and nephrotoxicity (↑BUN, creatinine) were also noted. The findings were similar whether dosing was continued for 14-180 days. The only study conducted with a schedule similar to the recommended clinical schedule (weekly x 4 out of 6 weeks) was study #7219-54-105 in which the rats were observed for two years prior to sacrifice. Hematology and Clinical Chemistry data were not collected during the course of that study and gross pathology and histopathology was obtained 1.75 years after the last CPT-11 dose. Nonetheless, thirteen weekly doses of 150 mg/m² had no obvious toxic effect on the rats. When administered as multiple doses, dogs were more sensitive to CPT-11 than rodents. The dose-limiting toxicities in humans, diarrhea and leukopenia, were thus accurately predicted by both the single and multiple dose animal studies. The toxicology data for CPT-11 is summarized as follows:

Single Dose

			LD_{10}		
study#	species	route	mg/kg	mg/m²	selected toxicities
94-18	mouse	*i.v.*	110	330	↑platelets, ↑thymus weights, swollen spleen
94-18	mouse	oral	671	2013	diarrhea, hair loss, ↓WBCs, ↑thymus & spleen wts, GI mucosa atrophy, atrophy ♂ reproductive organs
94-18	rat	*i.v.*	70	420	↓RBCs, ↓platelets, ↑spleen weight, hepatotoxicity
94-18	rat	oral	688	4128	soft stools, ↓RBCs, ↑platelets, ↑spleen weight, atrophy multiple organs including ♂ reproductive organs
94-20	dogs	*i.v.*	40[a]	800	vomiting, diarrhea, ↑platelets, ↑CPK, thymus atrophy, skin redning

[a]highest non-lethal dose

Multiple Dose

				LD_{10}		
study#	species	route	schedule	mg/kg	mg/m²	selected toxicities
94-21	rat	*i.v.*	daily x 28	>20	>120	↓RBCs, Ht, Hgb, WBCs; ↑platelets, ↑BUN, multiple organ wt changes, thymus atrophy, hypocellularity of bone marrow & lymph nodes
94-22	rats	*i.v.*	daily x 28[a]	>20[b]	>120	↓RBCs, Ht, Hgb, WBCs w/ partial recovery; ↑AST, LDH, CPK, A/G and ↓AP, TP all reversible; reversible organ wt changes; reversible thymic atrophy; reversible hypocellularity (bone marrow, spleen)
94-15	dog	*i.v.*	daily x 28	1.6[c]	32	diarrhea, ↓leukocytes, ↓spleen thymus wts, atrophy ♂ reproductive organs
94-14	dog	*i.v.*	daily x 14	2.5[c]	50	vomiting, diarrhea, ↓RBCs, Hct, Hgb, WBCs, & platelets; ↑AP, creatinine, BUN, albumin, TP; atrophy of spleen, lymph nodes, intestinal mucosa, & liver; intestinal hemorrhage; hypocellularity of spleen, bone marrow, lymph nodes
94-16	dog	*i.v.*	daily x 91	1.6[c]	32	vomiting, diarrhea, ↓RBCs, Hgb, ↑WBCs; ↓CPK; GI tract ulceration/inflammation/necrosis; hypocellularity of thymus, spleen, lymph nodes; pneumonitis

94-105	rats	*i.v.*	weekly x 13	(2 yr recovery)	CPT-11 moderated findings that were seen in controls (enlarged liver and pituitary, coarse kidney surface, s.c. adipose tissue), ↑ uterine horn polyps and sarcomas

[a] with 2 and 4 week recovery groups, [b] only dose studied, [c]highest non-lethal dose

Long Term

				LD_{10}		
study#	species	route	schedule	mg/kg	mg/m²	selected toxicities
94-07	rats	*i.v.*	daily x 180	>4	>24	hair loss, ↓WBCs, ↓lymphocytes, ↑platelets, ↓globulins, ↑albumin, ↑cholesterol, hypoplasia of teeth, tumors found
94-01	dogs	*i.v.*	daily x 180	>1	>20	discolored skin, hair loss, diarrhea; ↓RBCs, Hct, Hgb

In addition, the single dose toxicity of CPT-11 metabolites and degradation products and the multiple dose toxicity of SN-38 have been investigated. On a weight basis, SN-38 and PP were 3-fold less toxic to rats than CPT-11 when LD_{10}s were compared (1380 and 1326 mg/m² respectively). The differences were more pronounced on a molar basis where the LD_{10}s in rats for CPT-11, SN-38, and PP were 620, 2870, and 6200 μmol/m² respectively. A caveat is that SN-38 was administered as a pH 9.0 solution (due to poor solubility at neutral pH) which favors the carboxylate over the lactone form. The carboxylate is inactive as a topoisomerase I inhibitor, but it is unknown if its whole animal toxicity is more or less than the lactone. Photodegradation products, however, were 3 to 7-fold more toxic in mice than CPT-11 when LD_{10}s were compared. The LD_{10}s for D-1, D-2, and Y-1 were 60, 47.7, and 119.1 mg/m² respectively (108, 85, and 186 μmol/m² on a molar basis). With multiple dosing for 28 days, SN-38 was about 2-fold more toxic as CPT-11 as assessed by the dose that caused significant effects on hematopoiesis, organ weights, and histopathology (70 mg/m²=146 μmol/m² *versus* 120 mg/m²=177 μmol/m² for CPT-11). Note that on a molar basis they were approximately equally toxic. Again, SN-38 was administered as a pH 9.2 solution which favors the carboxylate over the lactone form and it is unknown how this affects systemic toxicity.

Carcinogenicity. A conventional carcinogenicity study was not conducted. Two studies, however, indicated that CPT-11 has carcinogenic potential. When rats received 13 weekly doses of CPT-11 and were then allowed to recover for 90 weeks, skin masses were increased in ♀s that received 2 mg/kg as noted by gross observation and at autopsy. Histologically, these masses corresponded to mammary gland neoplasms, acinar proliferation, and cystic dilatation of the glandular lumina and were attributed to spontaneous acinar proliferation unrelated to the test article rather than neoplastic growth. An increased incidence of animals with neoplastic lesions was noted in the HD ♂s (11/50) which was attributed the low control value (4/50). In support of this interpretation, the ♀ controls had 9/50 animals with malignant neoplasms and two previous studies from this test facility had 8/50 and 10/50 animals with malignant neoplasms. When the tumors were categorized as malignant, benign, by tissue, and by histomorphology, only the increase in combined uterine horn polyps and sarcomas had a significant positive linear trend with dose. The tumor incidences at the individual doses, however, did not significantly differ from controls. In summary, 13 weekly doses of 150 mg/m² CPT-11 showed some evidence of carcinogenicity in F344 rats. In a second study, rats received daily doses of CPT-11 for 180 days. Sporadic tumors were found in control and treatment groups (leukemia, pituitary adenoma, mammary gland carcinoma, pancreatic carcinoma), but statistically significance was not assessed. The potential carcinogenic activity of CPT-11 is consistent with its mechanism of action (inhibition of re-sealing of topoisomerase I induced strand break), its clastogenic activity, and the established carcinogenic activity of topoisomerase II inhibitors.

Reproductive toxicity. The reproductive toxicology is summarized in the following table.

Reproductive Toxicology Summary for CPT-11

species	study #	Stage	NOAEL mg/kg/day	comments (number are mg/kg/day)
rat	94-08	A,B	0.24	paternal toxicity at 1.2 (atrophy of epididymis & testis, thin incisors), maternal toxicity at 6.0 (lacrimation, salivation), ↑fertility at 6.0, abnormal fetal development at 6.0 (unilateral microphthalmia, unilateral hydronephrosis)
rat	94-09	C	<0.24	maternal toxicity at 6.0 (↓food, death), ↓placental weights at 1.2, embryo-toxic & ↓fetal weights at 6, teratogenic at 1.2 (skeletal), delayed development of newborns at 6.0, post-weaning toxicity at 1.2 (↓ambulation, rearing), ↓learning ability at 0.24, ↓fertility in F1 ♀s at 0.24, hydrocephaly in F_1 autopsies at 6.0
rat	94-02	D,E	1.2	↓♂ body weights after weaning at 6.0, ↓learning ability at 6.0, autopsy findings at 10 weeks at 6.0
rabbit	94-6	C	0.06	teratogenic at 0.6 mg/kg/day (external, visceral, and skeletal abnormalities), embryo-toxic at 6.0

Genetic toxicity. Neither CPT-11 nor SN-38 were mutagenic to five strains of bacteria in an Ames test. In contrast, CPT-11 was clastogenic as indicated by an *in vivo* micronucleus test in mice and an increased incidence of chromosomal aberrations in Chinese hamster ovary cells *in vitro*.

RECOMMENDATIONS Product is considered approvable from a pharmacology perspective provided the following labeling changes are made.

a) Comments for further studies: none
b) Discussed with Medical Officer: pregnancy labeling

NDA Issues: none

LABELING REVIEW

1 **Clinical Pharmacology**

Replace sentences 3-5, paragraph 1 with:
Topoisomerase I relieves torsional strain in DNA by inducing reversible single strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I - DNA complex and prevent religation of these single strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA and either irinotecan or SN-38. Mammalian cells cannot efficiently repair these double strand breaks.

Replace 2nd sentence of paragraph 2 with:
SN-38 is approximately 1000-fold more potent than irinotecan as an inhibitor of topoisomerase I purified from human and rodent tumor cell lines, while *in vitro* cytotoxicity assays show that the potency of SN-38 relative to irinotecan varies from 2 to 2000-fold.

Delete last sentence, paragraph 3.

2 **Pharmacokinetics (metabolism)**

Replace last sentence with:

SN-38 glucuronide was 50-100 fold less potent than SN-38 in cytotoxicity assays using two cell lines *in vitro*.

3. **Warnings**

Replace sentences 2 and 3 of last paragraph with:

Irinotecan crosses the placenta following i.v. administration of 10 mg/kg to rats (which produces an irinotecan C_{max} and AUC about 3 and 0.5 times, respectively, the corresponding values in patients at the recommended weekly dose). Administration of 6 mg/kg/day i.v. irinotecan to rats (which produces an irinotecan C_{max} and AUC about 2 and 0.2 times, respectively, the corresponding values in patients at the recommended weekly dose) and rabbits (about one half the recommended human dose on a mg/m^2 basis) during the period of organogenesis, is embryotoxic as characterized by increased post-implantation loss and decreased numbers of live fetuses. Irinotecan was teratogenic in rats at doses greater than 1.2 mg/kg/day (which produces an irinotecan C_{max} and AUC about about ⅔ and 1/40th, respectively, of the corresponding values in patients at the recommended weekly dose) and in rabbits at 6.0 mg/kg/day (about one half the recommended weekly human dose on a mg/m^2 basis). Teratogenic effects included a variety of external, visceral, and skeletal abnormalities. Irinotecan administered to rats during the period of organogenesis at doses as low as 0.24 mg/kg/day (about one hundredth of the recommended weekly human dose on a mg/m^2 basis) also delayed development of newborns, decreased post-weaning ambulation and rearing, decreased learning ability, and decreased the fertility of F1 females. Irinotecan administered to rat dams for the period following organogenesis through weaning at doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights in the offspring.

4. **Carcinogenesis, Mutagenesis, & Impairment of Fertility**

Replace first sentence with:

A conventional carcinogenicity study was not conducted. When rats were administered i.v. doses of 2 mg/kg or 25 mg/kg irinotecan once per week for 13 weeks (the 25 mg/kg dose produced a plasma irinotecan C_{max} and AUC that were about 7.0 times and 1.3 times the respective values in patients at the recommended weekly dose) and were then allowed to recover for 91 weeks, there was an increased incidence of combined uterine horn polyps and sarcomas. The tumor incidences at each dose did not significantly differ from controls, but a linear trend with dose was significant.

Replace "Irinotecan was not mutagenic..." with:

Neither irinotecan nor SN-38 were mutagenic ....

Delete sentences 3 and 4, *replace* with:

Irinotecan was clastogenic both *in vitro* (chromosome aberrations in Chinese hamster ovary cells) and *in vivo* (micronucleus test in mice).

Insert as last sentence:

However, atrophy of male reproductive organs was observed after multiple daily irinotecan doses both in rodents at 20 mg/kg (which produces an irinotecan C_{max} and AUC about 5 and 1 times, respectively, the corresponding values in patients at the recommended weekly dose) and dogs at 0.4 mg/kg (which produces an irinotecan C_{max} and AUC about one half and 1/15th, respectively, the corresponding values in patients at the recommended weekly dose).

5 **Nursing Mothers**

Insert as first sentence:

Radioactivity appeared in rat milk within 5 minutes of i.v. administration of radiolabeled irinotecan and was concentrated up to 65-fold relative to plasma concentrations.

8 **Overdosage**

Replace second paragraph and table with:

Lethality was observed after single i.v. irinotecan doses of 110 mg/kg in mice and 70 mg/kg in rats (about 2.6 and 3.4 times the recommended weekly human dose, respectively, on a mg/m^2 basis). Death was preceded by cyanosis, tremors, respiratory distress, and convulsions.

Draft Letter, Requests for Sponsor

Please make the following changes to the labeling.

1 **Clinical Pharmacology**

Replace sentences 3-5, paragraph 1 with:

Topoisomerase I relieves torsional strain in DNA by inducing reversible single strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I - DNA complex and prevent religation of these single strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA and either irinotecan or SN-38. Mammalian cells cannot efficiently repair these double strand breaks.

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8. **Overdosage**

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Paul A. Andrews 5/24/96

Paul A. Andrews, Ph.D. Date
Pharmacologist

5/27/96

————Review Notes————

Previous Review(s), Date(s), and Reviewer(s):

IND	10/3/90	Goheer
	10/7/94	Andrews
	9/23/94	Andrews
	4/10/95	Andrews

Studies reviewed in this NDA:

Upjohn

\# #TR-

I. Pharmacology

ref 15 Therapeutic efficacy of the topoisomerase I inhibitor 7-ethyl-10-(4-[1-piperidino]-1-pipendino)-carbonyloxy-camptothecin against human tumor xenografts: lack of cross-resistance in vivo in tumors with acquired resistance to the topoisomerase I inhibitor 9-dimethylaminomethyl-10-hydroxycamptothecin. Cancer Res, 53:2823, 1993. (Vol 1.16, p.335)

ref 16 Growth inhibition of human gastrointestinal cancer xenograft lines by treatment with CPT-11 and VP-16. J Surg Oncol, 54:211, 1993 (Vol 1.16, p.342)

ref 20 Effects of CPT-11 (a unique DNA topoisomerase I inhibitor) on a highly malignant xeno-transplanted neuroblastoma. Med Pediatr Oncol, 23:487, 1994. (Vol 1.16, p.386)

ref 46 Intracellular roles of SN-38, a metabolite of the camptothecin derivative CPT-11, in the antitumor effect of CPT-11. Cancer Res, 51:4187, 1991. (Vol 1.17, p.222)

ref 48 DNA damage and cell killing by camptothecin and its derivative in human leukemia HL-60 cells. Jpn J Cancer Res, 84:566-73, 1993. (Vol 1.17, p.227)

ref 49 Comparison of topoisomerase I inhibition, DNA damage, and cytotoxicity of camptothecin derivatives presently in clinical trials. J Natl Cancer Inst, 86:836, 1994 (Vol 1.17, p.235)

ref 50 In vitro cytotoxicity of CPT-11 (SN-38) alone and in combination with cisplatin on ovarian cancer cells. Nara Igaku Zasshi, 45:273, 1994. (Vol 1.17, p.242)

ref 57 Antitumor effect of SN-38, active form of CPT-11, on human colorectal cancer cell line. Jpn J Cancer Chemother, 21:1601, 1994. (Vol 1.17, p.255)

ref 58 Cytotoxicity of CPT-11 and SN-38 for gastrointestinal and recurrent carcinomas cultured on contact-sensitive plates. Anticancer Res, 14:405, 1994. (Vol 1.17, p.261)

ref 68 Establishment of a camptothecin analogue (CPT-11)-resistant cell line of human non-small cell lung cancer: characterization and mechanism of resistance. Cancer Res, 50:5919, 1990. (Vol 1.17, p.340)

ref 80 Camptothecin analog (CPT-11) -sensitive human pancreatic tumor cell line QGP-1N shows resistance to SN-38, an active metabolite of CPT-11. Biochem Biophys Res Commun, 188:70, 1992. (Vol 1.17, p.414)

ref 83 Establishment of a CPT-11 -resistant human ovarian cancer cell line. Anticancer Res, 14:799, 1994. (Vol 1.18, p.1)

ref 94 Effects of CPT-11 in combination with other anti-cancer agents in culture. Int J Cancer, 50:604, 1992 (Vol 1.18, p.73)

7252-95-011 Inhibitory effect of camptothecin derivatives on DNA topoisomerase I (Topo 1) (Vol 1.21, p.202)

7252-95-013 Cell-killing kinetics of CPT-11 against a cultured human tumor cell line. (Vol 1.21, p.280)

7252-95-025 Studies on the inhibitory effect of CPT-11 and its related compounds against cell proliferation in culture. (Vol 1.21, p.294)

7252-95-016 In vitro growth-inhibitory effect of DQ-2805 (Vol 1.21, p.363)

7252-95-015 In vitro study on cell killing action of DQ-2805. (Vol 1.21, p 374)

II. Safety Pharmacology

A. Organ Systems

7256-94-145 CPT-11 (U-101440E) and SN-38 (U-101503) Inhibitory Activity against Acetylcholinesterase and Binding Activity to Acetylcholine Receptors. J Pharm Pharmacol, 45:444-448, 1993) (Vol 1.20, p.255)

7252-95-059 Gastrointestinal toxicity of DQ-2805 (CPT-11): Mechanism of emetic action. (Vol 1.33, p. 74-89)

7252-95-060 Gastrointestinal symptoms elicited by DQ-2805 (CPT-11): Emetic effect in dogs (Vol 1.33, p. 90-96)

B. Immunotoxicity

all previously reviewed

C. Local Irritation

7228-94-106 Dermal absorption and irritation study on CPT-11 bulk drug powder in albino rabbits. (Vol 1.32, p. 270-287)

III. Pharmacokinetics

mice

7262-94-111 Pharmacokinetics and Metabolism of CPT-11 and Metabolite SN-38 in Female CD2F$_1$ Mice Following Single Intravenous Administration. (Vol 1.16, p.183)

7256-94-122 Pharmacokinetics of CPT-11 and SN-38 Following a Single Intravenous Administration of CPT-11 to Female CDF1 Mice (Vol 1.34, p.88)

7256-94-125 Tissue Distribution of CPT-11 (U-101440E) and SN-38 (U-101603) After Intravenous Administration of CPT-11 (40 mg/kg) to Sarcoma 180-Bearing Mice (Vol 1.35, p.235)

7256-94-142 Pharmacokinetics and Tissue Distribution of CPT-11 and SN-38 after Intravenous Administration of CPT-11 to Tumor-Bearing Male Mice. (Vol 1.34, p.174)

7256-94-155 Relationship Between Development of Diarrhea and the Concentration of SN-38, an Active Metabolite of CPT-11, in the Intestine and the Blood Plasma of Athymic Mice Following Intraperitoneal Administration of CPT-11. (Vol 1.19, p. 36-44)

7256-94-120 *see rat listings*

ref 164 Tumor influence on pharmacokinetics of the camptothecin analogue irinotecan (CPT-11) and active metabolite SN-38 in mice. (Proc. Am. Assoc. Cancer Res., 35:432, 1994) (Vol 1.19, p. 253-254)

rats

AE-1290 7256-94-115 Tissue Distribution and Placental Transfer of [^{14}C]CPT-11 (U-10144OE) Following Single Intravenous Administration to Pregnant Female Wistar Rats. (Vol 1.18, p.311)

7256-94-116 Tissue Concentrations of CPT-11 and SN-38 Following a Single Intravenous Administration of [^{14}C]CPT-11 (U-101440E) to Male Wistar Rats. (Vol 1.19, p.487)

7256-94-119 Whole-body Autoradiography of Female Rats After Intravenous Injection of [^{14}C]CPT-11 (U-101440E) (DQ-2805). (Vol 1.35, p.275)

7256-94-120 Excretion and Changes in Plasma Concentration of SN-38 after Intravenous Administration in Rats and Mice. (Vol 1.34, p.59)

7256-94-123 Pharmacokinetics of CPT-11 and SN-38 after Intravenous Infusion of CPT-11 to Male Wistar Rats. (Vol 1.34, p.106)

7256-94-124 Excretion of [^{14}C]SN-38-(Sodium Salt) and Metabolites Following a Single Intravenous Administration to Bile Duct Cannulated Male Wistar Rats. (Vol 1.35, p.331)

YM102	7256-94-128	Pharmacokinetic study of CPT-11 (U-101440E) in male Wistar rats following single intravenous administration of 1 to 40 mg/kg. (Vol 1.16, p. 195-257)
	7256-94-141	Pharmacokinetics, Tissue Distribution, and Metabolism of [^{14}C]SN-38 (Sodium-Salt) Following Single Intravenous Administration to Male Wistar Rats (Vol 1.35, p.)
	7256-94-143	Concentration of [^{14}C]CPT-11 (U-101440E) in Milk and Plasma Following Single Intravenous Administration to Lactating Female Rats. (Vol 1.18, p.375)
	7256-94-144	Tissue Distribution of [^{14}C]SN-38 (U-101503) by Qualitative Whole Body Autoradiography After Single Intravenous Administration to Male Rats. (Vol 1.35, p. 287-305)
	7256-94-154	Tissue Distribution and Excretion of [^{14}C]CPT-11 (U-101440E) Following a Single Intravenous Administration to Female Wistar Rats. (Vol 1.19, p. 424-486)
ref 158	AR 94-222	Preliminary determination for the systemic exposure of CPT-11 and its active metabolite SN-38 in male Sprague-Dawley rats after intravenous administration at 40 mg/kg or oral administration at 182 mg/kg. (Vol 1.34, p. 287-316)
dogs		
	7256-95-005	U-101440E: A Fourteen-Day Oral and Intravenous Dose Toxicokinetic Study in Female Beagle Dogs - Additional Pharmacokinetic Studies of U-101440E (Irinotecan/CPT-11) and U-101503 (SN-38). *Addendum to Technical Report* 7227-94-019. (Vol 1.34, p.331)
	7256-94-156	Disposition and Excretion of [^{14}C]U-101440E (Irinotecan, CPT-11) in Male and Female Beagle Dogs Following a Single Intravenous Dose Administered at 2.5 mg/kg (Protocol 94-424). (Vol 1.35, p. 28-234)
metabolism		
	7256-94-114	Metabolic Fate of CPT-11: The chemical structure of the main metabolites in rat bile after a single intravenous dose. (Vol 1.20, p.10)
	7256-94-117	CPT-11 (U-101440E) Metabolism by Isolated Perfused Walker 256 Carcinosarcoma Tumors. (Vol 1.35, p.342)
	7256-94-121	Conversion of CPT-11 (U-101440E) into SN-38 in Human Tissues. (Vol 1.16, p.319)
	7256-94-129	In Vitro Human Protein Binding of CPT-11(DQ-2805). (Vol 1.35, p.306)
	7256-94-131	Enzyme Induction and Inhibition Studies on CPT-11 Using Rat Hepatic Microsomes. (Vol 1.20, p 79)
	7256-94-138	Protein Binding Studies on CPT-11 (U-101440E) and SN-38 (U-101503). (Vol 1.19, p.1)
	7256-94-140	Effect of Kampo herbal medicines on the β-glucuronidase-mediated hydrolysis of SN-38 glucuronide in vitro. (Jpn. J. Cancer Res., 86:978-984, 1995) (Vol 1.20, p.275)
	7256-94-146	Metabolic Activation of CPT-11 (U-101440E) by Hepatic Microsome Carboxylesterase. (Vol 1.20, p.238)
	7256-94-147	Bioactivation of CPT-11 (U-101440E) to the Active Metabolite SN-38 in vitro: Comparison of Rat, Dog and Human Tissues. (Vol 1.16., p. 258-283)
	7256-94-149	CPT-11 Converting Enzyme from Rat Serum: Purification and Some Properties. (Vol 1.20, p.107)
	ref 195	Human tumor carboxylesterase activity correlates with CPT-11 cytotoxicity in vitro. (Proc. Am. Assoc. Cancer Res., 35:365, 1994) (Vol 1.20, p. 283)
	ref 197	Role of carboxylesterase on metabolism of camptothecin analog CPT-11 in non-small cell lung cancer cell line PC7 cells. (Proc. Am. Assoc. Cancer Res., 33:427) (Vol 1.29, p. 284)
	ref 187	Differences in the induction of carboxylesterase isozymes in rat liver microsomes by xenobiotics. (Biochem. Pharmacol., 37:2708-2711, 1988) (Vol 1.20, p. 209)

ref 189 Human liver carboxylesterase. Properties and comparison with human serum carboxylesterase. (J. Biochem., 94:793-797, 1983) (Vol 1.20, p. 223-227)

IV. Toxicology

7219-94-007 A Chronic Toxicity Study of Repeated Intravenous Doses of CPT-11 Administered to Rats for 6 Months with a 1-Month Recovery Period. (Vol 1.24, p.1)

7219-94-001 The toxicity of repeated intravenous doses of DQ-2805 (CPT-11) administered to beagle dogs for 26 weeks. (Vol 1.28, p.1)

V. Special Toxicity

A. Reproductive Toxicity

DS121 7219-94-009 Teratology and Reproduction Studies of CPT-11 (DQ2805), Teratology Study in Rats (day 7-17). (Vol 1.30, p.1)

Studies not reviewed:

Pharmacology

The following Pharmacology studies were given cursory review (Abstracts examined) and are listed as not reviewed since no data was captured from them.

ref 1 Topoisomerase I inhibitors. An overview of the camptothecin analogs. Hematol Oncol Clin North Am, 8:333, 1994. (Vol 1.16, p.1)

ref 2 The current status of camptothecin analogues as antitumor agents. J Natl Cancer Inst, 85:271, 1993. (Vol 1.16, p.24)

ref 3 Plant antitumor agents. 1. The isolation and structure of camptothecin, a novel alkaloidal leukemia and tumor inhibitor from Camptothera accuminata. J Am Chem Soc, 88:3888, 1966. (Vol 1.16, p.45)

ref 4 The structural basis of camptothecin interactions with human serum albumin: impact on drug stability. J Med Chem, 37:40, 1994. (Vol 1.16, p.48)

ref 5 Mammalian DNA topoisomerase I and its inhibitors. In: Hickman JA, Tritton TR, eds. Cancer Chemotherapy. Oxford: Blackwell Scientific Publications, 1993, pp 21[illegible]-250. (Vol 1.16, p. 55)

ref 6 Cellular determinants of sensitivity and resistance to DNA topoisomerase inhibitors. Cancer Investig, 12:530, 1994. (Vol 1.16, p.530)

ref 7 Mechanisms of topoisomerase I inhibition by anticancer drugs. In: Liu LF, ed. Advances in pharmacology. New York: Academic Press, 1994, pp. 29B:73-92. (Vol 1.16, p.126)

ref 8 The biochemistry of camptothecin-topoisomerase I interaction. In: Potmesil M, Kohn KW, editors. DNA topoisomerases In cancer. New York, Oxford: Oxford University Press, 1991, pp 103-120. (Vol 1.16, p.144)

ref 9 Mechanistic aspects of DNA topoisomerases. Adv Protein Chem, 38:69, 1986.(Vol 1.16, p.144)

ref 19 Antitumor activity of the camptothecin derivative CPT-11 against malignant melanoma (strain SK-14) transplantable in nude mice. Skin Cancer, 5:239, 1990 (Vol 1.16, p.347)

ref 22 Chemotherapy responsiveness of human breast tumors in the 6-day subrenal capsule assay: an update. Breast Cancer Res Treat 3:33, 1983. (Vol 1.16, p.416)

ref 23 The subrenal capsule assay: a critical commentary. Eur J Cancer Clin Oncol, 22:757, 1986. (Vol 1.16, p.422)

7252-95-031 Study on preclinical evaluation of camptothecin derivative DQ-2805. Part II: in vivo antitumor effect. (vol 1.21, p.56)

ref 25 Antitumor activity of 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxy-camptothecin, a novel water-soluble derivative of camptothecin, against murine tumors Cancer Res, 47:5944, 1987. (Vol 1.16, p.430)

7252-95-021 Antitumor effect of CPT-11 against murine tumors. (Vol 1.21, p.89)

ref 27 Synthesis and antitumor activity of 20(S)-camptothecin derivatives: carbamate-linked, water-soluble derivatives of 7-ethyl-10-hydroxycamptothecin. Chem Pharm Bull, 39:1446, 1991 (Vol 1.16, p.438)

7252-95-023 Antitumor effect of SN-38 against various mouse experimental tumors. (Vol 1.21, p.128)

ref 29 Preclinical evaluation of CPT-11, a camptothecin derivative. Proc Am Assoc Cancer Res, 32:402, 1991. (Vol 1.17, p.1)

ref 30 Synthesis of water-soluble (aminoalkyl)camptothecin analogues: inhibition of topoisomerase I and antitumor activity. J Med Chem, 34:98, 1991. (Vol 1.17, p.2)

ref 32 Effects of CDDP, ADR, CPT-11 on rats with ENNG-induced gastrointestinal carcinogenesis - especially by cell kinetic study. Kitakanto Med, 41:743, 1991. (Vol 1.17, p.34)

ref 34 In vitro and in vivo effects of clinically important camptothecin analogues on multidrug-resistant cells. Oncol Res, 5:467, 1993. (Vol 1.17, p.69)

7252-95-018 Inhibitory effects of CPT-11 on liver metastases in nude mice injected with human pancreatic tumor cells into their spleens. Jpn J Cancer Chemother, 17:2433, 1990. (Vol 1.17, p.77)

7252-95-014 Inhibition of experimental and spontaneous metastasis by CPT-11. Cancer Chemother Pharmacol, 21:308, 1988. (Vol 1.17, p.91)

7252-95-007 Enhancement of the antitumor effect by combination of CPT-11, a camptothecin derivative, with various anti-cancer agents. Jpn J Cancer Chemother, 18:393, 1991. (Vol 1.17, p.174)

ref 40 Experimental studies on biochemical modulation targeting topoisomerase I and II in human tumor xenografts in nude mice. Int J Cancer, 50:760, 1992. (Vol 1.17, p.198)

ref 41 Enhanced antitumor efficacy of a combination of CPT-11, a new derivative of camptothecin, and cisplatin against human lung tumor xenografts. Jpn J Cancer Res, 84:203, 1993. (Vol 1.17, p.205)

ref 42 Advantages in combination chemotherapy using the camptothecin analogue CPT-11 and cisplatinum analogues for human testicular cancer xenografts. Acta Urol Jpn, 39:1221, 1993. (Vol 1.17, p.205)

ref 43 Combination chemotherapy of BOF-A2, a new 5-FU derivative, with various anticancer agents against human cancer xenografts in nude mice. Jpn J Cancer Chemother, 21:1619, 1994. (Vol 1.17, p.215)

7252-95-017 Inhibitory effect of CPT-11 on microtubule reassembly. (Vol 1.21, p.243)

ref 59 Activity of CPT-11 (irinotecan hydrochloride), a topoisomerase I inhibitor, against human tumor colony-forming units. Anti-cancer Drugs, 5:202, 1994. (Vol .17, p.266)

ref 60 Preclinical and phase I trials of topoisomerase I inhibitors. Cancer Chemother Pharmacol, 34(suppl):s41, 1994. (Vol 1.17, p.271)

ref 61 A new derivative of camptothecin, irinotecan hydrochloride (CPT-11) induces programmed cell death in leukemia/lymphoma cell lines. Int J Oncol, 3:679, 1993. (Vol 1.17, p.276)

ref 62 Apoptosis of lung cancer cells caused by some anti-cancer agents (MMC, CPT-11, ADM) is inhibited by bcl-2. Biochem Biophys Res Commun, 192:30, 1993. (Vol 1.17, p.283)

ref 63 bcl-2 gene prevents induction of apoptosis in Ll 21 0 murine leukemia cells by SN-38, a metabolite of the camptothecin derivative CPT-11. Int J Oncol, 4:649, 1994.

ref 64 Anticancer agents and apoptosis. Jpn J Cancer Chemother, 21:330, 1994. (Vol 1.17, p.296)

ref 65 Mechanisms of resistance to topoisomerase inhibitors. In: Goldstein LJ, Ozols RF, editors. Anticancer Drug Resistance: Advances in Molecular and Clinical Research. Boston: Kluwer 1994, pp. 263-81. (Vol 1.17, p.302)

ref 66 Cellular determinants of sensitivity and resistance to camptothecins. In: Potmesil M,

Pinedo H, editors. Camptothecins: New Anticancer Agents. Boca Raton: CRC Press, 1995:123-38. (Vol 1.17, p 321)

ref 67 Mechanism of camptothecin resistance: decreased uptake of SN-38 by resistant cell lines. CPT-T 4-9 and CPT-K 5. Igaku No Ayumi, 143:721, 1987. (Vol 1.17, p.338)

ref 69 Detection of topoisomerase I gene point mutation in CPT-11 resistant lung cancer cell line. Biochem Biophys Res Commun, 188:571, 1992. (Vol 1.17, p.346)

ref 70 Point mutation of topoisomerase I gene in CPT-11 resistant cell line. In: Miyazaki T, Takaku F, Sakurada K. eds. The Mechanism and New Approach on Drug Resistance of Cancer Cells. Amsterdam: Elsevier, 1993, pp.115-118.

ref 71 Decreased expression of DNA topoisomerase I in camptothecin-resistant tumor cell lines as determined by a monoclonal antibody. Cancer Res, 50:6925, 1990. (Vol 1.17, p.357)

ref 72 Activation of the human multidrug resistance 1 (MDR1) gene promoter in response to inhibitors of DNA topoisomerases. Int J Oncol, 1:73, 1992. (Vol 1.17, p.363)

ref 73 Characterization of a mammalian mutant with a camptothecin-resistant DNA topoisomerase I. Proc Natl Acad Sci USA, 84:5565, 1987. (Vol 1.17, p.368)

ref 74 Camptothecin-resistant mutant of human T-cells possessing altered DNA topoisomerase 1. In: Kimura K, Ota K, Carter SK, Pinedo HM, eds. Cancer Chemotherapy challenges for the future. Proc Fourth Nagoya Int Symp. Cancer Treat. Amsterdam: Elsevier 1026:317, 1989. (Vol 1.17, p.373).

ref 75 Molecular basis of resistance to CPT-11, a specific inhibitor of DNA topoisomerase. In: Miyazaki T, Takaku F, Sakurada K, eds. The mechanism and new approach on drug resistance of cancer cells. Int Symp; Amsterdam, New York: Elsevier, 1993, pp.95-101. (Vol 1.17, p.377)

ref 76 Drug resistance mechanisms of topoisomerase I drugs. In: Liu LF, editor. Advances in Pharmacology. New York: Academic Press, 1994, 29B:93-103. (Vol 1.17, p.384)

ref 77 Collateral drug sensitivity induced in CPT-11 (a novel derivative of camptothecin)-resistant cell lines. Biomed Pharmacother, 44:209, 1990. (Vol 1.17, p.395)

ref 78 Antileukemic effects of CPT-11 (a new derivative of camptothecin) in rat leukemias and the isolation of resistant human leukemic cells. In: Kimura K, Ota K, Carter SK, Pinedo HM, eds Cancer chemotherapy challenges for the future. Proc Fourth Nagoya Int Symp Cancer Treat, Amsterdam:Elsevier, 1989 pp. 312. (Vol 1.17, p.403)

ref 79 Mechanism of cross-resistance to a camptothecin analogue (CPT-11) in a human ovarian cancer cell line selected by cisplatin. Cancer Res, 52:328, 1992. (Vol 1.17, p.408)

ref 81 Differential expression of DNA topoisomerase I gene between CPT-11 acquired- and native-resistant human pancreatic tumor cell lines: detected by RNA/PCR-based quantitation assay. Biochem Biophys Res Commun, 84:618, 1992. (vol 1.17, p.422)

ref 82 Quantitative analysis of DNA topoisomerase I activity in human and rat glioma: characterization and mechanism of resistance to antitopoisomerase chemical, camptothecin-11. J Surg Oncol, 53:97, 1993. (Vol 1.17, p.430)

ref 84 Characterization of an etoposide-resistant human ovarian cancer cell line. Cancer Chemother Pharmacol, 34:183, 1994. (Vol 1.18, p.6)

ref 85 DNA topoisomerase: the mechanism of resistance to DNA topoisomerase II inhibitor VP-16. Hiroshima J Med Sci, 38:197, 1989. (Vol 1.18, p.14)

ref 86 Establishment and characterization of an etoposide-resistant human small cell lung cancer cell line. Acta Med Okayama, 46:203, 1992. (Vol 1.18, 25)

ref 87 Increased expression of DNA topoisomerase I gene and collateral sensitivity to camptothecin in human cisplatin-resistant bladder cancer cells. Cancer Res 54:3248, 1994. (Vol 1.18, p.35)

ref 88 7-Ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxy camptothecin: mechanism of resistance and clinical trials. Cancer Chemother Pharmacol, 34(suppl):S1 12, 1994. (Vol

1.18, p. 40)

ref 89 Semi-quantitative analysis of DNA topoisomerase-I MRNA level using reverse transcription-polymerase chain reaction in cancer cell lines: its relation to cytotoxicity against camptothecin derivative. Jpn J Cancer Res, 85:869, 1994. (Vol 1.18, p.46)

ref 90 Resistance to anticancer drugs in NIH3T3 cells transfected with c-myc and/or c-H-ras genes. Hum Cell, 4:33, 1991. (Vol 1.18, p. 52)

ref 91 Quantitative analysis of DNA topoisomerase I activity in human and rat glioma: characterization and mechanism of resistance to antitopoisomerase chemical, camptothecin-11. Brain Tumor Pathol, 11:59, 1994. (Vol 1.18, p.57)

ref 92 Intracellular distribution of CPT-11 in CPT-11 -resistant cells with confocal laser scanning microscopy. Jpn J Clin Oncol, 22:331, 1992. (Vol 1.18, p.63)

ref 93 Synergistic enhancement of cisplatin cytotoxicity by SN-38, an active metabolite of CPT-11, for cisplatin-resistant HeLa cells. Jpn J Cancer Res, 85:966, 1994. (Vol 1.18, p. 67)

ref 95 Effects of SN-38 in combination with other anticancer agents against cells. Jpn J Cancer Chemother, 21:1607, 1994. (Vol 1.18, p.80)

ref 96 In vitro modification of cytocoidal effects of CPT-11 in combination with DNA topoisomerase 11-related agents. In: Andoh T, Ikeda H, Oguro M, eds. Molecular biology of DNA topoisomerases and its application to chemotherapy: Proc Int Symp on DNA topoisomerases in chemotherapy, Boca Raton: CRC Press, 1993, pp.313-9. (Vol 1.18, p.85)

ref 97 Suramin inhibits DNA damage in human prostate cancer cells treated with topoisomerase inhibitors in vitro. Prostate, 23:25, 1993. (Vol 1.18, p. 92)

ref 98 Augmentation of antiproliferative activity of CPT-11, a new derivative of camptothecin, by tumor necrosis factor against proliferation of gynecologic tumor cell lines. Anticancer Drugs, 2:469, 1991. (Vol 1.18, p.104)

ref 99 Interaction of interferon gamma and CPT-11, a new derivative of camptothecin, in human endometrial carcinoma cell lines. Int J Gynecol Cancer, 3:36, 1993. (Vol 1.18, p.110)

ref 100 Enhanced expression of the DNA topoisomerase gene in response to heat shock stress in human epidermoid cancer KB cells. Cancer Res, 53:1085, 1993. (Vol 1.18, p.118)

ref 101 Enhanced cytotoxicity of CPT-11 for multicellular tumour spheroids by concomitant hyperthermia. Med Sci Res, 22:123, 1994. (Vol 1.18, p.124)

ref 102 Chemical modification of an antitumor alkaloid, 20(S)-camptothecin: glycosides, phosphates and sulfates of 7-ethyl-10-hydroxycamptothecin. Chem Pharm Bull, 40:131 (Vol 1.18, p. 127)

Pharmacokinetics

7256-94-139 Synthesis of [^{14}C]CPT-11 (U-101440E) labeled in the 11-ethyl substituent. (Vol 1.34, p.317)

7256-94-150 HPLC Method for the Determination of CPT-11 and SN-38 in Plasma. (Vol 1.34, p.42)

7256-94-151 Assay Methods for CPT-11 and SN-38 in Plasma, Urine, Bile, and Feces. (Vol 1.34, p.133)

7256-94-158 Reversed-Phase High-Performance Liquid Chromatographic Method for the Simultaneous Quantitation of the Carboxylate and Lactone Forms of the Camptothecin Derivative Irinotecan, CPT-11, and its Metabolite SN-38 in Plasma. (Vol 1.19, p.61)

7256-94-152 Selective and Sensitive Determination of Lactone and Hydroxy Acid Forms of Camptothecin and Two Derivatives (CPT-11 and SN-38) by High-Performance Liquid Chromatography with Fluorescence Detection. (Vol 1.19, p.53)

7256-94-153 Simultaneous Determination of the Camptothecin Analogue CPT-11 and its Active

Metabolite SN-38 by High-Performance Liquid Chromatography: Application to Plasma Pharmacokinetic Studies in Cancer Patients. (Vol 1.19, p.45)

Studies previously reviewed:

#	#TR-	
I.	**Pharmacology**	
	A.	**Mechanism of Action**
DP101		Effect of CPT-11, SN-38, and camptothecin on DNA topoisomerase I. (IND)
DP102	7252-95-008	DNA single- and double-strand breaks by CPT-11 in P388 leukemia cells. (Vol 1.21, p.229)
DP103	7252-95-012	Effect of CPT-11 on synthesis of nucleic acid and protein in vitro. (Vol 1.21, p.214)
YM108		Production of SN-38 (metabolite) from CPT-11 in vitro in sera and tissue homogenates of various animals. (IND)
YP106	7252-95-024	Effect of CPT-11 on cell proliferation and cell cycle. (Vol 1.21, p.329)
	B.	**Anti-Tumor Activity**
DP105	7252-95-009	Antitumor activity of CPT-11 administered intravenously against human tumor xenografts in nude mice. Cancer Chemother Pharmacol 28:192, 1991. (Vol 1.16, p.284)
DP108		Comparison of CPT-11 and SN-38 to other chemotherapeutic agents on the kinetics of cell killing of KB cells. (IND)
YP107		Growth inhibitory effects of CPT-11 and related agents on cultured tumor cells. (IND)
YP108		Activity of CPT-11 on various murine tumors transplanted in mice. (IND)
YP109	7252-95-006	Antitumor effect of CPT-11 against LI210 leukemia and Meth A fibrosarcoma with various times of administration. Jpn J Cancer Chemother, 17:121, 1990. (Vol 1.17, p 119)
YP110		Inhibition of experimental and spontaneous metastasis by CPT-11 in mice. (IND)
YP111	7252-95-022	Antitumor effect of CPT-11 against nude mice transplanted with human cancer QG-56. (Vol 1.21, p.26)
YP112	7252-95-005	Antitumor effect of CPT-11 against rat Walker 256. Jpn J Cancer Chemother, 15:2757, 1988. (Vol 1.17, p.13)
YP113	7252-95-020	Antitumor effect of CPT-11 against human tumors on subrenal capsule assay. Jpn J Cancer Chemother, 14:1264, 1987. (Vol 1.16, p. 392)
YP114	7252-95-019	Antitumor effect of CPT- 11 against pleiotropic drug-resistant tumors in vitro and in vivo. Cancer Chemother Pharmacol, 21:71, 1988. (Vol 1.17, p.42)
YP115		Activity of SN-38 against various murine tumors transplanted in mice. (IND)
	7252-94-031	Anticancer efficacy of oral irinotecan (CPT-11) in athymic mice bearing human mammary or colon xenografts. (SE# 068, p. 61-84 and 078, p. 14)
II.	**Safety Pharmacology**	
	A.	**Organ Systems**
DG101	7256-95-058	General pharmacological effects of CPT-11 on the central nervous system, the respiratory and cardiovascular system, gastrointestinal system, and skeletal muscle contraction. (IND)
DG102		Supplement: Effect on the gastrointestinal system. (IND)
DG103		Effect of CPT-11 on isolated organs. (IND)
	B.	**Immunotoxicity**
DS131	7219-94-10	Antigenicity test of CPT-11 in mice. (SE# 053, Vol 1.3, p. 1254-1285)

DS130	7219-94-11	Antigenicity Study of CPT-11 (DQ2805)-Experiments in Guinea Pigs. (SE# 053, Vol 1.3, p. 1286-1306)
DS132	7219-94-12	Antigenicity Study of CPT-11 in Guinea Pigs. (SE# 053, Vol 1.3, p. 1307-1327)
	7219-94-23	Antigenicity Test of CPT-11 in Rabbits. (SE# 053, Vol 1.6, p. 2544-2560)
	7219-94-24	Antigenicity study of PP [4-piperdinopiperidine, metabolite of U-101440] in guinea pigs. (SE# 053, Vol 1.6, p. 2561-2603)
	7219-94-27	Immunological study of CPT-11-Effects of infusion speed of CPT-11 and of pretreatment with epinephrine on guinea pigs sensitized with CPT-11 to prevent anaphylactic shock. (SE# 053, Vol 1.7, p. 3021-3029)

C. Local Irritation

YS150	7219-94-13	Local (i.m.) Irritation Test and Hemolysis Test of CPT-11. (SE# 053, Vol 1.4, p. 1328-1378)
	7224-93-59	Industrial toxicology evaluation - Acute eye irritation study in albino rabbits. (#69, p. 1-13)
	7224-93-60	Industrial toxicology evaluation - Acute dermal irritation study in albino rabbits. (#69, p. 14-24)
	7224-93-059	Amendment Memo No. 1 to TR 7224-93-059. (U-101440: Industrial Toxicology Evaluation - Acute Eye Irritation Study in Albino Rabbits). (# 78, p. 323-332)
	7224-93-060	Amendment Memo No. 1 to TR 7224-93-060. (U-101440: Industrial Toxicology Evaluation - Acute Dermal Irritation Study in Albino Rabbits). (# 78, p. 333-343)

III. Pharmacokinetics

Blood concentration, distribution and excretion after intravenous administration in rats.

DM105		a. Single administration of 14C-CPT-11 in rats. (IND)
DM107		b. Single and repeated administration of 14C-CPT-11. (IND)
DM106		c. Single administration of 14C-CPT-11 labeled in the piperdinopiperidine side chain. (IND)
DM110		Identification of biliary metabolites after single intravenous administration of 14C-CPT-11 in rats. (IND)
DM101		Enterohepatic circulation and biliary metabolites after single intravenous administration of ^{14}C-CPT-11 in rats. (IND)
YM102		Absorption and excretion of CPT-11 and SN-38 after single intravenous administration of unlabeled CPT-11 in rats. (IND)
DM103		Absorption and excretion after intravenous administration of unlabeled CPT-11 in dogs.
DM104		Metabolic fate of CPT-11 in Beagle dogs after a single intravenous infusion (30 and 90 minutes). (IND)
DM109		HPLC determination of CPT-11 and SN-38 in plasma. (IND)
DM105	7219-94-075	Tissue distribution and excretion of ^{14}C-CPT-11 following a single intravenous administration to male Wistar rats. (SE# 068, p. 1-60 and 078, p. 15-21, report# 7256-94-075)
DM107	7256-94-085	Tissue Distribution and Excretion of [^{14}C]-CPT-11 Following Single and Multiple Intravenous Administration to Male Wistar Rats (DM107). (SE# 078, p 68-163)
DM106	7256-94-087	Tissue Distribution and Excretion of [^{14}C]CPT-11 (U-101440E) Labeled in the Piperdinopiperidine Side Chain Following a Single Intravenous Administration to Male Wistar Rats (SE# 078, p. 164-226)
	7256-94-097	Preliminary Evaluation of the Oral Bioavailability of U-101440E, (CPT-11) From Bulk Drug and Solution in Beagle Dogs. (SE# 078, p. 227-266)
	7256-94-104	Determination of the Systemic Exposure of U-101440 (Irinotecan, CPT-11) and Its Active Metabolite U-101503 (SN-38) in Female Athymic Mice After Intravenous or Oral Administration at Pharmacologically Active Dose Levels. (SE# 078, p.

267-289).

DM106 7256-94-106 Metabolite Profiles in Bile and Enterohepatic Recirculation of [^{14}C]CPT-11 (U-101440E) Following a Single Intravenous Administration to Male Wistar Rats. (SE# 078, p. 290-322)

DM103 7256-94-107 Pharmacokinetics of CPT-11 Following a Single Bolus Injection to Beagle Dogs (SE# 082, p. 83-101)

DM104 7256-94-108 Pharmacokinetics of CPT-11 in Beagle Dogs Following Single 30- and 90-Minute Intravenous Infusions. (SE# 082, p. 102-123)

IV. Toxicology

A. Single Dose Toxicity

DS101 7219-94-18 Acute Toxicity Study of DQ-2805 (CPT-11) in Mice and Rats. (SE# 053, Vol 1.5, 1976-2016)

DS103 7219-94-19 Acute Toxicity Study of Metabolites of DQ-2805 (CPT-11) in Rats. (SE# 053, Vol 1.5, p. 2017-2035)

DS102 7219-94-20 Acute Toxicity Study of DQ-2805 (CPT-11) in Beagle Dogs. (SE# 053, Vol 1.5, p. 2036-2076)

7219-94-25 Acute intravenous toxicity study of photodegradation products (d-1, D-2), byproduct (Y-1) of DQ2805 (CPT-11). (SE# 053, Vol 1.6, p. 2604-2625)

7227-94-019 A fourteen-day oral and intravenous dose toxicokinetic study in female beagle dogs. (SE# 080, p. 55-472)

B. Multiple Dose Toxicity

DS107 7219-94-14 Subacute Toxicity Study of DQ-2805 (CPT-11) Intravenously Administered to Beagle Dogs for 2 Weeks-Comparison with Camptothecin. (SE# 053, Vol 1.4, p. 1379-1442)

DS105 7219-94-15 Subacute Toxicity Study of DQ-2805 (CPT-11) Intravenously Administered to Beagle Dogs for 28 Days. (SE# 053, Vol 1.4, p. 1443-1571)

DS108 7219-94-16 Intravenous 13 week Toxicity Study in Beagle Dogs. (SE# 053, Vol 1.4, p. 1572-1797)

DS151 7219-94-17 Toxicity Study in Beagle Dogs Intravenously Treated with DQ-2805 (CPT-11) Injection - Comparison between Single and Split-Dose Methods. (SE# 053, Vol 1.5, p. 1798-1975)

DS104 7219-94-21 Subacute Toxicity Study of DQ-2805 Intravenously Administered to Rats for 4 Weeks. (SE# 053, Vol 1.5, 2077-2309)

DS106 7219-94-22 Subacute Toxicity Study of DQ-2805 (CPT-11) Intravenously Administered to Rats for 28 Days With Recovery Tests: Comparison With Adriamycin. (SE# 053, Vol 1.6, 2310-2543)

7219-94-26 SN-38 [metabolite of U-1-1440] Toxicity to Rats by Repeated Intravenous Injection for 4 Weeks Followed by a Recovery Period. (SE# 053, Vol 1.7, p. 2626-3020)

C. Long Term Toxicity

7219-94-007 A Chronic Toxicity Study of Repeated Intravenous Doses of CPT-11 Administered to Rats for 6 Months with a 1-Month Recovery Period. (SE# 053, Vol 1.2, p. 30-697)

7219-94-105 Carcinogenicity study of CPT-11 (DQ2805) in rats by intravenous, intermittent administration for 104 weeks. (# 71, p. 1-149)

7252-94-051 Observations of Toxicity in Tumor-Bearing Athymic Mice Treated with Protracted Oral Irinotecan (CPT-11): Addendum to Technical Report No. 7252-94-031. (# 78, p. 22-67 and correction #82, p. 82)

V. Special Toxicity

A. Reproductive Toxicity

DS122	7219-94-002	Teratology and Reproduction Studies of CPT-11 (DQ-2805) Peri- and postnatal Study in Rats (days 17 gestation-day 21 after delivery). (SE# 053, Vol 1.1, p. 3-291)
DS120	7219-94-008	Teratology and Reproduction Studies of CPT-11 (DQ2805), Fertility Study in Rats (♂ day -63 to 0, ♀ day -14 to 7). (SE# 053, Vol 1.2, p. 698-850)
DS121	7219-94-009	Teratology and Reproduction Studies of CPT-11 (DQ2805), Teratology Study in Rats (day 7-17). (SE# 053, Vol 1.3, p. 851-1253)
	7219-94-006	Effect of CPT-11 (DQ-2805) Administered Intravenously to Pregnant Rabbits during the Period of Fetal Organogenesis (days 6-18). (SE# 053, Vol 1.1, p. 345-429)

B. Genetic Toxicity

DS142	7219-94-3	Mutagenicity Study of DQ-2805, Micronucleus Test. (SE# 053, Vol 1.1, p. 292-303)
DS140	7219-94-4	Mutagenicity Study of DQ-2805, Reverse Mutation Assay. (SE# 053, Vol 1.1, p. 304-324)
DS141	7219-94-5	Mutagenicity Study of DQ-2805, Chromosomal Aberration Test with Mammalian Cells in Culture (In Vitro Cytogenetics). (SE# 053, Vol 1.1, p. 325-404)

Note that portions of this review were excerpted directly from the sponsor's submission.

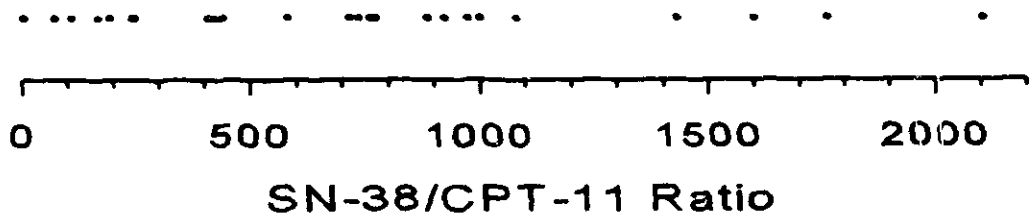
I. Pharmacology

Pharmacology studies pertaining to the efficacy of CPT-11 and SN-38 are summarized in the following tables. CPT-11 was active against a variety of *in vivo* human tumor models, including colon cancer. Data was captured from *in vitro* reports only when both CPT-11 and SN-38 were studied and is included in the second table which compares the potency of CPT-11 and SN-38 by various assays. When the inhibition of purified topoisomerase I was examined, SN-38 was 870 ± 383 (n=4) times more potent than CPT-11. When the ability to inhibit growth, DNA synthesis, or colony formation was compared, the potency of SN-38 relative to CPT-11 varied over a wide range; the mean ratio was 714 ± 574 (n=27). When the 3 lowest and 3 highest values from the data set were removed, the mean was 614 ± 370 (n=21). A scatterplot of the ratios (see figure) did not show any tendency for the ratios to distribute around a particular value. Interestingly, in two cell lines (gray boxes), SN-38 was only 2-3 fold more potent than CPT-11. In addition, in reference 58, one of twelve primary human GI tumor cultures was more sensitive to CPT-11 than SN-38. This suggests that CPT-11 may contribute significantly to the antitumor activity in some cases.

Selected Antitumor Activity of CPT-11[a]

Study #s	Tumor	Model	Dose and Schedule	tumor T/C & cures
7252-95-022 YP111	QG-56 human lung	s.c. xenografts	66.7 mg/kg q4x3[b]	14%, 0
7252-95-009[c] DP105	Co-4 colon	s.c. xenografts	100 mg/kg	25%, 0
	MX-1 mammary	s.c. xenografts	100 mg/kg 66.7 mg/kg q4x3	37%, 1/6 0%, 6/6
	St-15 gastric	s.c. xenografts	120 mg/kg 66.7 mg/kg q4x3	36%, 0 6%, 0
7252-95-020 YP113	human cervical	subrenal capsule	100 mg/kg q3x3	17%
	human ovarian	subrenal capsule	100 mg/kg q3x3	54%,
	human lung	subrenal capsule	100 mg/kg q3x3	42%
7252-95-005 YP112	Walker 256 rat lymphoma	s.c. in rats s.c. in rats i.p. in rats	65.7 mg/kg q4x3 65.7 mg/kg q1x5 65.7 mg/kg q4x3	8%, 0%, 10/10 199% ILS, 3/6
ref 15	4 human adult colon[d]	s.c. xenografts	20 mg/kg q1x5x2w	2-27%, 0-75%
ref 16	6 human colon	s.c. xenografts	30 mg/kg q2x3	≤25% in 5/6
	4 human stomach	s.c. xenografts	30 mg/kg q2x3	≤16%
ref 20	human neuroblastoma	s.c. xenograft	59 mg/kg q4x3	27%

[a] Captured data was restricted to *in vivo* results with primarily human tumors
[b] single dose and oral data also available
[c] ineffective against MKN-28, MKN-45 gastric, and QG-56 lung; oral data also available
[d] data on pediatric colon and rhabdomyosarcoma also available



Comparative Activity of CPT-11 and SN-38					
Study #s		Model	CPT-11	SN-38	"Ratio"
7252-95-009		QG-56 lung, growth inhibition	5.85 μM	4.05 nM	1444
		Co-4 xenografts	25% T/C	65% T/C	CPT11>SN38
7252-95-012	DP103	P388 cells, thymidine incorporation	21.1 μM	49.9 nM	422
ref 46 Kawato *et al.*		P388 cells, thymidine incorporation	19 μM	77 nM	247
		P388 cells, midine incorporation	61 μM	1.3 μM	47
		inhibition of relaxation of SV40 by P388 cell topo I	>1000 μM	0.74 μM	>1351
		inhibition of relaxation of SV40 by Ehrlich cell topo I	>1000 μM	1.9 μM	>526
		SSB[a] frequency in P388 cells	100μM CPT11=0.1μM SN38		1000
ref 48 Yoshida *et al.*		inhibition of relaxation of pBR322 by HL-60 topo I	>1000 μM	1 μM	>1000
7252-95-008 DP102		SSB frequency in P388 cells	.05μM SN38<50μM CPT11< .2μM SN38 < 200μM CPT11		250<R<1000
7256-94-111 Kaneda *et al.*		human KB cells, growth inhibition	1.62 μM	0.77 nM	2104
		L1210 cells, growth inhibition	8.1 μM	7.5 nM	1080
7252-95-011		inhibition of relaxation of pBR322 by Erhlich cell topo I	4600 μM[b]	7.65 μM	601
ref 49		HT-29 colon, clonogenic assay	>100 nM	8.8 nM	>11.4
		1000 radioactivity-eq SSB breaks	>1 μM	37 nM	>27
ref 50 growth inhibition		SHIN-3 ovarian cancer cells	192 μM	1.0 μM	192
		MN-1 ovarian cancer cells	3.84 μM	5.2 nM	738
7252-95-013		human KB cells, growth inhibition	2.4 μM	3.1 nM	774
7252-95-025[c] growth inhibition		KB cell	1.6 μM	0.91 nM	1760
		RPMI8402	1.57 μM	1.1 nM	1430
		L1210	8.11 μM	8.73 nM	925
		Walker 256	7.14 μM	4.5 nM	1600
7252-95-016 growth inhibition		HOC-21 ovarian	40 μM	97.7 nM	409
		MDA-MB-231 breast	39.6 μM	367 nM	108
		MKM28 stomach	31.9 μM	72.5 nM	440
		P388 leukemia	5.5 μM	7.2 nM	763
7252-95-015		P388 leukemia,	27.5 μM	31 nM	887
ref 57 growth inhibition		SNU-C4 colon	86.2 μM	120 nM	718
		SNU-C1 colon	44.4 μM	230 nM	193
		NCI-H630 colon	201.3 μM	2800 nM	72
		CNU-C2A colon	17.9 μM	5600 nM	3.2
ref 68 clonogenic assay		PC7 NSCLC	63 nM	0.38 nM	166
ref 80 growth inhibition		SUIT-2 pancreatic	2.6 μM	10.8 nM	240
		QGP-1N pancreatic	3.2 μM	1.64 μM	2
ref 83 growth inhibition		HAC2 ovarian	0.93 μM	1.6 nM	581
ref 94 growth inhibition		MOLT-3 leukemia	0.74 μM	0.72 nM	973

[a] DNA single-strand break; [b] concentrations causing "strong" inhibition; [c] The IC_{50}s for SN-38 glucuronide were 101 and 424 nM in KB and L1210 cells respectively (111 and 49 less potent than SN-38, respectively)

II. Safety Pharmacology

7256-94-145 CPT-11 (U-101440E) and SN-38 (U-101503) Inhibitory Activity against Acetylcholinesterase and Binding Activity to Acetylcholine Receptors. Conducted at Acetylcholinesterase activity was determined by the formation of thiocholine from acetylthiocholine iodide using DTNB (Ellman's reagent) which produced a product that absorbed light at 412 nm. The K_m for acetylthiocholine was 63-69 µM in all assays. CPT-11 and SN-38 were non-competitive inhibitors.

agent	K_i
CPT-11	0.22-0.30 µM
SN-38	450-540 µM

Acetylcholine receptor binding affinity was measured by the ability to compete with [^{3}H]QNB binding to rat synapse membrane crude fractions. The IC_{50} for inhibition of specific binding was 5.2 µM for CPT-11 and >100 µM for SN-38. The data support the hypothesis that early onset diarrhea is due to the cholinergic properties of CPT-11.

7252-95-059 Gastrointestinal toxicity of DQ-2805 (CPT-11): Mechanism of emetic action. Conducted by CPT-11 induced immediate emesis in 3/3 and 5/7 dogs administered 20 and 30 mg/kg respectively. It also induced delayed emesis (3-4 hr) in 2/3 and 1/7 dogs in those dose groups, respectively. The emesis induced by 20 mg/kg CPT-11 was almost completely blocked by 0.1 haloperidol, 1.0 mg/kg metoclopromide, and 1.0 mg/kg domperidone. An 0.5 mg/kg dose of scopolamine inhibited immediate emesis only. Emesis induced by 30 mg/k -11 was blocked by metoclopromide but was aggravated by domperidone (other drugs not teste- suggests that early emesis is mediated by D_2 receptors.

species:	beagle dogs (3 and 7/group)
drug:	CPT-11 lot# 801201 and 800503
dosage:	20 and 30 mg/kg
age; weight:	not stated; 6.5-17.5 kg
route:	i.v.

7252-95-060 Gastrointestinal symptoms elicited by DQ-2805 (CPT-11): Emetic effect in dog. Conducted by A 40 mg/kg CPT-11 dose caused emesis in 2/2 dogs within 1 min followed by death at 3 and 6 min. A 20 mg/kg dose caused emesis in 5/6 dogs in 1-2 min (observed for 50 min). Neither 50 mg/kg PP nor 11.6 mg/kg SN-38 caused emesis (these doses are equimolar to 20 mg/kg CPT-11). When a 50 µg/kg s.c. dose of haloperidol was administered 1 hr prior to 20 mg/kg CPT-11, emesis of food was seen in 2/6 dogs, emesis of foam in 2/6 dogs, and no emesis in 2/6 dogs. The data indicate that emesis is due to the parent drug only and that it may cause direct stimulation of the chemoreceptor trigger zone.

species:	beagle dogs (4-6/group, sex not stated)		
drug:	CPT-11	SN-38	PP
dosage:	20, 40 mg/kg	11.6 mg/kg	50 mg/kg
age; weight:	not stated; 11-6 kg		
route:	i.v.		

7228-94-106 Dermal absorption and irritation study on CPT-11 bulk drug powder in albino rabbits. Conducted by Upjohn Co. (Kalamazoo, MI). Bulk CPT-11 powder was wetted and applied as a paste to intact and abraded skin sites (4 in^2) at 100 mg/site/day x 5 days. The site was covered with cotton gauze and Saran wrap to simulate semi-occlusive contact. Blood was collected at 6 and 24 hr and analyzed

for CPT-11

CPT-11 was non-irritating to intact skin and slightly irritating to abraded skin with maximal total irritancy scores of 0.5 (out of 8) in one rabbit after the first application only. The LOD for CPT-11 in plasma was 1 ng/ml. The drug concentrations were 0-9.4 ng/ml (detected in only 4 of 20 samples) and 0-36.8 ng/ml (detected in 17 of 20 samples) in rabbits with intact and abraded skin respectively. The LOD for SN-38 was 1.1 ng/ml and it was not detected in any samples. If 100% of the dose was immediately absorbed, distributed to total body water and eliminated with a $t_{½}$ of 6 hr, then an estimated concentration of CPT-11 at 6 hr might be 30 µg/ml. CPT-11 is not a primary skin irritant and the amount absorbed, even through abraded skin, was less than 0.1% of the total drug applied.

species: New Zealand White rabbits (1/sex/group)
drug: CPT-11 lot# K017R
dosage: 100 mg/site/day x 5 or ~ 40 mg/kg/day
age, weight: weeks; 2.3-2.6 kg
route: topical

II. Pharmacokinetics

7262-94-111 Pharmacokinetics and Metabolism of CPT-11 and Metabolite SN-38 in Female CD2F$_1$ Mice Following Single Intravenous Administration. (Cancer Res., 50:1715-1720, 1990).
Conducted by The pharmacokinetics of CPT-11 and SN-38 were studied in mice. It is unclear whether total CPT-11 equivalents (lactone and open-ring), or the lactone form was quantified by the HPLC method. Mouse serum rapidly converted CPT-11 to SN-38 (~90% in 60 min). The pharmacokinetic parameters are listed in the following table. CPT-11 AUC values increased at a greater than dose proportional rate, whereas SN-38 after CPT-11 administration increased at a less than dose proportional rate. This suggested saturation of the carboxylesterase cleavage. CPT-11 concentrations decayed biexponentially. The SN-38 was administered as the sodium salt of the hydroxy acid due to solubility problems. The SN-38 concentrations declined 3 logs in 1 hr in a triexponential fashion. Theses results suggest that the carboxylate form of SN-38 will be rapidly removed from mouse plasma as it forms.

species: CD2F$_1$ ♀ mice (7-12/group)
drug: CPT-11 and SN-38 lot# not specified
dosage: CPT-11 at 10, 20, and 40 mg/kg and SN-38 at 10 mg/kg
age; weight: 7 weeks; not specified
route: i.v. via tail vein

PLASMA PHARMACOKINETIC PARAMETERS OF CPT-11 AND SN-38 AFTER IV ADMINISTRATION OF CPT-11 (MEAN±SD) AND OF SN-38 AFTER IV ADMINISTRATION OF SN-38-Na (MEAN)

Drug/Dose (mg/kg)	Compound Analysed	C_{max}[a] (µg/mL)	$AUC_{0-\infty}$ (µg·hr/mL)	t½ (hr)	Cl$_b$ (L/hr/kg)	Vd_{ss} (L/kg)
CPT-11/10	CPT-11	~5	2.96±0.12	0.95±0.22	3.38±0.15	3.34±0.24
CPT-11/20	CPT-11	~10	7.65±1.09	0.83±0.04	2.65±0.37	2.84±0.17
CPT-11/40	CPT-11	~4022	23.45±7.75	1.07±0.13	1.82±0.55	2.59±0.94
CPT-11/10	SN-38	~2	0.41±0.06	2.16±0.66	--	--
CPT-11/20	SN-38	~1.5	0.71±0.24	3.01±1.55	--	--
CPT-11/40	SN-38	~0.8	1.08±0.11	3.40±0.56	--	--
SN-38-Na/10	SN-38	~20-30	1.35	1.7	--	--

[a] Visually estimated from graphs.

7256-94-122 Pharmacokinetics of CPT-11 and SN-38 Following a Single Intravenous Administration of CPT-11 to Female CDF1 Mice. Conducted by Pharmacokinetics were determined both by non-linear least squares and moment analysis.

species: CDF1 ♀ mice (5/timepoint)
drug: CPT-11 lot# 100101
dosage: 10 mg/kg
age; weight: 7 weeks; 19.6-21.2 g
route: i.v.

Pharmacokinetic Data for CPT-11 in Mice

analysis		CPT-11	SN-38
compart -ment	C_{max} (µg/ml)	5.10	0.84
	$t_{1/2,\alpha}$ (hr)	0.47	-
	$t_{1/2,\beta}$ (hr)	2.72	-
moment	terminal $t_{1/2}$ (hr)	-	1.85
	$AUC_{0-\infty}$ (µg•hr/ml)	3.52	0.42
	C_L (liter/hr/kg)	2.86	-
	Vd_{ss} (liter)	3.03	-
	MRT (hr)	1.05	1.83

7256-94-125 Tissue Distribution of CPT-11 (U-101440E) and SN-38 (U-101603) After Intravenous Administration of CPT-11 (40 mg/kg) to Sarcoma 180-Bearing Mice. Conducted by Mice were inoculated with S180 cells in the inguinal region and after 10 days, treated with CPT-11. Blood and tissues were collected at 1, 2, 4, 8, 12, 24, and 48 hr and analyzed by HPLC. The $t_{1/2}$s, AUCs, and MRTs are shown in the table below arranged by decreasing AUC. The tumor had the lowest AUC for CPT-11 and 2nd lowest AUC for SN-38 of the tissues examined. The tumor and lung had CPT-11 $t_{1/2}$s that were 2-4 times the other tissues.
The SN-38 $t_{1/2}$ varied 15 fold with the tumor having the longest $t_{1/2}$.

species: ICR ♂ mice (5/timepoint)
drug: CPT-11 lot# 100701
dosage: 40 mg/kg
age; weight: 8 weeks; 40 g
route: i.v. via tail vein, 0.1 ml

Pharmacokinetic parameters in Tumor Bearing Mice

	CPT-11				SN-38			
	$t_{1/2}$ (hr)	AUC[a]	C_{max} (µg/ml)[b]	MRT (hr)	$t_{1/2}$ (hr)	AUC[a]	C_{max} (µg/ml)[c]	MRT (hr)
lg intestine	7.5	326.8	23.30	8.9	13.8	99.1	7.24	11.3
sm intestine	6.5	172.9	39.15	4.5	20.5	13.8	1.58	8
liver	9.6	133.8	55.19	2.9	3.3	10.2	1.52	5.5
stomach	9.5	121.6	32.23	6	11	5.2	0.52	9.2
lung	26.7	64	30.02	3.4	20	1.9	0.09	26.7
tumor	23.6	38	12.77	4.7	46.6	4	0.18	36.8
plasma	14.1	12.2	5.21	3	23	0.6	0.08	14.1

[a] µg•hr/g or µg•hr/ml for plasma
[b] at 1 hr except for lg intestine (4 hr)
[c] at 1 hr except for lg intestine (12 hr), sm intestine (2 hr), stomach (2 hr), and tumor (4 hr)

7256-94-142 Pharmacokinetics and Tissue Distribution of CPT-11 and SN-38 after Intravenous Administration of CPT-11 to Tumor-Bearing Male Mice. Conducted by
The CPT-11 pharmacokinetics and distribution to liver, kidney, and small intestine in normal athymic mice, and the pharmacokinetics and distribution to liver and tumor in MX-1 and Colon 26 tumor bearing athymic mice were determined after dosing with 40 mg/kg. The MX-1 human mammary tumor is sensitive to CPT-11 but the Colon 26 mouse colon tumor is refractory. No differences were seen in the pharmacokinetics or liver concentrations of CPT-11 or SN-38 in tumor-bearing mice vs. control mice. The AUC for CPT-11 in MX-1 tumors was 104.7 µg•hr/g compared to 75.2 µg•hr/g in Colon 26 tumors. The AUC for SN-38 in MX-1 tumors was 2.13 µg•hr/g compared to 1.37 µg•hr/g in Colon 26 tumors. The MX-1 tumor thus had a 38% greater exposure to CPT-11 and a 55% greater exposure to SN-38. This difference might explain the differential sensitivity of these tumors to CPT-11.

species:	Balb/c athymic ♂ mice (3/group)
drug:	CPT-11 lot# 800304
dosage:	40 mg/kg
age; weight:	7-8 weeks; 25-35 g
route:	i.v. via tail vein

7256-94-155 Relationship Between Development of Diarrhea and the Concentration of SN-38, an Active Metabolite of CPT-11, in the Intestine and the Blood Plasma of Athymic Mice Following Intraperitoneal Administration of CPT-11. (Japan. J. Cancer Res., 84:697-702, 1993) Daily i.p. administration of 50 mg/kg/dy CPT-11 induced diarrhea in 2/12 mice after 5 days and 12/12 mice after 8 days. Microscopic exam revealed inflammatory infiltrates, loss of epithelial cells, hemorrhagic colitis, loss of villi, glandular disruption, edema, crypt abscesses, submucosal fibrosis, and intraepithelial polymorphonuclear cells. On day 14 evidence of regeneration was seen (hyperplasia, ↓ inflammatory infiltrates). After a single injection CPT-11 and SN-38 concentrations in the plasma and intestinal wall decreased rapidly and were undetectable 48 hr later. In contrast, after multiple injections the concentrations in both plasma and intestinal wall decreased slowly and were detectable 48 hr after the 5th injection. In conclusion, diarrhea was associated with persistent levels of both CPT-11 and SN-38 in the plasma and intestinal tissue, but the cause of the diarrhea was not defined.

species:	athymic ♂ mice (/group)
drug:	CPT-11 lot# not stated
dosage:	25 and 50 mg/kg/day x 5 for histopathology 50 mg/kg/day x 1 or 5 for pharmacokinetics
age; weight:	not stated; 18-20 g
route:	i.p.

ref 164 Tumor influence on pharmacokinetics of the camptothecin analogue irinotecan (CPT-11) and active metabolite SN-38 in mice. (Proc. Am. Assoc. Cancer Res., 35:432, 1994) Control B6D2F1 mice and those bearing 0.6 g PO3 pancreatic adenocarcinoma tumors were dosed with 52.5 mg/kg/day CPT-11 x 5. The CPT-11 plasma levels in tumor-bearing mice were lower than the control mice and the $AUC_{0\text{-}24\ hr}$ was reduced 52%. In contrast SN-38 plasma levels were increased and the $AUC_{0\text{-}24\ hr}$ was 69% higher in tumor bearing versus control mice. The day the pharmacokinetic data was collected was not specified.

7256-94-115 Tissue Distribution and Placental Transfer of [^{14}C]CPT-11 (U-101440E) Following Single Intravenous Administration to Pregnant Female Wistar Rats. Conducted by
After administration of CPT-11 to rats at 13 or 18 days of gestation, whole body autoradiography was conducted at 5 min, 1 hr, or 24 hr and tissue concentrations were measured at 5 min, 1, 8, 24, or 48 hr. The total radioactivity in fetuses was <0.01% of the total dose at all times in animals treated on day 13 of gestation and was 0.7% at 5 min and then 0.01% from 8 hr on in animals treated at day 18 of gestation. The distribution in pregnant rats was not greatly different from nonpregnant rats (previous

studies) except that CPT-11 was found to concentrate in the amnion, mammary gland and clitoridean gland. The distribution in the fetus was similar to the maternal rats (high in liver and kidney). The data as captured below show very low but measurable placental transfer of CPT-11.

species	Wistar SPF pregnant ♀ rats (3/timepoint for tissues and 1/timepoint for autoradiography)
drug	[^{14}C-ethylpyridine]CPT-11 lot# CPT-1088 (5 μCi/mg, 98%)
dosage	10 mg/kg (50 μCi/kg)
age, weight	10 weeks; 287-396 g
route	i.v. via caudal vein, 2 ml

Whole-body autoradiography

Day 13 of gestation

5 min radioactivity was higher in the amnion, ovary, mammary gland, placenta, and uterus than in maternal blood, fetal concentration was lower than maternal blood

1 hr radioactivity was highest in the amnion and mammary gland followed by the ovary, uterus, and placenta all of which were higher than maternal blood; fetal concentrations were lower than maternal blood

24 hr radioactivity decreased at 24 hr, significant radioactivity was seen in the amnion but was undetectable in the uterus, ovary, mammary gland, placenta, or fetus

Day 18 of gestation

5 min radioactivity was highest in the amnion and placenta followed by the ovary, mammary gland, and uterus all of which were higher than in maternal blood; fetal radioactivity concentrations in the adrenal, liver, kidney, intestine, heart, ocular wall, and lung were comparable to maternal blood

1 hr radioactivity was highest in the amnion and mammary gland followed by the ovary, uterus, and placenta all of which were higher than maternal blood; concentrations were lower than maternal blood in fetal liver, adrenal, intestine, ocular wall, kidney, and lung

24 hr radioactivity decreased at 24 hr, radioactivity was seen in the amnion, mammary gland, and fetal intestinal contents

Relative Tissue Radioactivity After Administration of [^{14}C]CPT-11 to Pregnant Rats[a]
(multiple of maternal plasma level)

	13 days of gestation				18 days of gestation			
time	5 min	1 hr	8 hr	24 hr	5 min	1 hr	8 hr	24 hr
mat. plasma (μg/ml)	4.11	2.01	0.15	0.04	4.62	2.12	0.19	0.05
ovary	3.7	2.5	5.0	3.0	3.4	2.7	3.6	2.8
placenta	3.3	3.5	30.3	18.8	7.4	2.5	13.6	8.2
uterus	2.8	2.5	3.1	3.0	1.6	1.9	4.7	3.6
amnion	-	-	-	-	1.0	7.0	60.4	38.8
amniotic fluid	0.04	0.08	0.73	1.25	0.02	0.15	1.1	1.8
fetus	0.2	0.2	0.87	1.5	0.42	0.34	1.3	1.0
fetal liver					1.0	0.96	3.4	1.8
other							[b]	[c]

[a] concentrations at 48 hr were less than 1% of the peak in all tissues except amnion which in 18 day gestation animals was 4% of the peak, and therefore are not listed

[b] fetal lung, blood, and heart were 1x maternal plasma; fetal brain was 0.42x maternal plasma

[c] fetal blood and kidney were 1x; and fetal lung, brain, and heart were 0.4-0.6x maternal plasma

7256-94-116 Tissue Concentrations of CPT-11 and SN-38 Following a Single Intravenous Administration of [^{14}C]CPT-11 (U-101440E) to Male Wistar Rats. Conducted by

After administration of [^{14}C]CPT-11 to rats, concentrations of CPT-11 and SN-38 were determined in serum, liver, kidneys and wall of the upper small intestine at 5, 15, 30, 60 min, 2, 4, 8, and 24 hr by HPLC. The AUC, C_{max}, and $t_{½}$ are shown below. The T_{max} was 5 min except in intestinal wall where it was 15 min. CPT-11 accounted for 70% of the radioactivity in blood early after administration, but this declined with time. CPT-11 and SN-38 combined accounted for only 54% of the total radioactivity AUC suggesting the significant presence of other metabolites. The radioactivity in the 3 tissues, in contrast, was almost entirely accounted for by CPT-11 and SN-38. The ratio of SN-38 to CPT-11 AUC was 7.9%, 1.8%, 0.4%, and 2.7% in serum, liver, kidney, and intestine respectively. This suggested tissue variability in esterase activity or differential tissue accumulation of the two compounds from plasma. The high AUC and C_{max} levels of SN-38 in the intestinal wall relative to the liver and kidney may contribute to the GI toxicity associated with CPT-11 administration.

species: Wistar Crj ♂ rats (3/dose)
drug: [^{14}C-ethylpyridine]CPT-11 lot# CPT-898 (≥99%)
dosage: 10.62 mg/kg
age; weight: 7-8 weeks; 278-322 g
route: i.v. via caudal vein

Pharmacokinetic Parameters in Select Tissues

	AUC_{0-24} (µg-eq•hr/ml or g)			C_{max} (µg-eq/ml)			$t_{½}$ (hr)		
	^{14}C	CPT-11	SN-38	^{14}C	CPT-11	SN-38	^{14}C	CPT-11	SN-38
serum	7.5	3.55	0.28	3.65	2.52	0.065	2.9	0.8	2.8
liver	80.1	76.1	1.36	51.95	50.80	0.744	3.0	2.7	1.9
kidney	133.6	136.6	0.56	109.0	115.79	0.386	2.8	2.6	4.6
intestine	50.1	39.6	1.08	24.91	19.38	0.827	2.8	1.5	1.5

7256-94-119 Whole-body Autoradiography of Female Rats After Intravenous Injection of [14C]CPT-11 (U-101440E) (DQ-2805). Conducted by After administration of CPT-11 to rats, whole body autoradiography was conducted at 5 min, 1 hr, 8 hr, or 24 hr. The radioactivity distribution was similar to that found in male rats with additional radioactivity found in ovaries and the uterus. CPT-11 may thus have activity in female reproductive organ tumors.

species: Wistar Crj ♀ rats (5)
drug: [^{14}C-ethylpyridine]CPT-11 lot# CPT-898 (5 µCi/mg, ≥97%)
dosage, route: 10 mg/kg (20 µCi/kg) i.v. via caudal vein
age, weight: 8 weeks; 172-190 g

5 min	"markedly detected"	lungs, gastric wall, pancreas, kidneys, submaxillary gland, pituitary, upper digestive contents,
	"detected"	liver, myocardium, bone marrow, aortic wall, spleen, ovaries
	">blood"	nasal cavity, tongue, pharynx, trachea, esophagus, skeletal muscle, uterus, skin, and lower digestive wall
	"low"	brain, CNS, eyeball, and lower digestive tract
1 hr	"markedly detected"	upper intestinal contents
	">other tissues"	pancreas, pituitary, thyroid, submaxillary gland, gastric wall, bone marrow, spleen, liver, kidneys, and ovaries
	">blood"	uterus, skeletal muscle, and skin
	"depressed"	myocardium and lungs
8 and 24 hr	"obvious"	lower digestive contents
	"low level"	skin, liver
48 hr	"a little"	lower digestive contents

7256-94-120 Excretion and Changes in Plasma Concentration of SN-38 after Intravenous Administration in Rats and Mice. Conducted by Since SN-38 was dissolved in 0.1 N NaOH, the Na^+ salt of the open-ring form was the form actually administered in these studies. Pharmacokinetics were determined both by non-linear least squares and moment analysis. In rats AUC and C_{max} increased greater than proportional to dose. V_d declined with dose. At doses from 0.63 to 25.2 mg/kg approximately 50% of the dose was excreted in the bile and 12-19% in the urine within 15 min. These values increased ~10% after 3 hr. At 24 hr, 50% and 9.6% of the dose was excreted into the bile as SN-38 and SN-38-glucuronide respectively, and 8-15% and 8-15% of the dose was excreted into the urine as SN-38 and SN-38-glucuronide respectively. In non-cannulated rats, excretion was ~50% in the feces and 28% in the urine over 24 hr. The urinary excretion declined with increasing dose.

species: CDF1 ♀ mice (15) Wistar ♂ rats (2/dose)
drug: SN-38 lot#901102 and 610401
dosage: 10 mg/kg 2, 10, and 40 mg/kg
age; weight: 7 weeks; 20-21 g not stated; 200-300 g
route: i.v. via tail vein i.v. via right femoral vein

Pharmacokinetic Data for SN-38-Na^+

		mice	rats		
analysis	mg/m²	30	12	60	240
compart-ment	C_{max} (µg/ml)	19.6	1.98	13.64	99.83
	$t_{1/2,\alpha}$ (hr)	0.022	0.030	0.020	0.028
	$t_{1/2,\beta}$ (hr)	0.111	0.179	0.090	0.142
	$t_{1/2,\gamma}$ (hr)	1.470	-[a]	0.312	0.483
moment	terminal $t_{1/2}$ (hr)	1.03	0.208	0.278	0.370
	$AUC_{0-\infty}$ (µg•hr/ml)	1.25	0.18	1.21	8.20
	C_L (liter/hr/kg)	6.39	11.38	8.49	4.91
	Vd_{ss} (liter)	0.72	1.52	1.20	0.60
	MRT (hr)	0.116	0.133	0.140	0.121

[a] fitted to two compartment model

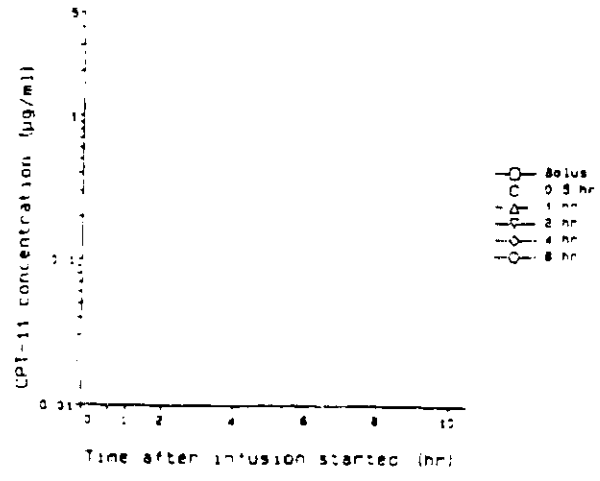
7256-94-123 Pharmacokinetics of CPT-11 and SN-38 after Intravenous Infusion of CPT-11 to Male Wistar Rats. Conducted by The pharmacokinetics of CPT-11 and SN-38 were compared as a function of infusion time.

species: Wistar ♂ rats (4/group)
drug: CPT-11 lot# 100701
dosage: 10 mg/kg bolus or infused over 0.5, 1, 2, 4 or 8 hr
age, weight: 7 weeks; 225-290 g
route: i.v. via femoral vein; ml

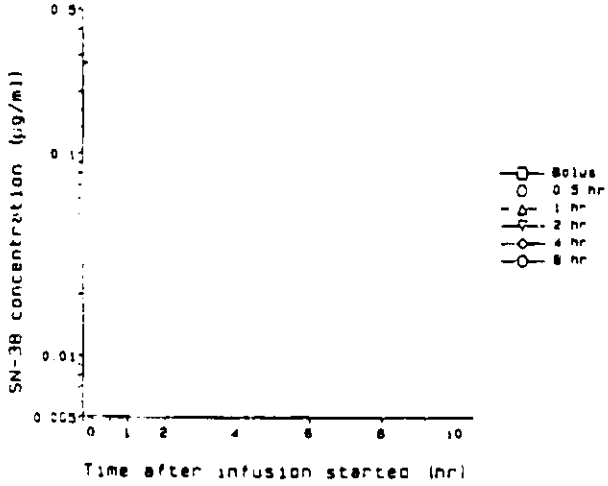
The concentration vs. time curves for CPT-11 and SN-38 with the various infusion times are shown below. The C_{max} for CPT-11 and SN-38 both declined steadily with infusion time, but unlike CPT-11 the SN-38 C_{max} after 0.5, 1, and 2 hr infusions were greater than after bolus infusion. The CPT-11 AUC was maximum for a 1 hr infusion (1.4 times the bolus value) whereas the SN-38 AUC was maximum for 2 and 4 hr infusions (1.7 times the bolus value). The CPT-11 $t_{1/2}$ maximized for the 1 hr infusion (2.22 hr vs. 1.35 hr for bolus) and the SN-38 $t_{1/2}$ maximized for the 2 hr infusion (4.42 hr vs. 2.19 hr for the bolus). The data indicate that a 2 hr infusion of CPT-11 produces the maximal combined AUC exposure to CPT-11 and SN-38 in rats.

Concentration vs. Time Plots

CPT-11

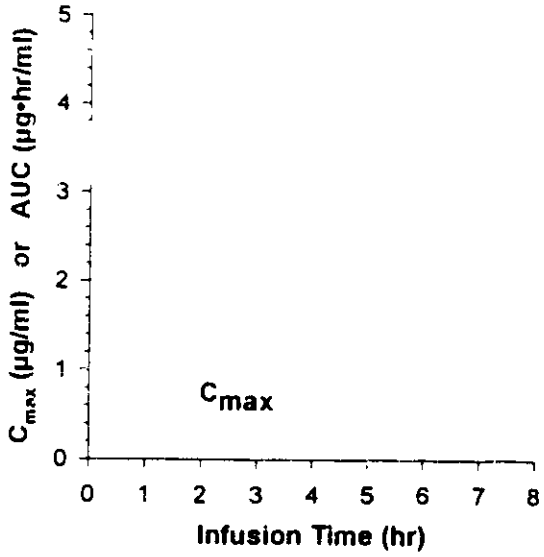


SN-38

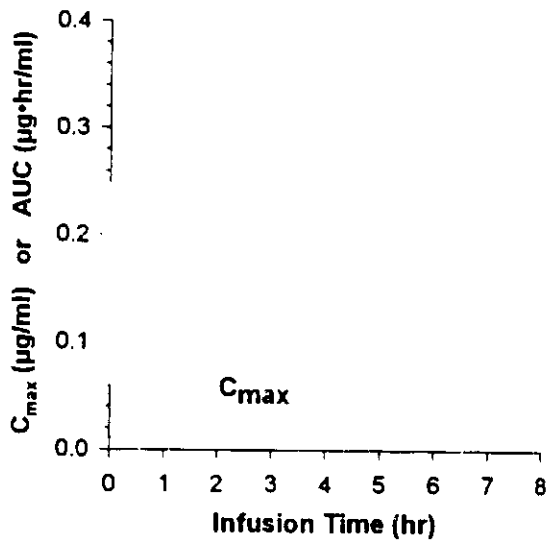


AUC and C_{max} vs. Infusion Time

CPT-11



SN-38



7256-94-124 Excretion of [^{14}C]SN-38-(Sodium Salt) and Metabolites Following a Single Intravenous Administration to Bile Duct Cannulated Male Wistar Rats. Conducted by

SN-38-Na^+ (carboxylate) not the SN-38 lactone was administered to cannulated rats. Radioactivity quickly appeared in the bile, excretion into which was essentially complete by 1 hr. Twenty % of the dose appeared in the urine after 24 hr. TLC analysis showed that the bile radioactivity was 9% SN-38 glucuronide at 2-8 hr.

species:	Wistar ♂ rats (4)
drug:	[^{14}C-ethylpyridine]SN-38 lot# CPT-11-1106 (58.6 Ci/ml, 98.3%)
dosage:	6.1 mg/kg
age; weight:	8-9 weeks; 241-267 g
route:	i.v. via tail vein at 2 ml/kg at pH 8.5

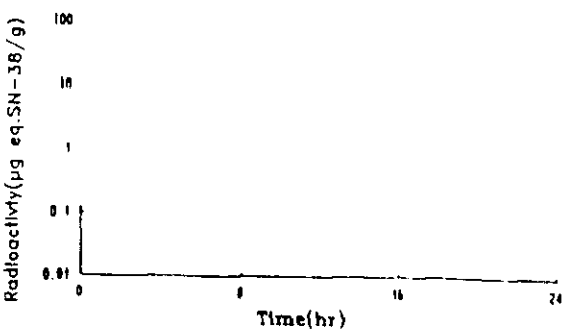
Cumulative Excretions (%) of ^{14}C after SN-38 Administration		
time	bile	urine
0-20 min	46.8 %	-
0-40 min	57.9	-
0-60 min	61.7	-
0-24 hr	64.1	20.3 %
0-48 hr	64.1	20.3

7256-94-128 Pharmacokinetic study of CPT-11 (U-101440E) in male Wistar rats following single intravenous administration of 1 to 40 mg/kg. (Cancer Res., 50:1721-1725, 1990.) Previously reviewed as YM102 by Dr. M.A. Goheer. In addition to the data captured in the original IND review, the following clearance data and commentary is added. The AUC of CPT-11 ↑'d above dose-proportionality whereas the AUC of SN-38 ↑'d below dose proportionality. The clearance data indicate that the non-linearity was likely due to saturation of metabolism as the dose increased. Fecal excretion of CPT-11 and SN-38 was greater than biliary excretion which indicated direct secretion of CPT-11 equivalents into the GI tract.

Clearance of CPT-11 (liters/kg•hr)						
	dose (mg/kg)					
	1	2	4	10	20	40
plasma	5.26	5.13	3.25	2.49	2.32	1.78
renal	0.67	0.77	0.58	0.48	0.48	0.48
biliary	0.66	0.82	0.60	0.68	0.68	0.54
metabolic[a]	3.93	3.54	2.07	1.33	1.16	0.76

[a] defined as CL_p-CL_r-CL_b

7256-94-141 Pharmacokinetics, Tissue Distribution, and Metabolism of [^{14}C]SN-38 (Sodium-Salt) Following Single intravenous Administration to Male Wistar Rats. Conducted by The carboxylate form of SN-38 was administered in two separate studies: pharmacokinetic and tissue distribution, and an excretion study. SN-38 was undetectable in plasma after 1 hr and the $t_{½}$ was 0.11 hr. Total radioactivity, however, was detectable to 24 hr and declined with a $t_{½}$ of 9.91 hr. The radioactivity:SN-38 AUC ratio was 4.4. TLC showed the predominant metabolite in plasma after the disappearance of SN-38 was SN-38-glucuronide. An unstable unidentified metabolite M-2 was also seen. The Vd_{ss} was 11.4 and 1.69 liter/kg and the C_L was 1.67 and 7.35 liter/hr/kg for total radioactivity and SN-38 respectively. No binding to RBCs was found; the plasma binding was 76-93%. At 24 hr, 24% and 38% of the total dose had been excreted into the urine and feces respectively. At 7 day, these values had changed to 28% and 70% respectively with 98% of the radioactivity recovered. In the urine at 24 hr 82% was intact SN-38 and 15% was SN-38-glucuronide. Tissue concentrations shown in the adjacent figure, were highest in kidney and liver after 1 hr. Radioactivity disappeared from tissues very slowly.

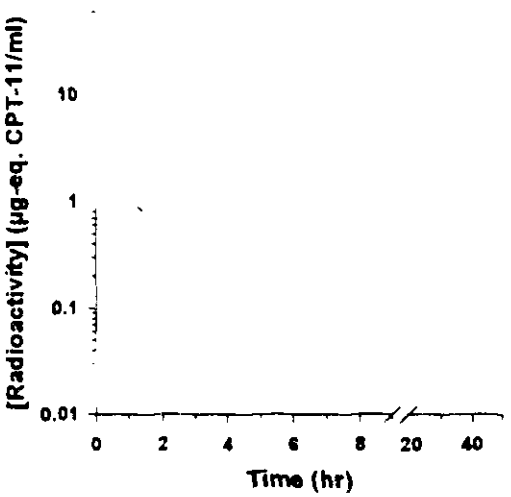


species: Wistar ♂ rats (3/time point)
drug: [^{14}C]SN-38-Na^+ lot# CPT-1106
dosage: 6.1 mg/kg (molar equivalent to 10 mg/kg CPT-11)
age; weight: 7-8 weeks; 221-324 g
route: i.v. into tail vein, 2 ml/kg

7256-94-143 Concentration of [^{14}C]CPT-11 (U-101440E) in Milk and Plasma Following Single Intravenous Administration to Lactating Female Rats. Conducted by After dosing rats with [^{14}C]CPT-11, milk and plasma were collected at 5 min, 1, 2, 4, 8, and 24 hr. Oxytocin was given i.p. to accelerate milk excretion.

species:	Wistar SPF ♀ rats (3/time point)
drug:	[^{14}C]CPT-11 lot# CPT-11-1088
dosage:	10 mg/kg; 100 µCi/kg
age; weight:	13 weeks (mated at 10 wk); 313-341 g
route:	i.v. via metatarsal vein; 2 ml/kg

As shown in the adjacent figure, radioactivity was rapidly transferred to and concentrated in milk. The milk:plasma ratio was 15 at 5 min and 65 at 4 hr. The $t_{½}$ in milk was 1.6 hr. Radioactivity was undetectable in milk after 24 hr.



7256-94-144 Tissue Distribution of [^{14}C]SN-38 (U-101503) by Qualitative Whole Body Autoradiography After Single Intravenous Administration to Male Rats. The SN-38 was administered as the sodium salt of the hydroxy acid due to solubility problems. Rats were sacrificed at 5 min, 1, 24, and 168 hr and prepared for qualitative whole body autoradiography.

species:	Wistar ♂ rats (/group)
drug:	[^{14}C]SN-38 lot# CPT-11-1106
dosage:	6.1 mg/kg (equimolar to 10 mg/kg CPT-11, 19.2 µCi/mg)
age; weight:	8-9 weeks; 286-331 g
route:	i.v. via tail vein, 2 ml/kg

The concentration of SN-38 in tissues was generally lower than for CPT-11. Radioactivity disappeared quickly from all tissues with most of the radioactivity cleared by 1 hr. Unlike CPT-11, distribution of SN-38-[Na^+] into the glandular epithelium was not seen. The radioactivity in the stomach was considered to be due to back flow of bile and not to secretion from the stomach wall. The kidney was the only tissue that retained radioactivity for any length of time. Radioactivity was present at the following levels.

5 min	upper GI tract > liver, kidneys > blood, lungs, skin, heart > muscle, salivary gland, pancreas, adrenals
1 hr	bladder contents, urethra, stomach, intestinal contents > kidneys > esophagus
24 hr	intestines > kidneys
168 hr	kidneys

7256-94-154 Tissue Distribution and Excretion of [^{14}C]CPT-11 (U-101440E) Following a Single Intravenous Administration to Female Wistar Rats. Conducted by see 7256-94-075 for data in male rats. After administration of CPT-11 to rats, plasma and tissues were collected at 5 min, 1, 4, 8, 24, or 72 hr and blood at 0.083, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, and 48, and 72 hr. Urine and feces were also collected. The radioactivity distribution was similar to that found in male rats with additional radioactivity found in ovaries and the uterus. CPT-11 may thus have activity in female reproductive organ tumors.

species: Wistar SPF ♀ rats (6)
drug: [^{14}C-ethylpyridine]CPT-11 lot# CPT-1088 (5 μCi/mg, ≥97%)
dosage: 10 mg/kg (20 μCi/kg)
age; weight: 7-8 weeks; 189-207 g
route: i.v. via metarsal vein, 2 ml/kg

The blood C_{max}, AUC, $t_{½,\alpha}$, $t_{½,\beta}$, and $t_{½,\gamma}$ for total radioactivity were 3.85 μg/ml, 15.8 μg•hr/ml, and 1.3 hr, 11.0 hr, and 120 hr respectively. The plasma C_{max} was 4.37 μg/ml (the blood C_{max} in these samples was 4.75 μg/ml). In the first 3 hr, 11% of the radioactivity was excreted in the urine. This rose to 16% at 6 hr and 18% by 24 with little more recovered up to 72 hr. In the feces, 33% of the radioactivity appeared by 6 hr, 72% by 24 hr, and 79% by 72 hr. Eighty percent of the plasma radioactivity was bound to plasma proteins from 5 min to 2 hr. The fraction bound to hemocytes was 54-58% at 5 min to 8 hr and 73% at 24 hr. Only 0.7% of the dose was retained in the carcass at 72 hr. The tissue levels were as follows.

	fold plasma	
5 min	15-20x	kidneys, adrenals
	10-13x	liver, lung, pancreas, thyroid
	2-8x	submaxillary gland, stomach, heart, hypophysis, brown fat, spleen, duodenum, ovary, bone marrow, harderian gland, lg intestine, ileum, muscle, jejunum, trachea, cecum, aorta, mesenteric lymph node
	1x	esophagus, uterus, thymus, blood, skin, urinary bladder, eyeball
	0.3-0.5x	fat, sciatic nerve
	0.03-0.07x	brain, spinal cord
1 hr	16-19x	pancreas, adrenal
	8-14 times	hypophysis, spleen, kidney, bone marrow, submaxillary gland, thyroid, harderian gland, liver
	2-6x	ileum, duodenum, lung, mesenteric lymph nodes, stomach, ovary, brown fat, trachea, jejunum, uterus, thymus, aorta, cecum, lg intestine, skin, heart, muscle, esophagus, urinary bladder
	1x	sciatic nerve, eyeball, fat
	0.06-0.1x	brain, bone marrow
4 hr	41x	pancreas
	10-16x	harderian gland, ileum, adrenal, bone marrow, hypophysis, cecum, submaxillary gland,
	2-8x	spleen, thymus, liver, kidney, mesenteric lymph nodes, thyroid, skin, duodenum, ovary, lg intestine, stomach, iejunum, trachea, lung, uterus, brown fat, aorta, urinary bladder, esophagus, heart
	1x	muscle, eyeball, fat, sciatic nerve
	0.09-0.13x	brain, spinal cord
8 hr		skin, cecum, pancreas; all others less than 13% of peak
24 hr		skin- 22% of peak
72 hr		highest in skin and blood

In comparison to the data for ♂ rats (7256-94-075), no differences were noted in excretion or plasma concentrations. However, the levels in whole blood were greater for ♀s after 8 hr showing biphasic disappearance compared to monoexponential for ♂s. This difference can be attributed to the higher hemocyte binding in ♀s than ♂s at 24 hr (73 vs. 50%). Radioactivity levels in many tissues were slightly higher in ♀s than ♂s. These differences could be due to increased metabolism in ♀s to a species that has a higher affinity for tissues and RBCs. Sex differences in carboxylesterases in rats have been documented. These pharmacokinetic differences, however, may be of little significance since the excretion profiles were not different and the tissue differences were only apparent after 8 hr.

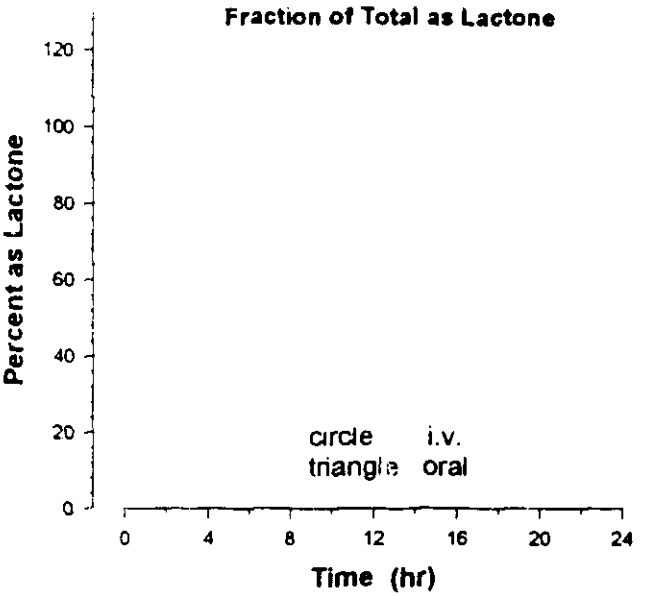
ref 158 AR 94-222 Preliminary determination for the systemic exposure of CPT-11 and its active metabolite SN-38 in male Sprague-Dawley rats after intravenous administration at 40 mg/kg or oral administration at 182 mg/kg. Conducted by Upjohn to determine the feasibility of oral administration. Rats were cannulated, but where and for what reason was not stated. Plasma was analyzed for total and lactone CPT-11 and SN-38.

species:	Sprague-Dawley ♂ rats (2 crossed over after 10 day washout)
drug:	CPT-11 lot# 22341-TGS-54
dosage:	40 mg/kg i.v. and 182 mg/kg oral
age; weight:	not stated; not stated
route:	oral and i.v. via tail vein

Based on total AUC or lactone AUC the bioavailability was ~25% for both CPT-11 and SN-38. The C_{max} for either total or lactone CPT-11 was 15-20 fold less by oral administration, but the total or lactone SN-38 was only 5-8 fold less. Dosing orally with 4 times the conventional i.v. dosage will thus give CPT-11 and SN-38 AUCs similar to the i.v. route, but reduce peak CPT-11 levels by 4-fold and peak SN-38 levels by 2-fold. This may allow dose escalation if the toxicities are related to peak levels. CPT-11 is rapidly absorbed with a T_{max} of 3 hr. The T_{max} for SN-38 was only 15 min which suggests pre-systemic formation in the gut. The C_{max} for total and lactone CPT-11 indicate that partial conversion to the hydroxy acid occurs within 2 hr of oral dosing. The lactone form accounts for 71% and 61%, or 32% and 37% of the AUC exposure to CPT-11 or SN-38 after oral and i.v. dosing respectively. The rate of conversion to the lactone appeared to be slower, however, as shown in the figure. The higher $t_{½}$ reported here compared to other studies may be due to the lower LOQ which allowed more accurate terminal measurements for the full 24 hr. The clearance was more rapid for the lactone than the total drug and the values are less than hepatic blood flow in the rat (3.3 L/hr•kg). The total and lactone V_{ss} greatly exceed total body water in the rat (0.67 L/kg).

Comparative I.V. and Oral Pharmacokinetic Parameters (mean ± range, n=2)

Compound	Route	Form	Dose (mg/kg)	t_{max} (hr)	C_{max} (ng/mL)	AUC (ng·hr/mL)	F (%)	CL (L/hr·kg)	V_{ss} (L/kg)	$t_{1/2}$ (hr)
U-101440	PO	Total	182	3.0 ± 1.4	3720 ± 220	27300 ± 12500	24 ± 8	-	-	6.0 ± 1.5
		Lactone	182	3.0 ± 1.4	2850 ± 280	19500 ± 10500	29 ± 15	-	-	6.2 ± 2.1
	IV	Total	40	-	12300 ± 1600	24700 ± 3000	-	1.63 ± 0.20	3.88 ± 0.96	6.1 ± 1.0
		Lactone	40	-	11600 ± 1200	15000 ± 100	-	2.66 ± 0.02	6.22 ± 0.59	5.9 ± 1.2
U-101503	PO	Total	182	0.25 ± 0.0	154 ± 4	1160 ± 710	26 ± 12	-	-	14.4 ± 7.0
		Lactone	182	0.25 ± 0.0	47.4 ± 14.9	368 ± 156	24 ± 10	-	-	14.6 ± 5.7
	IV	Total	40	0.083 ± 0.000*	171 ± 43	927 ± 159	-	-	-	8.2 ± 1.8
		Lactone	40	0.083 ± 0.000*	88.9 ± 4.8	339 ± 3	-	-	-	16.1 ± 5.8



7256-95-005 U-101440E: A Fourteen-Day Oral and Intravenous Dose Toxicokinetic Study in Female Beagle Dogs - Additional Pharmacokinetic Studies of U-101440E (Irinotecan/CPT-11) and U-101503 (SN-38): Addendum to Technical Report 7227-94-019. $t_{½}$, C_L, Vd_{ss}, and bioavailability data was submitted that was not in the original report. The $t_{½}$s for lactone and total CPT-11 were ~5-6 hr. The $t_{½}$s for total and lactone SN-38 ranged from 2.6 to 9.7 hr. The bioavailability ranged from 40-140%. The range of the $t_{½}$ and bioavailability did not correlate with dose, route, or form. The $t_{½}$ values did not change significantly after 5 days of dosing. The clearance of the total and lactone forms of CPT-11 were well below the hepatic and renal blood flows in dogs (1.9 and 1.3 liter/hr/kg respectively). The Vd_{ss} for both total and lactone CPT-11 greatly exceeded total body water (0.6 liter/kg), indicating extensive binding to tissues.

Day 1 Clearance and Vd data for CPT-11			
		2.5 mg/kg/day	7.5 mg/kg/day
C_L (liter/hr/kg)	lactone	0.72 ± 0.42	0.52 ± 0.07
	total	0.36 ± 0.16	0.27 ± 0.03
Vd_{ss} (liter/kg)	lactone	2.9 ± 1.5	3.2 ± 0.9
	total	1.6 ± 0.6	1.7 ± 0.4

7256-94-156 Disposition and Excretion of [^{14}C]U-101440E (Irinotecan, CPT-11) in Male and Female Beagle Dogs Following a Single Intravenous Dose Administered at 2.5 mg/kg (Protocol 94-424). Conducted by , according to GLP.

species:	beagle dogs (3/sex)
drug:	[^{14}C]CPT-11 lot# 28729-JAE-28A (5.847 µCi/mg)
dosage:	2.5 mg/kg
age; weight:	2 yr; 9.9-10.9 kg for ♂ and 7.5-9.2 kg for ♀
route:	i.v. via cephalic vein, 0.135 ml/kg

As shown in the following table, 25% and 72% of the radioactive dose was excreted in the urine and feces over 7 days, with the majority eliminated in the first 2 days. One ♂ animal was listless during acclimation and treatment and had no urine output for 0-12 hr and no feces for 0-24 hr. This distorted the excretion values for these time points. The hematocrit adjusted blood:plasma concentrations ratios ranged from 1.1 after injection to 2.7 at 3-7 days. This indicated that the radioactivity was primarily in the plasma at early

times with increasing association with blood cells with time, perhaps due to metabolism. This association was also reflected in a higher terminal $t_{½}$ in blood compared to plasma. No sex dependent differences were noted in either excretion or pharmacokinetics (it was not stated whether the higher C_{max} s and AUCs in ♂'s were statistically significant).

Radioactivity Excretion in Dogs (Percent of Dose)

urine			feces			cage rinse			total	
hr	♀	♂	hr	♀	♂	hr	♀	♂	♀	♂
0-4	2.17	3.16	0-12	4.35	3.95	0-24	1.02	1.35		
4-8	3.99	0.02								
8-12	12.3	5.65								
12-24	4.98	15.7[a]	12-24	52.3	52.2					
24-48	0.99	1.54	24-48	14.0	25.3[b]	24-48	0.21	0.37		
48-72	0.17	0.35	48-72	2.62	8.32	48-72	0.15	0.15		
72-96	0.12	0.18	72-96	0.58	0.80	72-96	0.09	0.14		
96-120	0.05	0.11	96-120	0.22	0.22	96-120	0.05	0.08		
120-144	0.04	0.06	120-144	0.11	0.15	120-144	0.03	0.06		
144-168	0.04	0.05	144-168	0.06	0.08	168[c]	0.07	0.46		
total	24.9	26.8	total	72.8	72.3	total	1.54	2.14	101	99.4

[a] xx; [b] 66.4, 4.66, and 4.7 in the 3 dogs; [c] complete wash instead of rinse

Pharmacokinetic Parameters for Radioactivity in Dogs

	blood		plasma	
	♀	♂	♀	♂
C_{max} (µg-eq/ml	2.80	3.68	4.31	5.91
T_{max} (hr)	0.033	0.033	0.033	0.033
AUC_{0-t} (µg-eq•hr/g)	7.23	8.65	9.2	11.3
$t_{½}$ (hr)	123	116	95.1	98.4
AUC ratio (blood/plasma)	0.778	0.769	-	-

7256-94-114 Metabolic Fate of CPT-11: The chemical structure of the main metabolites in rat bile after a single intravenous dose. (and Xenobiotica, 21:1159-1169, 1991). This was previously reviewed by Dr. Goheer as study DM110. Additional data is now captured from the Xenobiotica paper. In the bile, CPT-11, SN-38, SN-38-C_{10},O-glucuronide and 3 minor metabolites were detected. The cumulative excretion of radioactivity was 62% in the urine, 33% in the bile, and 9% in the feces. In the bile excreted over 24 hr, 55% was CPT-11, 9% was SN-38, and 22% was SN-38-C_{10},O-glucuronide. Injection of collected bile into the duodenum of bile duct cannulated rats demonstrated that 18% of the biliary radioactivity was absorbed from the intestine.

7256-94-117 CPT-11 (U-101440E) Metabolism by Isolated Perfused Walker 256 Carcinosarcoma Tumors. Conducted by Walker 256 carcinosarcoma cells were transplanted as s.c. tumors in ♀ rats. Two-three ~8 mm^3 blocks from s.c. tumors were minced and then surgically implanted into the fatty mesentery isolated from the ovaries and uterus. The inoculated tissue was sealed in Parafilm and placed between the muscular wall and the skin of the abdomen. A round mass 2-3 cm in diameter formed after 7 days that was solely supplied by the ovarian artery and vein. This tumor was perfused with 10 µg/ml CPT-11 in Krebs-Henseleit-Ringer's solution with 4% BSA from a 50 ml reservoir via the aorta and output recirculated via the inferior vena cava. The reservoir was sampled every 10 min (0.2

ml) and subjected to HPLC. Four tumors were studied. SN-38 was present in the perfusate at 3 ng/ml from impurities in the bulk CPT-11, but increased to 9.7 ng/ml after 60 min of perfusion. The study shows that Walker 256 tumors probably possess a carboxylesterase capable of cleaving CPT-11 to its active metabolite, SN-38. However, the role of endothelial cells in mediating this cleavage was not considered.

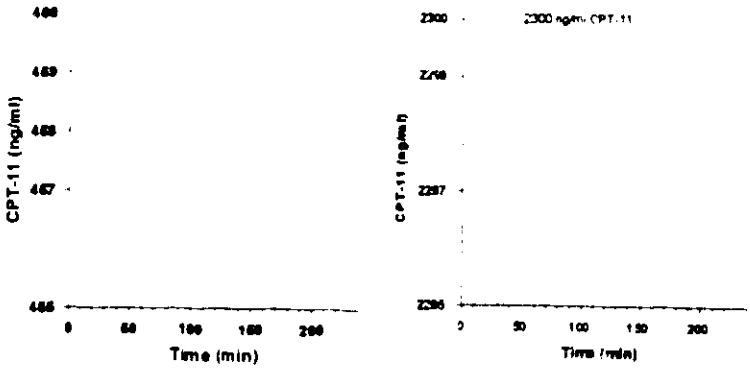
7256-94-121 Conversion of CPT-11 (U-101440E) into SN-38 in Human Tissues. Conducted by Tissues were homogenized in 6.7 volumes of 0.25 M sucrose, 0.5 M $CaCl_2$ and centrifuged at 3000 x g to remove debris. Homogenates were incubated with 1 mg/ml CPT-11 for 60 min and analyzed for SN-38 by HPLC. Activity in fresh surgical tissue specimens is shown in the following table; the data was presumed to be paired normal and tumor tissue from the same patient. The activities in autopsy tissues from a single patient were (ng/mg protein/hr): liver 42.4, kidney 10.2, stomach 6.8, spleen 6.7, lung 6.6 and pancreatic tumor 7.5. (note the unit change compared to table values; presumes protein measurement rather than wet weight?). In summary, activity was higher in colon and stomach tumors than equivalent normal tissue. Activity was high in normal liver. Rat serum had 7.7-fold higher activity than human serum. There was 40-fold inter-individual variation in the activity in the liver. Activity was abolished by 95°C for 10 min. A narrative was provided that indicates the tissue activity is present in the microsomal/lysosomal fraction which suggests that the activities in serum and tissue are is due to different enzymes.

CPT-11 Cleavage Activity of Fresh Tissues (µg SN-38/g wet weight/hr)

tissue	type	human												rat
liver	normal	0.5	7.9	1.6	1.0	0.3	5.9	3.0	3.1	1.9	3.6	19.9	17.2	5.7
	tumor	0.1	4.3	0.3	0.8									
lung	normal	0.23	0.27											1.5
	tumor	0.23	0.28	1.8										
colon	normal	0.5	0.8											
	tumor	0.9	1.2											
stomach	normal	0.1	0.2											
	tumor	0.2	0.6	0.2										
uterus	normal	0.4	0.7											
	tumor	0.5	0.1											
pancreas	tumor	3.6												
kidney	normal													2.7
serum		0.06												0.46

7256-94-129 In Vitro Human Protein Binding of CPT-11(DQ-2805). Conducted by The *in vitro* affinity of CPT-11 and SN-38 for human plasma and serum albumin was determined by ultrafiltration and HPLC using concentrations typically found in patients treated with 100 mg/m^2. This study is complicated by the esterase activity of human plasma and the presence of closed (lactone) and open (free acid) forms of both CPT-11 and SN-38. The findings were:

- The adsorption of CPT-11 and SN-38 to the ultrafiltration cartridge appeared to be minimal based on recoveries of 92.8-113.6% and 97.9-120.2% respectively from phosphate buffer.



▸ SN-38 was generated by first order kinetics from CPT-11 in plasma as shown in the adjacent figures. The percent of CPT-11 hydrolyzed to SN-38 after 4 hr at 37°C at 460 and 2300 ng/ml was only 0.22% and 0.18%, respectively.

▸ The time to reach binding equilibrium in plasma at 37°C appears to be <10 min for 18 ng/ml SN-38 (94.5% bound at 10 min, 96.9 % bound at 240 min). In disagreement with the study report, I believe the data show that the time to reach equilibrium was ≥120 min for 1750 ng/ml CPT-11 (39.5 % bound at 10 min, 55.4 % bound at 240 min). This might be attributed to steady conversion to the carboxylate form which could have a higher binding affinity than the lactone form.

▸ The fractional plasma protein binding after 30 min at 37°C is shown in the following table.

Fractional Human Plasma Protein Binding

CPT-11		SN-38	
µg/ml	% Binding	ng/ml	% Binding
3.51	42.7	36.2	94.9
1.75	29.6	18.1	95.5
0.88	36.6	9.1	95.9
0.35	38.2	3.6	92.4

▸ [^{14}C]CPT-11 and [^{14}C]SN-38 were used to assess binding to albumin. The binding of CPT-11 to human serum albumin was ~27% at concentrations of µg/ml. In contrast, the binding of SN-38 to human serum albumin was ~90% at concentrations of ng/ml. Binding constants could not be obtained from Scatchard plots due to high variability.

In conclusion, SN-38 has a much higher affinity for human plasma proteins than CPT-11. The binding can be attributed predominantly to albumin.

7256-94-131 Enzyme Induction and Inhibition Studies on CPT-11 Using Rat Hepatic Microsomes. Conducted by Rats were dosed as indicated, sacrificed either at the end of dosing or after 1 week recovery, the livers removed, and homogenates prepared for various assays.

species: Wistar ♂ rats (#/group not stated)
drug: CPT-11 lot# not stated
dosage: 0, 0.8, 4, and 20 mg/kg/day x 5 days of CPT-11
80 mg/kg/day x 5 days of i.p. phenobarbital
age; weight: 4 weeks; not stated
route: i.v., 2 ml/kg

The MD and HD groups had ↓ body weights on days 4-6; weight gain recovered after cessation of dosing. The liver/body weight ratio ↑ 35% in the PB group. Microsomal protein ↑ 8%, 18%, 0%, and 24% in the LD, MD, HD, and PB groups respectively but returned to control levels after 7 days. Whereas PB markedly increased cytochrome P450 levels, cytochrome b_5 levels, and NADPH cytochrome *c* reducing activity, CPT-11 had no effect. PB also markedly increased the activity of aminopyrine *N*-demethylase, aniline *p*-

hydroxylase, and 7-ethoxycoumarin *O*-deethylase (CYP 2B marker). The LD CPT-11 increased aminopyrine *N*-demethylase and 7-ethoxycoumarin *O*-deethylase activity 23% and 60% when activity was normalized to liver weight or 0% and 49% when based on mg microsomal protein. The HD CPT-11 decreased both aminopyrine *N*-demethylase and aniline *p*-hydroxylase by ~30%. Although the PB-induced activity returned to control after 7 days of recovery, the CPT-11 pattern did not change. Finally, microsomes from PB and 3-MITOMYCIN C induced rats were studied *in vitro*. CPT-11 (5, 25, and 125 µM) had no effect on the aminopyrine *N*-demethylation or aniline hydroxylation activity of the microsomes whereas the positive control, SKF-525A, had clearcut inhibitory action. In conclusion, repetitive CPT-11 dosing caused only slight non-dose dependent effects on P450 activity and did not inhibit P450 catalyzed reactions in vitro. The Upjohn summary of this report noted that CPT-11 has not been shown to date to be metabolized by cytochrome P450 in any species *in vivo* although it is likely that the piperdinopiperdine fragment produced by hydrolysis is metabolized by cytochrome P450.

7256-94-138 Protein Binding Studies on CPT-11 (U-101440E) and SN-38 (U-101503). Conducted by Human blood, plasma, serum albumin, LDL, RBC ghosts, and hemoglobin stabilized the lactone form of CPT-11 and SN-38 as indicated by a greater $t_{1/2}$ for hydrolysis and a higher percentage (2-fold) in the lactone vs. the carboxylate forms at equilibrium. γ-Globulin, α-acid glycoprotein, fibrinogen, and platelets had slight stabilizing effects. The opposite effect was seen for camptothecin and analogues without 7- or 9- substituents. Since it was the total drug that was analyzed, it is unclear what affect these plasma constituents had on the free forms of the drug. The data may explain the superior antitumor activity of CPT-11 relative to other camptothecins (i.e. more drug in the active lactone form).

7256-94-140 Effect of Kampo herbal medicines on the β-glucuronidase-mediated hydrolysis of SN-38 glucuronide in vitro (and Jpn. J. Cancer Res., 86:978-984, 1995) Conducted at SN-38 glucuronide can undergo enterohepatic recirculation after cleavage to SN-38 by intestinal microflora. This studied examined the ability of 4 glucuronides and 1 glucoside (geniposide) purified from *Kampo* (Japanese herbal) medicines to inhibit the cleavage of SN-38 glucuronide by β-glucuronidase. The inhibitory activity was compared to the known inhibitor saccharic acid 1,4-lactone. The kinetic constants of the isolated products are shown in the table. Geniposide had no inhibitory activity. Three of the 4 natural products were as potent as saccharic acid 1,4-lactone. The inhibition was competitive. *Kampo* medicines might be useful for altering the pharmacokinetics of CPT-11 by inhibiting enterohepatic recirculation and thus reducing diarrhea if it is mediated by lumenal SN-38.

Kinetic Constants for *Kampo* Herbal as β-Glucuronidase Inhibitors[a]

	IC_{50} (µM)	K_i (µM)
glycyrrhizin	120.3	240.0
baicalin	2.9	10.7
wogonoside	4.0	16.7
luteolin-3'-glucuronide	5.2	9.2
saccharic acid 1,4-lactone	3.2	11.7

[a] reaction was 16.7 µM SN-38 glucuronide, 4 FU/ml β-glucuronidase, 25 mM KPi, 0.1% BSA, 37°C, 20 min

7256-94-146 Metabolic Activation of CPT-11 (U-101440E) by Hepatic Microsome Carboxylesterase. (Biol. Pharm. Bull., 17:662-664, 1994) Conducted at The hydrolysis of 0.2 µM CPT-11 to SN-38 by 13 purified hepatic carboxylesterases from 9 species was determined by HPLC. Activity ranged fold from nmol/mg/min with the rat RL2 isozyme to nmol/mg/min with the guinea pig GPL1 isozyme determined in the min. The human HU1 isozyme

provided a rate of 0.129 nmol/mg/min. The hydrolytic rates for CPT-11 correlated with the rates for ester type substrates (*p*-nitrophenyl acetate and malathion) but not amide type substrates (isocarboxyazide and butanilicaine). This implies that cleavage takes place directly at the ester side of the carbamate bond of CPT-11. The results of kinetic analysis using 4 isozymes is shown in the following table. The hydrolytic activity is consistent with pharmacokinetic data between species. Treatment of rat with the carboxylesterase inhibitor bis-*p*-nitrophenylphosphate reduced plasma levels of SN-38 2-fold after CPT-11 administration. The data indicate that hepatic microsomal carboxylesterases play a major role in hydrolyzing CPT-11 to SN-38.

Kinetic Parameters for CPT-11 Hydrolysis by Purified Carboxylesterases			
	Km	Vmax	Vmax/Km
RL1 (rat)	0.034	0.737	21.7
RH1 (rat)	0.142	0.326	2.30
DI (dog)	0.096	0.715	7.45
HU1 (human)	0.169	0.161	0.96

7256-94-147 Bioactivation of CPT-11 (U-101440E) to the Active Metabolite SN-38 in vitro: Comparison of Rat, Dog and Human Tissues. (Yakubutsu Dotai, 5:899-907, 1991) Tissue homogenates and plasma were prepared from rats, dogs, and humans and incubated at 9-10 mg/ml protein with 100 µM CPT-11. At specified times, the reaction was stopped and extracts analyzed by HPLC. The rates at 2, 5, and 30 min are shown in the following table. In rats, the predominant carboxylesterase activity was in the plasma whereas in dogs and humans it was in the liver. The absolute rates in liver homogenates were similar across species. Michaelis-Menton kinetics were observed indicating enzyme catalysis. Lineweaver-Burke plots of reaction rates in rat tissues and plasma at 1-2 min gave apparent K_ms of 20-25 µM and 8.5 µM, respectively. Fractionation of rat liver homogenates showed more activity in microsomes than mitochondria or lysosomes (8.1, 6.0, and 2.8 pmol/mg protein/min, respectively). Activity in human liver homogenates was 18%, 61%, and 100% of controls in the presence of DFP (carboxyl- and cholin-esterase inhibitor), phytostigmine (cholinesterase inhibitor), and PCMB (arylesterase inhibitor), respectively. It was noted that carobxylesterases are regulated by a variety of hormones and conditions and that SN-38 production may thus vary substantially between and within individuals.

Table 1 Generation of SN-38 from CPT-11 by plasma and tissue homogenates of rat, dog, and man.

Tissue	Generation of SN-38 (pmol/mg protein/min)								
	Rat			Dog			Man		
	2 min	5 min	30 min	2 min	5 min	30 min	2 min	5 min	30 min
Plasma	14.6	6.08	1.26	0.042	0.028	0.013	0.19	0.087	0.019
Liver	1.90	1.62	0.79	1.02	1.59	1.11	0.74	0.79	0.42
Intestine	4.30	2.81	0.98	0.18	0.14	0.035	0.51	0.74	0.12
Kidney	1.02	1.32	0.63	0.17	0.46	0.31	—	—	—
Lung	2.07	1.30	0.50	0.59	0.83	0.49	—	—	—
Pancreas	—	—	—	0.23	0.28	0.29	—	—	—
Skin	—	—	—	—	—	—	0.48	0.18	0.043

7256-94-149 CPT-11 Converting Enzyme from Rat Serum: Purification and Some Properties. (J. Pharmcobio.-Dyn., 14:341-349, 1991) Conducted at [redacted]. An enzyme capable of converting CPT-11 to SN-38 was purified from rat serum. The enzyme had the following properties: 57-60 kDa, pI 4.6, optimum pH 7.5, stable at pH 4-9 for 1 hr at 30°C, CPT-11 Km of 0.28 µM, inhibited by DFP

and PMSF but not eserine, active towards *p*-nitrophenyl acetate but not acetylcholine. It thus had properties consistent with a carboxylesterase as opposed to an arylesterase or choline esterase. It also was similar to a previously isolated rat serum carboxylesterase (J. Biochem., 34:1325, 1978) except for the MW. The homology and relative role of this enzyme in producing SN-38 compared to the rat hepatic microsomal carboxylesterase is not known.

ref 187 Differences in the induction of carboxylesterase isozymes in rat liver microsomes by xenobiotics. (Biochem. Pharmacol., 37:2708-2711, 1988) As shown in the following table, ♂s had higher levels of carboxylesterase activity and content for RL1 and RH1 than ♀s, but ♀s had higher activity and content for RL2. All 3 isozymes were induced in ♂s by aminopyrine and clofibrate, but only RL2 was induced by *trans*-stilbene oxide or Aroclor 1254. The activity in ♀s was also induced by aminopyrine. Clofibrate induced microsomal activity, but not cytosolic activity. There are thus sex dependent differences in carboxylesterase activity between ♂s and ♀s and the isozymes can be induced to different extents.

Carboxylesterase Activity and Isozyme Content in Rats

		activity				content		
hydrolase:		RL1	RL1	RH1	RL2			
substrate:		p-nitrophenyl acetate	malathion	butanilicaine	isocarboxazid	RL1	RH1	RL2
control	♂	1.52	52.3	116	38.3	7.5	16.4	44.9
control	♀	0.87	27.2	32.5	45.4	1.1	7.8	99.8
aminopyrine	♂	1.94	1.71	1.15	3.52	2.81	1.47	1.93
aminopyrine	♀	1.69	1.99	2.47	2.47	5.45	1.50	1.66
t-stilbene oxide	♂	1.23	1.12	1.21	1.42	0.93	0.97	1.29
Aroclor 1254	♂	1.00	1.02	1.23	1.19	1.00	1.05	1.48
clofibrate- μsomes	♂	1.32		4.17	2.75	1.57	2.15	1.71
clofibrate- cytosol	♂	0.72		-	.61	-	-	-

ref 189 Human liver carboxylesterase. Properties and comparison with human serum carboxylesterase. (J. Biochem., 94:793-797, 1983) The data show that serum carboxylesterase is not derived from liver carboxylesterase

<u>similarities</u>

same pH optimum of 8.0

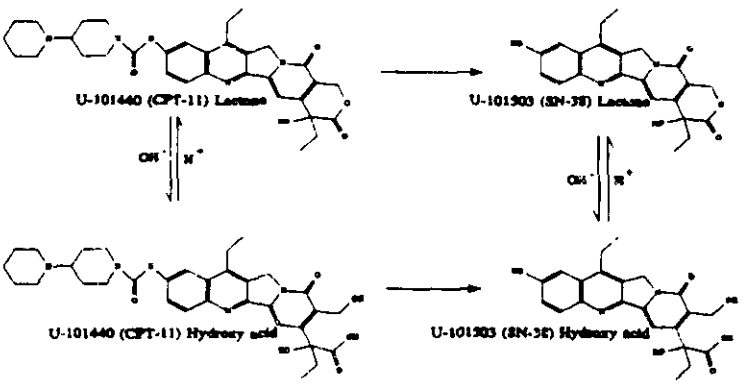
<u>differences</u>

not inhibited by neostigmine, *p*-TMAA, and less sensitive to PMSF than serum carboxylesterase
maximal activity at 20 mM methyl butyrate vs. a K_m of 110 mM for serum carboxylesterase
antibody to serum enzyme did not cross react with liver enzyme
different substrate specificities
three 60,000 M_r subunits vs. four 80,000 M_r subunits for serum carboxylesterase
pI 6.3 vs 4.0 for serum carboxylesterase

ref 195 Human tumor carboxylesterase activity correlates with CPT-11 cytotoxicity in vitro. (Proc. Am. Assoc. Cancer Res., 35:365, 1994) Carboxylesterase activity was evaluated in 179 fresh human tumors from 18 different tumor types. Carboxylesterase activity ranged from 0.009 to 1.274 μmol/min/mg protein. The median was 0.125. The highest activity was in lymphoma, small cell lung cancer, corpus uteri, and mesothelioma. Fourteen tumors were also evaluated for their in vitro sensitivity to 3 μg/ml CPT-11. There was a statistically significant correlation between carboxylesterase activity and growth inhibition by this concentration (Spearman rank correlation test). Carboxyiesterase may thus be an important determinant of CPT-11 sensitivity.

ref 197 Roie of carboxylesterase on metabolism of camptothecin analog CPT-11 in non-small cell lung cancer cell line PC7 cells. (Proc. Am. Assoc. Cancer Res., 33:427) Carboxylesterase activity was compared in CPT-11 sensitive and resistant PC7 cells. CPT-11 accumulation was the same between cell lines, but resistant PC7/CPT-11 cells accumulated less SN-38. PC7/CPT-11 cells had ⅛ the carboxylesterase activity of parent cells. The data indicates that carboxylesterase is an important determinant of CPT-11 sensitivity and can play a role in acquired resistance.

SUMMARY OF PHARMACOKINETICS



The pharmacokinetic parameters of CPT-11 and SN-38 after single i.v. doses of CPT-11 are collected in the following tables. C_{max} and AUC data are also presented in graphical form. Data from total radioactivity were included in the C_{max} graphs, but excluded from the AUC graphs. CPT-11 C_{max} generally correlated with mg/m² dose in mice, rats, and dogs (r^2=0.700). This would be expected after i.v. dosing where the C_{max} occurs immediately after dosing and precludes any inter-species differences in metabolism or elimination from having an effect. Inter-species differences were noted, however, in the CPT-11 AUC. Mice and dogs had similar AUCs at a given mg/m² dose and these were approximately double the rat AUC. Clear differences were seen in SN-38 C_{max} and AUC between mice, rats, and dogs. The mouse C_{max} and AUC were 10 fold and 3-5 fold higher, respectively, than in rats. SN-38 production was very low in the dog representing either low carboxylesterase activity or rapid elimination. Note that all the pharmacokinetic studies were done at doses well below the lethal doses (300-400 mg/m² in rodents and 750 mg/m² in dogs). The rodent toxicity thus correlated best with CPT-11 C_{max}, whereas the lesser sensitivity of the dog to CPT-11 administration correlated best with the absence of SN-38 production. It is also possible that the greater sensitivity of the rodents is due to saturation of elimination pathways as the dose is raised, *e.g.* saturation of glucuronidation. This would lead to greater than expected systemic exposures compared to the dog.

CPT-11 is primarily eliminated in the bile and 70% can be recovered in the feces. The remainder appears in the urine.

Distribution studies are summarized in the following table. The significant presence in the liver and GI tract are consistent with the predominant biliary/fecal excretion and entero-hepatic re-circulation. High concentrations were found in adrenals, thyroid, and pancreas. The presence in spleen and bone marrow was consistent with the myelosuppresion induced by CPT-11. In general, however, there was not a good correlation of end-organ toxicities with the tissue distribution.

Tissue Distribution of CPT-11

study #	species	label	Primary tissues						
7226-94-119	rats	ethyl	upper GI	pancreas	spleen	liver	kidneys	marrow	thyroid
7256-94-125	mice	(hplc)	intestines	liver	stomach	lung			
7256-94-154	rats	ethyl	pancreas	adrenal	spleen	kidney	liver	thyroid	marrow
7219-94-75	rats	ethyl	kidney	GI tract	marrow				
7256-94-085	rats	ethyl	thyroid	kidney	adrenal	pancreas	lung	liver	
7256-94-087	rats	PP	kidney	adrenal	thyroid	pancreas	lung	liver	

In addition to CPT-11 and SN-38, the glucuronide of SN-38 can be found in the bile and accounts for 20% of the excreted dose, ~15% of the biliary excretion are unknown metabolites. Some of the dose may be excreted directly by the intestines. Approximately 20% of the dose excreted in the bile undergoes entero-hepatic re-circulation. Radiolabeling of the piperdinopiperidine side chain which is released upon conversion to SN-38 did not alter these observations noticeably except that the $t_{1/2,\alpha}$ and $t_{1/2,\beta}$ were tripled, the urinary excretion doubled, and the RBC binding kinetics altered. The metabolic fate of the piperdinopiperdine side-chain was not studied.

Summary of CPT-11 and SN-38 Pharmacokinetic Parameters in Mice after Single Dose I.V. CPT-11

		CPT-11							SN-38						
study:		94-111			94-122	94-125	94-104		94-111			94-104		94-122	94-125
matrix:		plasma			plasma	plasma	plasma		plasma			plasma		plasma	plasma
analyte[a]:		T			T	T	T	L	T			T	L	T	T
dose mg/kg:		10	20	40	10	40	40	40	10	20	40	40	40	10	40
C_{max} (µg/ml)	♂					5.21[b]									0.08[c]
	♀	~5	~10	~22	5.1		9.73	8.31	~0.8	~1.1	~1.2	0.794	0.610	0.84	
AUC (µg•hr/ml)[b]	♂					12.2									0.6
	♀	2.96	7.65	23.45	3.52		15.3	6.67	0.41	0.71	1.08	2.19	1.04	0.42	
$t_{½}$ (hr)	♂					14.1									23
	♀	0.95	0.83	1.07	2.7		0.86	0.94	2.16	3.01	3.40	1.6	1.6	1.85	
Cl_p (L/hr/kg)	♂														
	♀	3.38	2.65	1.82	2.86		2.62	6.00							
Vd (L)	♂														
	♀	3.34	2.84	2.59	3.03		3.58	10.4							

[a] T = total, L=lactone

[b] AUCs 0-∞ unless indicated

[c] Concentration at 1 hr

Summary CPT-11 Pharmacokinetic Parameters in Rats after Single Dose I.V. CPT-11

study:		94-116	94-123	ref 158		94-085		94-087	94-075	94-128						94-154
matrix:		serum	plasma	plasma		blood	blood	plasma[c]	plasma[c]	plasma						blood
analyte[a]:		T	T	T	L	RadEt	RadEt	RadPP	RadEt	T						RadEt
dose mg/kg:		10.6	10	40		4	20	10	10.6	1	2	4	10	20	40	10
C_{max} (µg/ml)	♂	2.5	3.53	12.3	11.6	2.21	11.7	5.22	4.22	0.511	0.96	2.78	7.24	12.09	20.37	
	♀															3.85[e]
AUC (µg·hr/ml)[b]	♂	3.55[d]	3.32	24.7	15.0	6.8[e]	46.9[e]	25.0[e]	7.55[d]	0.19	0.39	1.23	4.02	8.63	22.46	
	♀															15.8
$t_{½,\beta}$ (hr)	♂	0.8	1.35	6.1	5.9	5.9	8.0	18.0	6.08	0.81	0.76	1.12	1.30	1.36	2.35	
	♀															11.0
Cl_p (L/hr/kg)	♂			1.63	2.66					5.26	5.13	3.25	2.49	2.32	1.78	
	♀															
Vd (L/kg)	♂			3.88	6.22					-	4.26		3.15		4.02	
	♀															
urinary excretion (%)	♂					22.1	27.1	41.2	22	15.4	17.2	19.5	20.3	21.5	27.6	
	♀															18.7
biliary excretion (%)	♂									21.2	24.0	24.0	31.5	32.7	32.7	
	♀															
fecal excretion (%)	♂					76.4	66.7	54.5	77	65.8	59.5	60.2	71.8	62.9	71.4	
	♀															79.3

[a] T = total, L=lactone; RadEt, radiolabel in ethyl group; RadPP, radiolabel in piperidino sidechain

[b] AUCs 0-∞ unless indicated

[c] blood data also available

[d] 0-24 hr AUC

[e] 0-72 hr AUC

[e] plasma C_{max} was 4.37 µg/ml

Summary SN-38 Pharmacokinetic Parameters in Rats after Single Dose I.V. CPT-11

study:		94-116	94-123	94-128						ref 158	
matrix:		serum	plasma	plasma						plasma	
analyte[a]:		T	T	T						T	L
dose mg/kg:		10.6	10	1	2	4	10	20	40	40	
C_{max} (µg/ml)	♂	0.065	0.088	0.056	0.078	0.102	0.125	0.146	0.175	0.171	0.089
	♀										
AUC (µg•hr/ml)[b]	♂	0.28[c]	0.19	0.047	0.086	0.106	0.211	0.308	0.421	0.927	0.339
	♀										
$t_{½,\beta}$ (hr)	♂	2.8	2.19	1.56	1.96	1.96	3.43	3.59	3.45	8.2	15.1
	♀										

[a] T = total, L=lactone

[b] AUCs 0-∞ unless indicated

[c] 0-24 hr AUC

Summary of CPT-11 and SN-38 Pharmacokinetic Parameters in Dogs after Single-Dose I.V. CPT-11

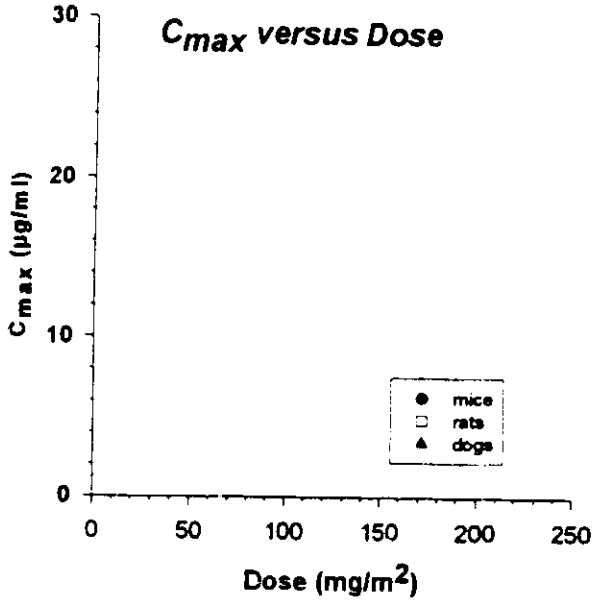
		CPT-11							SN-38					
study:		94-097	94-019				94-156	94-107	94-097	94-019				94-107
matrix:		plasma	plasma				plasma[c]	plasma	plasma	plasma				plasma
analyte[a]:		T	T	L	T	L	RadEt	T	T	T	L	T	L	T
dose mg/kg:		2.5	2.5		7.5		2.5	10	2.5	2.5		7.5		10
C_{max} (µg/ml)	♂	5.93					5.91	23.8	0.0061					0.021
	♀		4.20	4.19	12.7	10.1	4.31			0.0037	0.0030	0.0117	0.0079	
AUC (µg•hr/ml)[b]	♂	8.54					11.3	47.2	0.022					0.09
	♀		7.78	4.24	27.7	14.7	9.2			0.0188	0.0148	0.0535	0.0231	
$t_{½}$ (hr)	♂	3.1					98.4	2.4	2.4					1.65
	♀						95.1							
Cl_p (L/hr/kg)	♂	0.30												
	♀		0.36	0.72	0.27	0.52		~0.24						
V_d (L)	♂													
	♀		1.6	2.9	1.7	3.2		14.1						
urinary excretion (%)	♂						26.8	20.9						
	♀						24.9							
fecal excretion (%)	♂						72.3							
	♀						72.8							

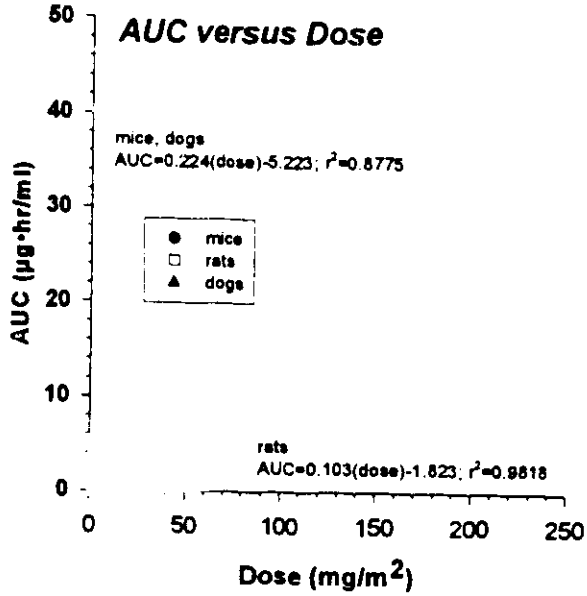
[a] T = total, L=lactone; RadEt, radiolabel in ethyl group; RadPP, radiolabel in piperidino sidechain

[b] AUCs 0-∞ unless indicated

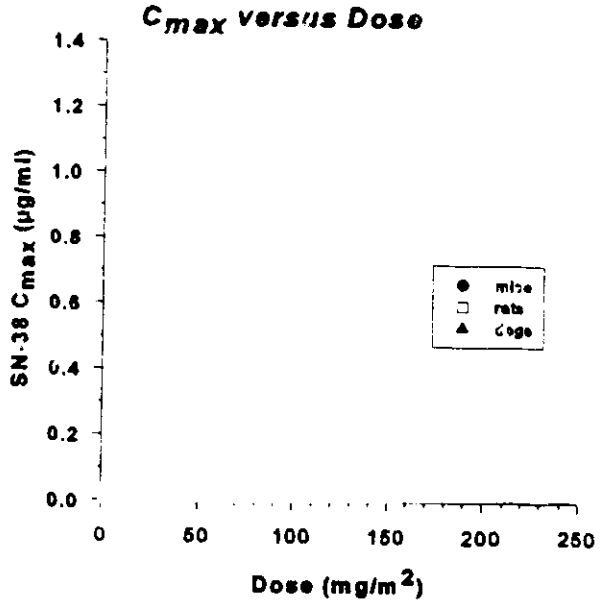
[c] blood data also available

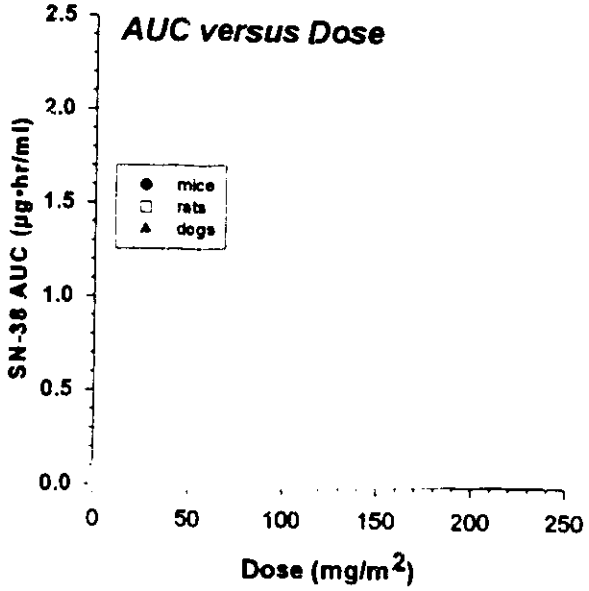
CPT-11 Pharmacokinetics





SN-38 Pharmacokinetics





III. Toxicology

7219-94-001 The toxicity of repeated intravenous doses of DQ-2805 (CPT-11) administered to beagle dogs for 26 weeks. Conducted by according to GLP.

species: beagle dogs (3/sex/group)
drug: CPT-11 lot# K006
dosage: 0, 0.01, 0.1, and 1.0 mg/kg/day
age; weight: 5-6 mo; 7.3-9.7 kg for ♂ and 7.1-9.1 kg for ♀
route: i.v. via cephalic vein, 1 ml/kg

Observations

Clinical signs	twice daily
Body weights	pre-study, day 2, weekly
Food consumption	pre-study, day 2, weekly
Water Consumption	pre-study, day 2, weekly
Hematology	pre-study, weeks 4, 13, and 26
Clinical chemistry	pre-study, weeks 4, 13, and 26
Urinalysis	pre-study, weeks 4, 13, and 26
Ophthalmoscopy	pre-study, weeks 13 and 26
EKG	pre-study, weeks 13 and 26
Gross pathology at sacrifice (organs p.)	
Histopathology	at sacrifice (organs p.)

a. Clinical signs: deaths-1 HD♂ on wk 22 was killed due to thickening of the injection site black discoloration of skin in MD and HD; partial hair loss in HD, astasia in HD ♂; soft stools and diarrhea in HD ♀s

b. Body weights: no treatment related changes

c. Food consumption: no treatment related changes

d. Water consumption: transient decrease in LD ♂s on wk 21

e. Hematology: Effects were limited to erythrocytes. The findings below the dotted line are considered sporadic.

Effects of CPT-11 on Hematology (% change)

		Week 4	Week 13			Week 26		
parameter	sex	HD	LD	MD	HD	LD	MD	HD
RBC	♂					↓13	↓21	↓35
	♀				↓16		↑10	↓21
Hct	♂							↓29
	♀	↓12	↓11		↓14		↑9	↓10
Hgb	♂				↓20			↓31
	♀	↓12			↓12	↓8		↓12
seg neu	♂							↑16
stab neu	♂	↑100						
platelets	♂				↑32			
fibrinogen	♀						↓35	

f. Clinical chemistry: The changes in blood chemistry were relatively minor: ~10% ↓protein in HD groups wks 13 and 26; HD ♂s had ↓cholesterol (43%), triglycerides (22%), and phospholipids (33%) on wk 13, 8% ↓calcium and 21% ↓phosphate in HD ♀s on wk 26

g Urinalysis: no treatment related changes
h Ophthalmoscopy: no treatment related changes
I. EKG: wk 26 LD ♂s high T-waves
MD, HD ♀s low T-waves
j. Gross pathology: HD ♀s had a 32% ↑relative right adrenal weight
lung dark red area in 1 HD ♀
thyroid cyst adhesion in 1 MD ♂
GI tract 1 HD ♂ had subserosal white mass filled with green liquid in ileum
skin black discoloration of ears in 2 MD ♀, 2 HD ♂s, and 3 HD ♀s; loss of hair in 1, MD ♀, 1 HD ♂, and 2 HD ♀s;
k. Histopathology:
liver slight fibrous thickening of capsule and hyperplasia of bile duct in 1 MD ♂
kidney slight hyperplasia of the mesangium and deposition of eosinophilic and electron dense substance in the glomerulus in 1 HD ♂, slight urinary casts in 1 HD ♀
spleen slight congestion of marginal area in 2 MD and 2 HD ♂s but this was also observe in 1 control ♂and 2 control ♀s
lung slight aveolitis with organization in 1 HD ♀; slight granuloma in 1 HD ♂; peribronchial infiltration in 1 HD ♂
parathyroid slight ciliated epithelial cells in 1 HD♂
pancreas slight interstitial infiltration of cells and interstitial edema in 1 HD ♂
GI tract slight encapsulated abscess in ileum, slight infiltration of cells in duodenum, slight serositis in rectum
urinary bladder slight focal atrophy of muscle fibers in 1 HD ♂
bone marrow slight ↓ in erythrocytic series in 1 HD ♂
skin slight-moderate vasculitis, folliculitis, thickening of the epidermis, scab formation, deposition of melanin granules, and ulcers
vasculature vacuolation of epithelial cells in vascular walls

7219-94-07. A Chronic Toxicity Study of Repeated Intravenous Doses of CPT-11 Administered to Rats for 6 Months with a 1-Month Recovery Period. Conducted by according to GLP. This study was previously reviewed (Review #2). Since a conventional carcinogenicity study was not submitted, the tumor data is now being more precisely captured to aid with the labeling. CPT-11 was administered daily for 180-182 consecutive days.

species: Crj:CD (SD) rats (20/sex/group plus 30/sex for 0, 0.8, and 4.0 groups so that 10 could be followed during 1 mo of recovery)
drug: CPT-11 lot# 801208 (99.96%,
dosage: 0, 0.0064, 0.032, 0.16, 0.8, and 4.0 mg/kg
age; weight: 6 weeks, 133-209 g
route: 5 ml/kg *i.v.* via tail vein

There was no clear dose-dependency in the tumor incidence. It appears likely that the tumors found were sporadic and un-related to CPT-11 administration.

Incidence of Tumors in Rats Dosed Daily for 180 Days

tumor site	diagnosis	gender	0	0.0064	0.032	0.16	0.8	4.0
mammary gland	adenocarcinoma	♀	1/20			1/20		1/20
pituitary	adenoma	♀	1/20			2/20	2/29[a]	
pancreas	adenocarcinoma	♀		1/20				
bone marrow	lymphocytic leukemia	♂			1/20			

[a] includes one tumor found in recovery group, no other tumors were found in any recovery group animals

SUMMARY OF TOXICOLOGY

Toxicology. The toxicologic effects of CPT-11 were primarily confined to rapidly dividing tissues. Single *i.v.* doses induced increases in thymus and spleen weights in mice and rats, variable effects on platelets, and indications of hepatotoxicity in rats (vacuolar degeneration and congestion). Mice and rats had similar sensitivity to the lethal effects of CPT-11 (LD_{10}=300-400 mg/m²), but the lethal dose on a mg/m² basis was at least 2 times greater in dogs. Dogs exhibited vomiting and diarrhea after single *i.v.* doses of CPT-11.

Daily dosing produced more pronounced effects on hematopoiesis and the GI tract than single doses. The major effects of multiple daily dosing with CPT-11 were anemia (↓RBCs, Hct, Hgb); ↓WBCs; hypocellularity of bone marrow, spleen, thymus, and lymph nodes; vomiting; and diarrhea. Occasional signs of hepatotoxicity (↑AST, LDH, AP, atrophy) and nephrotoxicity (↑BUN, creatinine) were also noted. The findings were similar whether dosing was continued for 14-180 days. The only study conducted with a schedule similar to the recommended clinical schedule (weekly x 4 out of 6 weeks) was study #7219-54-105 in which the animals were observed for two years prior to sacrifice. Hematology and Clinical Chemistry data were not collected during the course of that study and gross pathology and histopathology was obtained 1.75 years after the last CPT-11 dose. Nonetheless, thirteen weekly doses of 150 mg/m² had no obvious toxic effect on the rats. When administered as multiple doses, dogs were more sensitive to CPT-11 than rodents. The dose-limiting toxicities in humans, diarrhea and leukopenia, were thus accurately predicted by both the single and multiple dose animal studies. The toxicology data for CPT-11 is summarized as follows:

Single Dose

study#	species	route	LD_{10} mg/kg	LD_{10} mg/m²	selected toxicities
-18	mouse	*i.v.*	110	330	↑platelets, ↑thymus weights, swollen spleen
94-18	mouse	oral	671	2013	diarrhea, hair loss, ↓WBCs, ↑thymus & spleen wts, GI mucosa atrophy ♂ reproductive organs
atrophy,					
94-18	rat	*i.v.*	70	420	↓RBCs, ↓platelets, ↑spleen weight, hepatotoxicity
94-18	rat	oral	688	4128	soft stools, ↓RBCs, ↑platelets, ↑spleen weight, atrophy multiple including ♂ reproductive organs
organs					
94-20	dogs	*i.v.*	40[a]	800	vomiting, diarrhea, ↑platelets, ↑CPK, thymus atrophy, skin reddening

[a]highest non-lethal dose

Multiple Dose

study#	species	route	schedule	LD_{10} mg/kg	LD_{10} mg/m²	selected toxicities
94-21	rat	*i.v.*	daily x 28	>20	>120	↓RBCs, Ht, Hgb, WBCs; ↑platelets, ↑BUN, multiple organ wt changes, thymus atrophy, hypocellularity of bone marrow & lymph nodes
94-22	rats	*i.v.*	daily x 28[a]	>20[b]	>120	↓RBCs, Ht, Hgb, WBCs w/ partial recovery; ↑AST, LDH, CPK, A/G and ↓AP, TP all reversible; reversible organ wt changes; reversible thymic atrophy; reversible hypocellularity (bone marrow, spleen)
94-15	dog	*i.v.*	daily x 28	1.6[c]	32	diarrhea, ↓leukocytes, ↓spleen thymus wts, atrophy ♂ reproductive organs
94-14	dog	*i.v.*	daily x 14	2.5[c]	50	vomiting, diarrhea, ↓RBCs, Hct, Hgb, WBCs, & platelets, ↑AP, creatinine, BUN, albumin, TP; atrophy of spleen, lymph nodes, intestinal mucosa, & liver; intestinal hemorrhage; hypocellularity of spleen, bone marrow, lymph nodes

94-16	dog	*i.v.*	daily x 91	1.6[c]	32	vomiting, diarrhea ↓RBCs, Hgb, ↑WBCs, ↓CPK, GI tract ulceration/inflammation/necrosis; hypocellularity of thymus, spleen, lymph nodes; pneumonitis
94-105	rats	*i.v.*	weekly x 13	(2 yr recovery)		CPT-11 moderated findings that were seen in controls (enlarged liver and pituitary, coarse kidney surface, s c adipose tissue), ↑ uterine horn polyps and sarcomas

[a] with 2 and 4 week recovery groups, [b] only dose studied, [c]highest non-lethal dose

Long Term

				LD_{10}		
study#	species	route	schedule	mg/kg	mg/m²	selected toxicities
94-07	rats	*i.v.*	daily x 180	>4	>24	hair loss, ↓WBCs, ↓lymphocytes, ↑platelets, ↓globulins, ↑albumin, ↑cholesterol, hypoplasia of teeth, tumors found
94-01	dogs	*i.v.*	daily x 180	>1	>20	discolored skin, hair loss, diarrhea; ↓RBCs, Hct, Hgb

In addition, the single dose toxicity of CPT-11 metabolites and degradation products and the multiple dose toxicity of SN-38 have been investigated. On a weight basis, SN-38 and PP were 3-fold less toxic to rats than CPT-11 when LD_{10}s were compared (1380 and 1326 mg/m² respectively). The differences were more pronounced on a molar basis where the LD_{10}s in rats for CPT-11, SN-38, and PP were 620, 2870, and 6200 µmol/m² respectively. A caveat is that SN-38 was administered as a pH 9.0 solution (due to poor solubility at neutral pH) which favors the carboxylate over the lactone form. The carboxylate is inactive as a topoisomerase I inhibitor, but it is unknown if its whole animal toxicity is more or less than the lactone. Photodegradation products, however, were 3 to 7-fold more toxic in mice than CPT-11 when LD_{10}s were compared. The LD_{10}s for D-1, D-2, and Y-1 were 60, 47.7, and 119.1 mg/m² respectively (108, 85, and 186 µmol/m² on a molar basis). With multiple dosing for 28 days, SN-38 was about 2-fold more toxic as CPT-11 as assessed by the dose that caused significant effects on hematopoiesis, organ weights, and histopathology (70 mg/m²=146 µmol/m² *versus* 120 mg/m²=177 µmol/m² for CPT-11). Note that on a molar basis they were approximately equally toxic. Again, SN-38 was administered as a pH 9.2 solution which favors the carboxylate over the lactone form and it is unknown how this affects systemic toxicity.

Histopathology Inventory for NDA #20-571

Study	018	019[a]	020	025[b]	015	021	026	007	019	105	031	001
Species	rat	rat	dog	mice	dog	rat	rat	rat	dog	rat	mice	dog
Adrenals					X	X	X	X	X	X		X
Aorta							X	X	X	X		X
Bladder	X	X			X	X	X	X	X	X		X
Bone Marrow smear	X	X	X		X	X	X	X		X		X
Bone (femur)					X	X	X	X	X	X		X
Brain					X	X	X	X	X	X	X	X
Cecum							X		X	X	X	X
Cervix							X		X	X		
Colon (lg intestine)	(X)		(X)		(X)	(X)	X	(X)	X	X	X	X
Diaphragm									X			
Duodenum					X	X	X	X	X	X	X	X
Epididymus							X	X		X		X
Esophagus					X	X	X	X	X	X		X
Eye					X	X	X	X	X	X		X
Fallopian tube												
Gall bladder									X			X
Gross lesions										X		X
Harderian gland						X	X	X		X		
Heart			X		X	X	X	X	X	X	X	X

Hyphophysis						X						
Ileum (sm intestine)	(X)		(X)		(X)	(X)	X	(X)	X	X	X	X
Injection site					X	X	X	X		X		X
Jejunum							X		X	X	X	X
Kidneys	X	X	X		X	X	X	X	X	X	X	X
Lachrymal gland							X					
Larynx							X					X
Liver	X		X		X	X	X	X	X	X	X	X
Lungs	X				X	X	X	X	X	X		X
Lymph nodes, cervical							X			X		
Lymph nodes mandibular					X				X			
Lymph nodes, mesenteric	X				X	X	X	X	X	X		X
Lymph nodes, submaxillary												X
Mammary Gland					X	X	X	X	X	X		X
Nasal cavity							X					
Optic nerves												
Ovaries			X		X	X	X	X	X	X		X
Pancreas					X	X	X	X	X	X	X	X
Parathyroid					X	X	X	X	X	X		X
Peripheral nerve										X		
Pharynx							X					
Pituitary					X		X	X	X	X		X
Prostate					X	X	X	X		X		X
Rectum							X			X		X
Salivary gland					X	X	X	X	X	X		X
Sciatic nerve							X	X	X			
Seminal vesicles						X	X	X		X		
Skeletal muscle							X	X	X	X		X
Skin					X	X	X	X	X	X		X
Spinal cord					X	X	X		X	X		
Spleen	X	X	X		X	X	X	X	X	X	X	X
Sternum					X	X	X	X	X	X	X	X
Stomach	X	X			X	X	X	X	X	X	X	X
Testes	X	X	X		X	X	X	X		X		X
Thymus	X	X	X		X	X	X	X		X		X
					X	X	X	X	X	X		X
					X	X	X	X	X	X		X
Trachea					X	X	X	X	X	X		X
Uterus					X	X	X	X	X	X		X
Vagina					X	X	X	X		X		X
Zymbal gland							X					
Other paranasal sinuses							X					
oral cavity							X					
middle ear							X					
teeth							X					
nasopharynx							X					
abnormal tissue							X					
incisor								X				
molar								X				
Sublingual gland												X
Haw gland												X
Submaxillary gland												X
Bronchia												X
Vertebra								X				X
coagulating gland										X		

[a]formal list not supplied, only organs with reported changes are listed

[b] all organs examined macroscopically, those with changes examined microscopically

V. Special Toxicity

7219-94-009 Teratology and Reproduction Studies of CPT-11 (DQ2805), Teratology Study in Rats (day 7-17). Originally reviewed by Dr. Goheer in the IND. This data was re-examined to capture external, visceral, and skeletal findings by litter since there was a discrepancy regarding the teratogenic dose level between the Sponsor's proposed labeling (6.0 mg/kg/day) and my assessment of the original review (1.2 mg/kg/day). Based on the distinct dose-dependent increase in skeletal variations and decrease in "degree of ossification" beginning at 1.2 mg/kg/day, the labeling should state that CPT-11 is teratogenic at doses greater than 1.2 mg/kg/day

Litters with Fetal Abnormalities Induced by CPT-11[a]				
dose mg/kg:	0	0.24	1.2	6.0
external	0	0	0	16 (64)
visceral	1 (1)	0	1 (1)	20 (54)
skeletal:				
ossification-CCV[b]	2.3	2.0	1.6*	1.0*
ossification-SCB[c]	9.3	9.4	9.4	8.9*
variations	3 (4)	3 (3)	8 (15)	24 (67)
abnormalities	2 (2)	0	0	11 (28)

[a] number of litters with findings (number of total fetuses); the total number of litters examined was 24 in all cases

[b] cervical's corpus vertebrae: mean degree of ossification per litter, "degree of ossification" was not defined

[c] sacral and coccygeal bones: mean degree of ossification per litter, "degree of ossification" was not defined

* statistically significant

cc:
IND ORIG and Div. File
HFD-150
/JJDeGeorge
/AMurgo
/LVaccan
/PAAndrews

Clin. Pharm

&

Bio

Clinical Pharmacology and Biopharmaceutics Review

NDA 20,571

Submission Dates: December 28, 1995
February 22, 1996

Type of Submission:	NDA, NME, IP
Generic Name:	Irinotecan Hydrochloride Injection
Formulation:	Injection
Sponsor:	The Upjohn Company 7000 Portage Road Kalamazoo, Michigan 49001-0199
Reviewer	Gene M. Williams, Ph.D.

I. Synopsis

1. Pharmacokinetics

CPT-11 is converted by carboxylesterase enzymes to an active metabolite SN-38 (7-ethyl-10-hydroxycamptothecin). The pharmacokinetic characteristics of CPT-11 and SN-38 following administration of CPT-11 were evaluated in 306 patients with cancer who were enrolled in four Phase I and in three Phase II studies.

After intravenous infusion, total CPT-11 plasma concentrations decline in a multi-exponential fashion, with a mean elimination half-life of about 6 hours. The average systemic clearance of total CPT-11 is approximately 13 L/hr/m^2. SN-38 area under the curve values are approximately 5% of those observed for CPT-11. The mean terminal half-life of total SN-38 ia approximately 10 hrs. The half-lives of the lactone forms of CPT-11 and SN-38 approximate the half-lives of the total forms.

CPT-11 exhibits moderate plasma protein binding (approximately 50% bound) over the concentration range achieved in clinical studies. SN-38 is highly protein bound to human plasma proteins (approximately 95% bound). The major plasma protein to which CPT-11 and SN-38 bind is albumin.

Human liver is believed to be a major site of conversion of CPT-11 to SN-38, with extrahepatic metabolism and metabolism in tumors also occuring. SN-38 is subsequently metabolized to a glucuronide conjugate (SN-38 glucuronide, SN-38G). Urinary excretion of CPT-11, SN-38, and SN-38 glucuronide is low, generally 15%, <1%, and 3% of the dose, respectively. Thus, renal excretion does not represent a major route of elimination for CPT-11 or its two known major circulating metabolites. Cumulative biliary and urinary excretion of CPT-11 and its metabolites (SN-38 and SN-38 glucuronide)

in two patients over a period of 48 hours following administration of CPT-11 ranged from approximately 25% to 50%.

Female patients demonstrated a small (16.7%), but statistically significant, increase in dose-normalized CPT-11 C_{max} compared with males. All other CPT-11 and SN-38 parameter values were within 10% of corresponding values determined in males. Gender-specific dosing guidelines based on pharmacokinetic differences appear unnecessary.

CPT-11 clearance was 17% lower in patients aged 65 years or older (mean, 71 ± 5 years) than in patients younger than 65 years (mean, 52 ± 10 years). The terminal half-life of CPT-11 was 5.5 hours in patients younger than 65 years and 6.0 hours in patients 65 years or older. Statistically significant differences in mean SN-38 parameters between the two age groups were not observed. While statistically significant differences in CPT-11 pharmacokinetic parameters were observed, the observed differences would likely not result in clinically relevant differences between patients younger than 65 years and patients 65 years or older.

CPT-11 clearance and dose-normalized SN-38 $AUC_{0\text{-}24}$ were independent of creatinine clearance over the range of values (28 to 184 mL/min) estimated in patients with metastatic colorectal cancer. While the pharmacokinetics of CPT-11 have not been formally examined in patients with severe renal insufficiency, alterations in renal function might not be expected to have a major influence on CPT-11 or SN-38 pharmacokinetics, since renal excretion does not represent a major route of excretion for these compounds.

CPT-11 and SN-38 $AUC_{0\text{-}24}$ values (dose-normalized) were 21% and 23% higher, respectively, in patients with liver metastases than in those without liver metastases. While these results are consistent with the hypothesis that liver dysfunction may impair the metabolism of both CPT-11 and SN-38, all patients in this analysis had adequate hepatic function (i.e., serum total bilirubin $\leq$ 2 mg/dL and SGOT (AST) $\leq$ 3 times the upper limit of the normal range, unless the liver was involved with the tumor, in which case the SGOT value must have been $\leq$ 5 times the upper limit of the normal range). Formal investigations of CPT-11 and SN-38 pharmacokinetics in patients with severe hepatic impairment have not been undertaken.

2. Pharmacodynamics

Investigations to examine potential relationships between CPT-11 and/or SN-38 pharmacokinetics and principal toxicities (i.e., late diarrhea or neutropenia) demonstrated considerable overlap in the magnitude of the pharmacokinetic measures (AUC and Cmax) for patients experiencing grades 0 to 4 late diarrhea and neutropenia. Thus, identification of patients who are at risk of experiencing severe diarrhea and neutropenia using pharmacokinetic endpoints appears impractical. Significant differences in CPT-11 or SN-38 pharmacokinetic parameters between responders (i.e., patients who demonstrated a partial or complete antitumor response) and non-responders were not observed.

3. Biopharmaceutics

Eleven formulations were used in clinical development (see Appendix 3 for a list of formulations, differences in manufacturing process and a list of which formulations were used in each study). The sponsor states that the only process change that affects compostion is terminal sterilization and that the to-be-marketed formulation (not terminally sterilized) lacks a thermal degradation product present in

formulations prepared with terminal sterilization. This matter is currently under review by the chemists assigned to this NDA.

4. *In Vitro* Results

Based upon the relative ability of various human tissue homogenates to produce SN-38 from CPT-11, the major site of formation of SN-38 is the liver.

CPT-11 is 30 - 70% protein bound, SN-38 is 92 - 96% protein bound. Plasma protein binding of both species appears to occur primarily to albumin and to be concentration-independent. No investigations into the ability of the cytochromes P450 to metabolize CPT-11 or its metabolites were performed.

II. Recommendation

The submission has adequately addressed the Office of Clinical Pharmacology and Biopharmaceutics' requirements and/or guidelines. The Comments and Labeling Changes need to be conveyed to the sponsor.

FT

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

Gene M. Williams, Ph.D.
Reviewer
Division of Pharmaceutical Evaluation I

cc:

NDA 20571	original
HFD-150	division file
HFD-150	Vaccari, Chico, Murgo, JJohnson
HFD-205	FOI
HFD-850	Lesko
HFD-860	Malinowski, Mehta, Rahman, GeWilliams
HFD-870	MChen
HFD-870	Drug File (Clarence Bott, PKLN Rm. 13B-31)
HFD-870	Chron File (Clarence Bott, PKLN Rm. 13B-31)
HFD-870	Reviewer's File (Clarence Bott, PKLN Rm. 13B-31)
HFD-880	NFleischer

III. Table of Contents

IV Background and terminology

The indication sought in this NDA is treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU based therapy.

Five chemical species were quantitated in pharmacokinetic studies: irinotecan hydroxyacid, irinotecan lactone, SN-38 hydroxyacid, SN-38 lactone and SN-38 glucuronide. Irinotecan hydroxyacid and irinotecan lactone exist in a pH-dependent equilibrium. Establishment of this equilibrium is not instantaneous: *in vivo* there is a measurable conversion half-life for the lactone (predominant form administered) going to the hydroxyacid. Although the hydroxyacid form appears to predominate at pH 7.4, pharmacologic activity is attributed to the lactone form. SN-38 is an irinotecan metabolite that appears more potent than irinotecan in *in vitro* assays. Unlike irinotecan, the lactone form appears to predominate at pH 7.4; like irinotecan, biological activity is attributed to the lactone form. In the NDA irinotecan is usually referred to as CPT-11 and SN-38 glucuronide is often referred to as SN-38G. Unless otherwise stated, the words "irinotecan", "CPT-11" and "SN-38" refer to total drug (hydroxyacid + lactone).

An attempt to determine all of the chemical species present in human plasma following irinotecan administration does not appear in section 6 of the NDA. Thus, it appears that the decision of which species to quantitate in pharmacokinetic studies was not based upon knowledge of human metabolites and their pharmacologic activity.

Of the seven studies included in section 6 of this NDA, only two, studies M/6475/0006 and DM 111, used reasonably validated analytical methods (see Appendix 4 Anaytical Methods Summary). Thus, results from studies other than M/6475/0006 and DM 111 should be interpreted conservatively.

V Summary

1 General Pharmacokinetic Characteristics

The pharmacokinetic characteristics of CPT-11 and its major metabolite SN-38 following administration of irinotecan hydrochloride were evaluated in 306 cancer patients who were enrolled in four Phase I (M/6475/0026, M/6475/0027, M/6475/0008 and DM 111) and three Phase II (M/6475/0001, M/6475/0006, and M/6475/0010) trials. Pharmacokinetic parameter estimates for CPT-11 and SN-38 as determined in these studies are summarized in Tables 6 and 7, respectively.

a Absorption

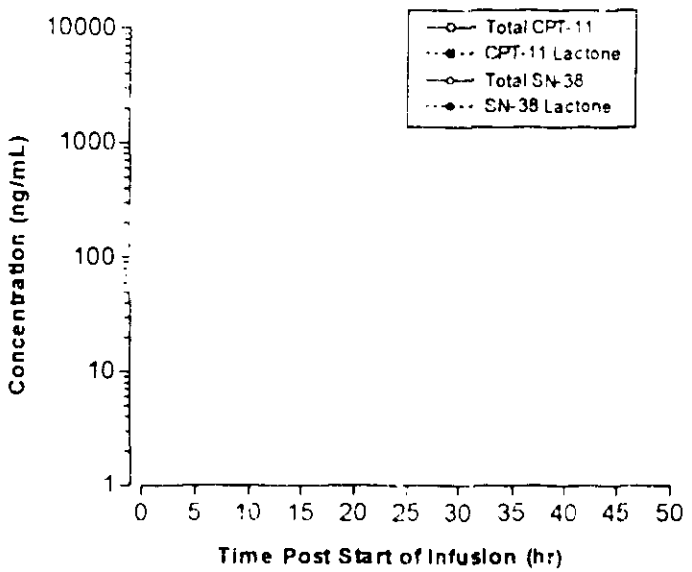
Irinotecan Hydrochloride Injection is supplied as a sterile solution intended for dilution with 5% Dextrose Injection, USP (preferred) or 0.9% Sodium Chloride Injection, prior to peripheral intravenous infusion over 90 minutes. Information on drug absorption when administered by other routes was not included in the NDA.

b Time Course of CPT-11 and SN-38 Plasma Concentrations

(1) Lactone-Specific Pharmacokinetics

The pharmacokinetics of both the lactone and total (lactone plus hydroxy acid) forms of CPT-11 and SN-38 were elucidated in two Phase I dose-escalation studies (M/6475/0027 and M/6475/0026). In study M/6475/0027, 17 patients with histologically proven solid malignancies received a 90-minute intravenous infusion of 50 to 180 mg/m^2 of CPT-11. CPT-11 and SN-38 plasma concentration-time curves for a patient given 125 mg/m^2 of CPT-11 are shown in Figure 1.

Figure 1. CPT-11 and SN-38 Plasma Concentration-Time Curves Following a 90-minute Infusion of CPT-11 (125 mg/m^2)



Peak plasma concentrations (C_{max}) of CPT-11 occurred at the end of the 90-minute infusion. Post-infusion CPT-11 plasma concentrations decreased in a multi-exponential fashion with a mean half-life of 7.9 ± 2.8 hours for total CPT-11 and 6.3 ± 2.2 hours for the lactone form. Plasma clearance of CPT-11 was independent of dose, with a mean clearance of 15.3 ± 3.5 L/hr/m^2 for the total and 45.6 ± 10.8 L/hr/m^2 for the lactone form. The C_{max} for SN-38 occurred from 30 to 90 minutes after the end of infusion. The mean terminal half-life of the active metabolite SN-38 was longer (13.0 ± 3.8 hours and 11.5 ± 3.8 hours for the total and lactone ring forms, respectively) than that of CPT-11. Mean peak plasma concentrations of total SN-38 were approximately 1% to 3% of the peak total CPT-11 concentrations, while mean SN-38 AUC values represented about 3% to 8% of the corresponding total CPT-11 AUC values. The lactone AUC to total AUC ratio remained relatively constant over the entire dose range for both CPT-11 (~34%) and SN-38 (~45%). The relationship between the AUC of total CPT-11 and AUC of CPT-11 lactone or AUC of total SN-38 and AUC of SN-38 lactone is illustrated in Figure 2.

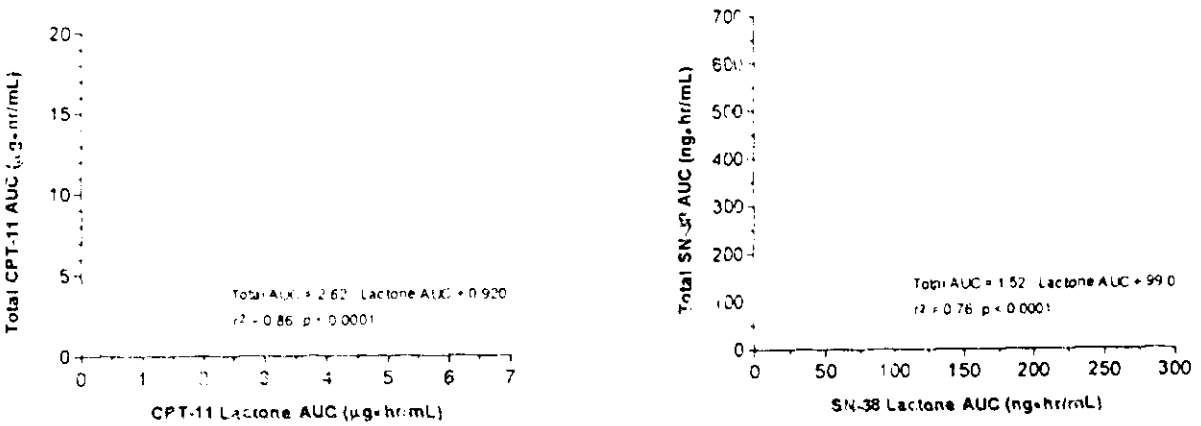


Figure 2. Relationship Between the AUC of Total CPT-11 and AUC of CPT-11 Lactone or AUC of Total SN-38 and AUC of SN-38 Lactone in Patients with Solid Tumors Who Received CPT-11 (Protocol M/6475/0027)

In study M/6475/0026, 31 patients with histologically documented solid tumors received a minute infusion of CPT-11 at doses ranging from mg/m^2. Following infusion, CPT-11 plasma concentrations declined in a biexponential fashion, with a mean half-life of 5.2 hours for total CPT-11

and 5.0 hours for the lactone form. Mean clearance was 21.1 ± 2.0 L/hr/m^2 (352 ± 34 mL/min/m^2) for total CPT-11 and 53.5 ± 1.2 L/hr/m^2 (891 ± 20 mL/min/m^2) for the lactone form. Peak plasma concentrations of SN-38 were generally observed between 1.5 and 4 hours post-infusion. The mean harmonic half-life for total SN-38 (5.9 hours) was slightly longer than that observed for CPT-11. Mean C_{max} values for both total SN-38 and the SN-38 lactone at each dose level represented about 2% to 4% of the corresponding values for CPT-11. Similarly, mean AUC values for both total SN-38 and the SN-38 lactone represented approximately 3% to 8% of the corresponding values for CPT-11. The mean lactone AUC to total AUC ratio at each dose level remained relatively constant for both CPT-11 (~44%) and SN-38 (~51%).

Investigators in France and Japan have recently reported the results of studies which examined the pharmacokinetic variability of the lactone forms of CPT-11 and SN-38 compared with that of total CPT-11 and SN-38. Rivory et al [1] determined the kinetics of the in vivo interconversion of the hydroxyacid (carboxylate) and lactone forms of CPT-11 and SN-38 in five patients who received irinotecan hydrochloride (300 to 500 mg/m^2) as a 30- to 90-minute infusion. The apparent conversion of CPT-11 lactone to the carboxylate in vivo was rapid, with a mean conversion half-life of 9.5 minutes. The CL, V_{ss}, and $t_{1/2}$ for CPT-11 lactone were 39.0 ± 9.6 L/hr/m^2, 263 ± 102 L/m^2, and 9.6 ± 3.9 hr, respectively. The ratio of the CPT-11 lactone to total AUC was 36.8% ± 3.5%. SN-38 was present in plasma predominantly as the lactone at all times and with little interpatient variability (mean lactone/total AUC ratio = 64.0% ± 3.4%, range 60% to 68%). Sasaki et al [2,3] measured lactone and total concentrations of CPT-11 and SN-38 in 12 patients who received 100 mg/m^2 of CPT-11 intravenously over 90 minutes. The ratio of CPT-11 lactone to total CPT-11 concentrations was highest (66%) just after the end of infusion and decreased to 33% at 24 hours post-infusion. In contrast, the ratio of SN-38 lactone to total SN-38 concentration was almost 70% after the end of infusion and only decreased to about 50% at 24 hours after the end of infusion. The standard errors for percent lactone CPT-11 or SN-38 to total drug concentrations at each sampling point were less than 12%. Mean (±SEM) plasma clearance of CPT-11 was 18.8 ± 1.6 L/hr/m^2 for the total and 49.5 ± 4.2 L/hr/m^2 for the lactone form. The mean C_{max} for SN-38 occurred within 1 hour after the end of infusion. The mean terminal half-life of the active metabolite SN-38 was longer (11.3 ± 1.6 hours and 9.1 ± 1.5 hours for the total and lactone ring forms, respectively) than that of CPT-11 (6.8 ± 0.4 hours and 6.8 ± 0.3 hours for the total and lactone forms, respectively). The mean ratios of lactone to total were 37% and 53% for CPT-11 and SN-38, respectively.

In summary, these four studies demonstrated mean lactone to total AUC ratios which ranged from 34% to 44% for CPT-11 and from 45% to 64% for SN-38. A strong correlation between lactone and total AUCs was found for both CPT-11 and SN-38.

(2) Pharmacokinetics of Total Forms

In addition to the studies outlined above, pharmacokinetic parameters based on measurement of total concentrations were estimated in two other Phase I trials (DM111 and M/6475/0008) and in two pivotal safety and efficacy studies in patients with metastatic colorectal cancer (M/6475/0001 and M/6475/0006).

Study DM111 was a multicenter, Japanese Phase I study conducted to evaluate the safety and pharmacokinetics of CPT-11 administered as a single intravenous infusion. A total of 18 patients (13 male, 5 female) with histologically proven solid malignant tumors had pharmacokinetic evaluations. Groups of 3, 4, 5, 5, and 1 patient each were given 50-, 100-, 165-, 250-, or 350-mg/m^2 doses of CPT-

11, respectively. CPT-11 was administered by a single drip infusion over approximately 30 minutes. Plasma pharmacokinetic analyses were performed on samples collected before dosing and at 1, 4, 8, 24, 72, and 168 hours post-infusion. Mean peak plasma concentrations of SN-38 were approximately 1% to 3% of the peak total CPT-11 concentrations, while mean SN-38 AUC values represented about 2% to 5% of the corresponding CPT-11 AUC values. Plasma concentrations of CPT-11 declined with a mean half-life ranging from 5.0 to 7.2 hours. Plasma concentrations of SN-38 declined more slowly with mean half-lives ranging from 11.4 to 18.5 hours.

Study M/6475/0008 was a NCI-sponsored, single-center, open-label, dose-escalation study to determine the maximum-tolerated dose of CPT-11 when administered to patients with solid tumors or lymphomas. CPT-11 was administered intravenously in 500 mL of normal saline solution over 90 minutes on a weekly basis for four doses in a 6-week cycle. Pharmacokinetic results were reported for 21 patients who received doses ranging from 100 to 175 mg/m^2. Mean CPT-11 systemic clearance ranged from 12.9 to 21.9 L/hr/m^2. Two metabolites were measured in plasma: SN-38 and the glucuronide conjugate of SN-38 (SN-38G). AUC of SN-38G was 2 - 4X greater than that of SN-38; peak plasma concentrations of SN-38G peak exceeded those of SN-38 and occured 0.5 - 3 hrs after the SN-38 peak. These observations are consistent with preclinical studies in rats, which demonstrated that 55%, 22%, and 9% of the biliary radioactivity excreted over 24 hours was unchanged CPT-11, SN-38G, and SN-38 [4, 5]. Identification and characterization of the pharmacokinetics of SN-38 glucuronide following administration of CPT-11 to one patient have also been reported Rivory and Robert [6]. The elimination phases of the plasma concentration-time profile of SN-38 and its glucuronide were parallel, suggesting that the transformation of SN-38 to the glucuronide is the rate-limiting step in the elimination of SN-38.

Study M/6475/0001 was an open-label, US Phase II study in which the antitumor activity, toxicity, and pharmacokinetics of CPT-11 were evaluated in patients with metastatic colorectal cancer that progressed or recurred after one previous 5-FU-based chemotherapeutic regimen. Patients were treated at a starting dose of 125 or 150 mg/m^2 intravenously over 90 minutes once weekly for 4 weeks, followed by a 2-week rest (1 course). Dosage adjustments were made for each patient based on toxicity. Blood specimens were collected using a sparse sampling schedule for up to 24 hours after the end of the infusion on week 1 (35 patients) and again on week 3 (27 patients) of the first course of therapy. Model-independent analyses of all data sets resulted in a mean CPT-11 clearance of 9.8 L/hr/m^2 and a terminal half-life of 5.0 hours. The metabolic ratio (percentage SN-38 $AUC_{0\text{-}24}$ / CPT-11 $AUC_{0\text{-}24}$) averaged 3.2%.

In study M/6475/0006, the pharmacokinetics of total CPT-11 and SN-38 were determined in patients with metastatic colorectal cancer that progressed or recurred following one previous 5-FU-based chemotherapeutic regimen or that recurred within 6 months after completion of adjuvant chemotherapy. CPT-11 was administered over 90 minutes once weekly for 4 consecutive weeks. The 4-week CPT-11 treatment period was followed by a 2-week rest period (one course). The first 64 patients received a 125-mg/m^2 starting dose, while the remaining 102 patients received a 100-mg/m^2 starting dose. Dosage adjustments after the initial starting dose were made for each patient based on toxicity. Up to six blood specimens were collected from each patient on week 1 and week 3 of the first course of therapy. During the study, 288 pharmacokinetic data sets were obtained in 162 of the 166 patients who received CPT-11. Mean (± SD) pharmacokinetic parameters for CPT-11 and SN-38 following a 90-minute infusion of a 100- or 125-mg/m^2 dose of CPT-11 on week 1 are summarized in Table 1.

Table 1. Summary of Mean (± SD) CPT-11 and SN-38 Pharmacokinetic Parameters in Colorectal Cancer Patients Receiving 100-mg/m^2 or 125-mg/m^2 Doses of CPT-11 on Week 1 of Therapy

Parameter	Dose (mg/m^2)		% Difference	p Value[a]
	100 [N=98]	125 [N=64]		
Age (yr):	59.0 (13.4)	61.1 (9.90)	- 3.6 %	0.7773
CPT-11:				
T_{max} (hr)	1.61 (0.223)	1.68 (0.352)	- 4.3 %	0.2622
C_{max} (µg mL)[b]	1.29 (0.488)	1.66 (0.797)	- 28.7 %	0.0001
AUC_{0-24} (µg•hr/mL)[c]	8.20 (3.19)[d]	10.2 (3.27)[e]	- 24.4 %	0.0001
Cl (L/hr m^2)	13.2 (4.32)[d]	13.3 (6.01)[e]	- 0.8 %	0.3578
V_z (L/m^2)	107 (29.4)[d]	110 (48.5)[e]	- 2.8 %	0.4539
$t_{1/2}$ (hr)[f]	5.68[d]	5.70[e]	- 0.4 %	0.7059[g]
SN-38:				
T_{max} (hr)	2.17 (0.742)	2.21 (0.718)	- 1.8 %	0.6485
C_{max} (ng mL)[b]	21.8 (10.1)	26.3 (11.9)	- 20.6 %	0.0087
AUC_{0-24} (ng•hr/mL)[c]	206 (104)[d]	229 (108)[e]	- 11.2 %	0.0862
$t_{1/2}$ (hr)[f]	9.79[h]	9.77[i]	- 0.2 %	0.8438[g]
Metabolic Ratio (%)[j]	2.58 (1.10)[d]	2.25 (0.799)[e]	- 12.8 %	0.1214

[a] Wilcoxon Rank Sum test
[b] Peak plasma concentration
[c] Area under the concentration-time curve from time zero to 24 after the end of the infusion
[d] N=90
[e] N=61
[f] Harmonic mean half-life
[g] Comparison of elimination rate constant values
[h] N=87
[i] N=60
[j] Ratio of SN-38 to CPT-11 AUC_{0-24} expressed as a percent

Peak CPT-11 concentrations were generally observed at the end of the infusion. Thereafter, concentrations declined with a mean half-life of approximately 5.7 hours. SN-38 C_{max} levels were about 60-fold lower than the corresponding CPT-11 C_{max} levels. The time at which mean SN-38 peak concentrations were reached was within 1 hour after the end of the 90-minute infusion. The terminal half-life for SN-38 was 9.8 hours which is comparable to values reported in Phase I studies.

2 Distribution

(1) Protein Binding

Using ultrafiltration and HPLC assay methodology for total (lactone plus hydroxy acid) CPT-11 and SN-38, *in vitro* protein binding of CPT-11 and SN-38 was investigated in two studies [7,8] In the first study, fresh human plasma was spiked with 0.35, 0.88, 1.75, or 3.51 µg/mL CPT-11 or with 3.6, 9.1, 18.1, or 36.2 ng/mL SN-38 [8] Fractional human plasma protein binding was 30% to 43% for CPT-11 and 92% to 96% for SN-38, with no apparent concentration dependence Human serum albumin was the major protein to which CPT-11 (25% to 32%) and SN-38 (88% to 94%) were bound In the second investigation, the protein binding of CPT-11 and SN-38 was determined using pre-infusion plasma specimens collected from patients with cancer who were enrolled in study M/6475/0027 [7] Plasma was spiked with 50, 500, or 1000 ng/mL CPT-11 or with 10, 100, or 160 ng/mL of SN-38. The protein binding for both CPT-11 and SN-38 was concentration-independent over the concentration ranges examined Approximately 68% of CPT-11 was bound to plasma proteins, whereas approximately 96% of SN-38 was protein bound These studies demonstrate that SN-38 is highly bound to human plasma proteins

CPT-11 and its active metabolite SN-38 both exhibit a pH-dependent equilibrium between lactone (active) and hydroxy acid (inactive) forms Burke et al [9] used HPLC and fluorescence spectroscopy to study the kinetics of CPT-11 and SN-38 lactone ring opening in the presence of various proteins and blood components *in vitro* Some blood components, especially albumin, were found to alter the rate and extent of conversion of the lactone ring of both CPT-11 and SN-38 to the hydroxyacid form A summary of representative data is shown in Table 2 When compared to degradation kinetics in phosphate buffer at pH 7.4, slower lactone degradation and significantly higher percentages of active lactones were observed at equilibrium in the presence of albumin Time-resolved fluorescence spectroscopy was used to investigate binding stoichiometry and interactions with albumin at the molecular level These results showed that, unlike camptothecin, the active lactone forms of SN-38 and CPT-11 are selectively bound by albumin, altering both the rate and extent of hydrolysis Of all of the camptothecin analogues studied, stabilization of the lactone form by protein was greatest for SN-38 The hypothesized result of this interaction *in vivo* would be to significantly prolong and increase systemic exposure to the lactone form of prodrug and metabolite (the putative active forms)

Table 2. Summary of Kinetic and Equilibrium Parameters for the Hydrolysis of the Lactone Ring of CPT-11 and SN-38 at 1 µM in PBS Buffer at 37°C and pH 7.4-7.6 in the Presence or Absence of Human Serum Albumin, Plasma, or Whole Blood [a]

Compound	Solution	$T_{½}$ (min)[b]	% Lactone Form at Equilibrium[a]
CPT-11	PBS		13 ± 2
CPT-11	HSA		21 ± 1
CPT-11	Human Blood		21.0 ± 0.5
CPT-11	Human Plasma		19 ± 4
SN-38	PBS		13 ± 1
SN-38	HSA		38 ± 1
SN-38	Human Blood		19.5 ± 1.8
SN-38	Human Plasma		35.4 ± 2.9

[a] Reference [9] on **Reference List**
[b] Mean ± standard deviation (SD)
Abbreviations: PBS = phosphate buffered saline, HSA = human serum albumin

Physiological levels of other components of human blood also increase the half-life of SN-38 lactone and increase the percent of lactone at equilibrium [9]. Half-life prolongation was maximal for albumin, low-density lipoproteins (LDLs), high-density lipoproteins (HDLs), and red blood cell (RBC) ghosts, with values ranging between 34.1 and 39.5 minutes compared with 20.9 minutes in phosphate buffered saline (PBS). The percent of lactone at equilibrium was at least doubled relative to the PBS control (15.3% lactone) for plasma, albumin, LDLs, HSA-free RBCs, and hemoglobin, with all other matrices showing intermediate values. These data add to earlier work suggesting that the lactone form of SN-38 is selectively bound by serum albumin.

The distribution of CPT-11 into human RBCs has not been determined.

(2) Volume of Distribution

Consistent with its lipophilicity and moderate protein binding, CPT-11 has a large volume of distribution. Following infusion of 125-mg/m² CPT-11 on week 1 of therapy to 64 patients in study M/6475/0006, the volume of distribution during the terminal elimination phase was 110 ± 48.5 L/m². In study M/6475/0026, 31 patients with solid tumors received 90-minute infusions of escalating doses of CPT-11 (110 to 345 mg/m²). The steady-state volume of distribution (V_{ss}) was independent of dose, averaging 148 ± 20 L/m² across all dose levels. Mean V_{ss} ranging from 105 to 266 L/m² have been reported in the literature and indicate that CPT-11 is extensively distributed to body tissues.

d Metabolism

The proposed metabolic pathway for CPT-11 in various animal species, including humans, is presented in Figure 3

Figure 3. Proposed Metabolic Pathway for CPT-11

The enzymatic hydrolysis of the carbamate bond of CPT-11 to form the active metabolite SN-38 plus piperidinopiperidine (PP) and CO_2 has been shown to occur in all species studied and in a wide variety of tissues and purified enzyme preparations The reaction is catalyzed by carboxylesterases (E.C. 3.1.1.1) [10] Carboxylesterases, which are also known as B-esterases or aliesterases (aliphatic esterases), are

most concentrated in liver tissue and are widely distributed in other tissues such as kidney, lung, intestine, brain, and blood cells

To date, there is no direct evidence for the involvement of the cytochromes P450 in the metabolism of CPT-11 or SN-38. It seems likely that the secondary metabolites of the PP moiety are products of mixed function oxidases, such as the cytochromes P450; however, this has not been studied. The identification of a glucuronide conjugate of SN-38 implicates the involvement of uridine diphosphate glucuronyltransferase (UDPGT)

The ability of various human tissues and serum to produce SN-38 from CPT-11 (91 µg/mL) have been compared [11]. SN-38 production in human serum was only a factor of two greater than in heat-denatured serum and was 7.6-fold lower than the corresponding hydrolysis rate in rat serum. Enzymatic hydrolysis was fastest in the human liver (42.4 ng SN-38/mg protein/hr), with the kidney showing the second highest activity at 24% of the liver value. Activity in normal spleen, lung, and pancreatic tumor tissue ranged between 16% to 18% of the liver value. Liver tumors produced significant, but slightly lower, amounts of SN-38. In another *in vitro* study [12], similar activity was initially observed in human liver and intestine homogenates, but only the liver demonstrated sustained activity. Based on these results, human liver was proposed to be the major site of bioactivation of CPT-11, with extrahepatic metabolism and metabolism in tumors likely [11]

Quantitative analysis of CPT-11, SN-38, and SN-38 glucuronide in bile and urine has also been reported [13]. The cumulative biliary and urinary excretion of CPT-11 and its metabolites (SN-38 and SN-38G) over a period of 48 hours following administration of CPT-11 to two patients ranged from approximately 25% (100 mg/m^2 weekly) to 50% (300 mg/m^2 every 3 weeks). Thus, the metabolic disposition of irinotecan hydrochloride has not been fully elucidated in humans.

e. Excretion

(1) Urinary Excretion

Urinary excretion of CPT-11, SN-38 and SN-38G has been investigated in four Phase I studies (M/6475/0008, M/6475/0026, M/6475/0027 and DM111). Mean (± SD) urinary recovery of CPT-11, SN-38, and SN-38G from these studies as well as from French and Japanese studies cited in the published literature are summarized in Table 3

Table 3. Mean ± SD CPT-11, SN-38, and SN-38 Glucuronide (SN-38G) Urinary Excretion Following Administration of CPT-11 to Patients with Cancer

Reference	No. of Patients	CPT-11 Dose (mg/m^2)	Urinary Recovery (% of Dose)		
			CPT-11	SN-38	SN-38G
9	21	100-175	—[a]	0.25%	3%
11	31	100-345	37.4 ± 4.3[b]	—[a]	—[a]
10	13	50-180	16.0 ± 9.1	0.26 ± 0.18	—[a]
15	3	165-250	17.0 ± 0.611[c]	0.13 ± 0.021[c]	—[a]
26	168	33-750	16.7 ± 1.0[b]	0.23 ± 0.02[b]	—[a]
34	2	100-300	17.0 ± 0.849[d]	0.678 ± 0.527[d]	3.28 ± 1.03[d]
24	60	100-750	19.9 ± 1.4[b]	0.25 ± 0.03[b]	—[a]
25	21	33-115	11.4	0.15	—[a]
27	26	50-145	11.1 ± 1.2	0.18 ± 0.03	—[a]
31	36	100	~15	[a]	—[a]

[a] Not reported
[b] Mean ± standard error of the mean
[c] Calculated from individual patient data provided in the report
[d] Urinary excretion determined in 2 patients on two separate occasions, mean calculated from average excretion for each patient

The urinary excretion of CPT-11, SN-38 and SN-38 glucuronide is low, generally 15%, <1%, and 3% of the dose, respectively. Thus, renal excretion does not represent a major route of elimination for CPT-11 and its two known major circulating metabolites.

(2) Biliary Secretion

Simultaneous plasma and bile specimens collected in five patients with extrahepatic biliary obstruction demonstrate CPT-11 and SN-38 bile levels were 10- to 113-fold and 2- to 40-fold higher, respectively, than corresponding plasma levels [7, 14, 13]. Cumulative biliary excretion of intact CPT-11 over a period of 48 hours was approximately 3% of the administered dose for a patient who received a 100-mg/m^2 dose of CPT-11 and approximately 20% for another patient who received 300 mg/m^2 of CPT-11 [13]. Cumulative biliary secretion of SN-38 and its metabolite, SN-38G, represented less than 2% of the dose in these two patients.

f Dose Proportionality

Dose proportionality has been assessed in four Phase I, dose-escalation studies (M/6475/0026, M/6475/0027, M/6475/0008, and DM111) and in one multicenter Phase II study of patients with metastatic colorectal cancer (M/6475/0006). In these studies, the pharmacokinetics of CPT-11 and its active metabolite SN-38 have been described over the CPT-11 dose range of 50 mg/m^2 to 350 mg/m^2.

Plasma pharmacokinetic analyses were performed on samples collected in 31 patients with histologically proven malignant tumors who received CPT-11 in study M/6475/0026. In this Phase I, dose-escalation trial, CPT-11 was administered as a 90-minute intravenous infusion every 21 days at the following dose levels: 100, 150, 200, 240, 290, or 345 mg/m^2. There was significant interindividual variability in total CPT-11 C_{max} and $AUC_{0-\infty}$ values at all dose levels but the relationship of these parameters with dose appeared to be linear. Clearance (CL), steady-state volume of distribution (V_{ss}), and terminal elimination half-life ($t_{1/2}$) values for CPT-11 did not change with dose, also indicating linear pharmacokinetic behavior over the dose range studied. Dose proportionality in CPT-11 pharmacokinetics was also observed in patients receiving doses ranging from 50 to 180 mg/m^2 in study M/6475/0027 and from 50 to 350 mg/m^2 in study DM111. In contrast, the AUC of SN-38 did not increase proportionately to the increase in CPT-11 dose in these studies. The ratio of the AUC of SN-38 to that of CPT-11 (i.e., metabolic ratio) tended to decrease with higher doses of CPT-11, suggesting that SN-38 formation is not proportional to dose.

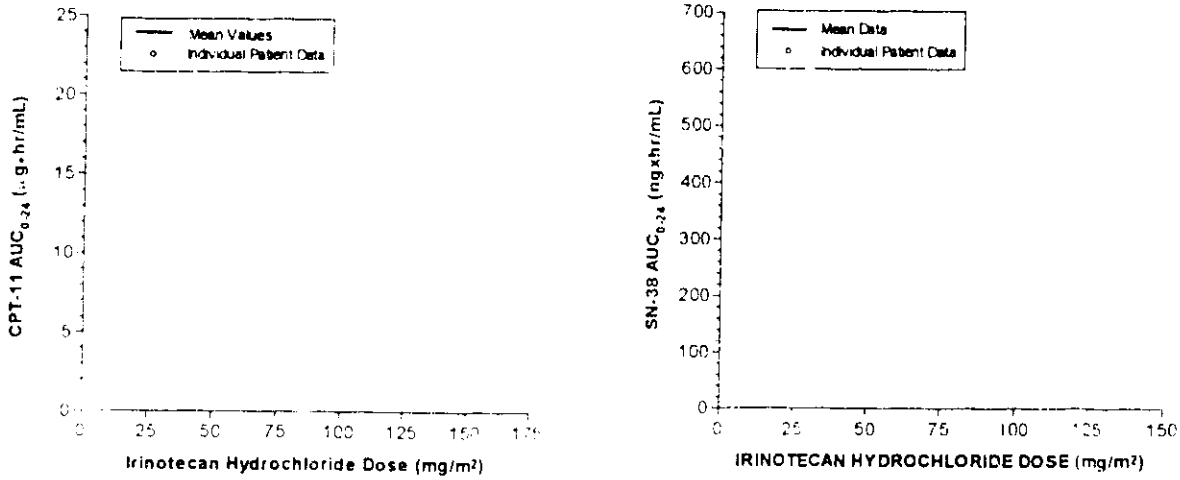
Because of the large interpatient variability in CPT-11 and SN-38 AUC values and the small number of patients evaluated at each dose level, dose proportionality in CPT-11 and SN-38 pharmacokinetics was difficult to assess in Phase I studies. Dose proportionality was further investigated in 162 patients with metastatic colorectal cancer in the Phase II clinical study M/6475/0006. CPT-11 and SN-38 pharmacokinetic parameters were determined during week 1 and week 3 in patients who received doses ranging from 60 to 125 mg/m^2. Week 1 and week 3 pharmacokinetic parameters were pooled at each dose level. A summary of the mean (± SD) pharmacokinetic parameters by CPT-11 dose are provided in Table 4 and illustrated graphically in Figure 4. As expected, CPT-11 C_{max} and AUC_{0-24} increased with increases in dose. CPT-11 pharmacokinetics were linear with respect to the dose administered, as evidenced by no statistical differences in clearance or volume of distribution across the dose range of 60 to 125 mg/m^2. CPT-11 clearance, determined from the slope of the linear relationship, was 12.8 L/m^2, a value comparable to clearance values observed in other studies. Although SN-38 C_{max} and AUC_{0-24} values increased across the dose range of 60 to 125 mg/m^2, the increase was less than dose proportionate. The metabolic ratio decreased from 4.0% in patients who received a 60-mg/m^2 dose to 2.2% in patients who received the 125-mg/m^2 dose.

Table 4. Summary of Mean (± SD) CPT-11 and SN-38 Pharmacokinetic Parameters Relationship with CPT-11 Dose [No. Patients] (Protocol M/6475/0006)

Parameter	CPT-11 Dose (mg/m^2)				ANOVA p-Value[a]
	60 [N=6]	75 [N=18]	100 [N=166]	125 [N=98]	
CPT-11					
C_{max} (µg/mL)	0.667 (0.099)	1.42 (1.57)	1.29 (0.650)	1.58 (0.709)	0.0019
$AUC_{0\text{-}24}$ (µg•hr/mL)	4.66 (1.56)	6.11 (1.51)[b]	7.94 (2.98)[c]	9.85 (3.21)[d]	0.0001
CL (L/hr/m^2)	13.6 (4.49)	12.4 (3.14)[b]	13.6 (4.33)[c]	13.9 (5.64)[e]	0.7946
V_Z (L/m^2)	109 (30.4)	106 (25.0)[b]	110 (31.8)[c]	114 (53.9)[e]	0.8379
$t_{1/2}$ (hr)[f]	5.58	5.88[b]	5.60[c]	5.67[e]	
SN-38					
C_{max} (ng/mL)	16.3 (6.11)	17.7 (8.92)	19.8 (9.84)	23.8 (11.1)	0.0058
$AUC_{0\text{-}24}$ (ng•hr/mL)	186 (84.4)	168 (83.5)[b]	188 (93.8)[c]	215 (103)[d]	0.1131
$t_{1/2}$ (hr)[f]	9.39	10.78[b]	9.69[g]	9.93[h]	---
Metabolic Ratio[i]	4.00 (1.44)	2.71 (1.08)[b]	2.47 (1.10)[c]	2.18 (0.745)[d]	0.0001

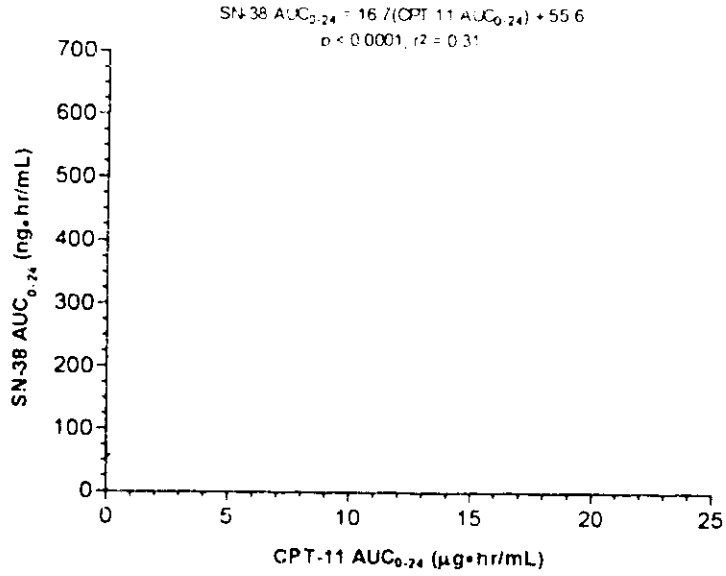
[a] One-way analysis of variance, dose comparison
[b] N=16
[c] N=154
[d] N=94
[e] N=93
[f] Harmonic mean
[g] N=151
[h] N=92
[i] Ratio of SN-38 to CPT-11 $AUC_{0\text{-}24}$ expressed as a percent

Figure 4. Relationships Between CPT-11 and SN-38 $AUC_{0\text{-}24}$ and CPT-11 Dose in Patients with Metastatic Colorectal Cancer



The correlation between CPT-11 $AUC_{0\text{-}24}$ and the corresponding SN-38 $AUC_{0\text{-}24}$ observed in patients enrolled in this study is shown below (Figure 5).

Figure 5. Correlation Between CPT-11 $AUC_{0\text{-}24}$ and the Corresponding SN-38 $AUC_{0\text{-}24}$ in Patients with Metastatic Colorectal Cancer (Protocol M/6475/0006)



Although the pharmacokinetics of CPT-11 were highly variable among patients, the results of these studies consistently demonstrated that CPT-11 exhibited linear pharmacokinetics over the dose range of 50 to 350 mg/m^2. SN-38 C_{max} and AUC_{0-24} values increased with increases in CPT-11 dose, but the increase was less than dose proportionate.

2 Factors Potentially Affecting Pharmacokinetics

a Pharmacokinetics in Special Populations

(1) Influence of Gender

The potential difference in CPT-11 and SN-38 pharmacokinetics between males and females was assessed in study M/6475/0006. Table 5 summarizes the pharmacokinetic results during week 1 of therapy for 80 male (60 ± 11 years) and 82 female (60 ± 13 years) patients who received 100-mg/m^2 or 125-mg/m^2 of CPT-11. Mean dose-normalized CPT-11 C_{max} was slightly (16.7%), but significantly, higher in females than in males. All other CPT-11 and SN-38 parameter values in females were within 10% of corresponding values in males.

Table 5. Comparison of Mean (± SD) CPT-11 and SN-38 Pharmacokinetic Parameters in Male and Female Patients with Colorectal Cancer after Administration of CPT-11 (100 mg/m^2 or 125 mg/m^2) on Week 1 of Therapy

Parameter	Male (N=80)	Female (N=83)	% Difference	p-Value[a]
CPT-11				
Tmax (hr)	1.64 (0.294)	1.64 (0.272)	0 %	0.6894
Cmax (μg/mL)[b]	1.20 (0.249)	1.40 (0.682)	+ 16.7 %	0.0400
AUC$_{0-24}$ (μg•hr/mL)[c]	7.95 (3.00)[d]	8.40 (2.92)[e]	+ 5.7 %	0.1741
CL (L/hr/m^2)	13.6 (4.76)[d]	12.9 (5.33)[e]	- 5.1 %	0.1747
V_z (L/m^2)	111 (34.0)[d]	105 (41.7)[e]	- 5.4 %	0.1459
$t_{1/2}$ (hr)[f]	5.69[d]	5.67[e]	- 0.4 %	0.9510[g]
SN-38				
Tmax (hr)	2.22 (0.686)	2.15 (0.774)	- 3.2 %	0.4904
Cmax (ng/mL)[b]	22.4 (9.87)	20.7 (9.85)	-7.6 %	0.1775
AUC$_{0-24}$ (ng•hr/mL)[c]	200 (95.9)[d]	194 (99.4)[e]	- 3.0 %	0.6658
$t_{1/2}$ (hr)[f]	9.65[h]	9.90[i]	+ 2.6 %	0.5467[g]
Metabolic Ratio (%)[j]	2.56 (0.973)[d]	2.34 (1.02)[e]	- 8.6 %	0.0411

[a] Wilcoxon Rank Sum test
[b] Dose-normalized (100 mg/m^2) peak plasma concentration
[c] Dose-normalized (100 mg/m^2) area under the concentration-time curve from time zero to 24 after the end of the infusion
[d] N = 73
[e] N = 78
[f] Harmonic mean half-life
[g] Comparison of elimination rate constant values
[h] N = 71
[i] N = 76
[j] Ratio of SN-38 to CPT-11 AUC$_{0-24}$ expressed as a percent

(2) Influence of Age

While a formal evaluation of the influence of age on the pharmacokinetics of CPT-11 and SN-38 has not been undertaken, a significant proportion of patients with metastatic colorectal cancer in whom pharmacokinetics assessments were made in study M/6475/0006 were over 65 years of age. In this study, mean (± SD) systemic clearance of CPT-11 was 11.8 ± 3.50 L/hr/m^2 in 67 patients (34 male, 33 female) aged 65 years or older (mean, 71 ± 5 years) and 14.3 ± 5.74 L/hr/m^2 in 95 patients (46 male, 49 female) younger than 65 years (mean, 52 ± 10 years). The terminal half-life of CPT-11 was 5.5 hours in patients younger than 65 years and 6.0 hours in patients 65 years or older. These differences in CPT-11 parameters were statistically significant. Dose-normalized area under the curve (AUC$_{0-24}$) for SN-38 in patients aged 65 years or older was 11% higher than the AUC$_{0-24}$ determined in patients younger than 65 years. Statistically significant differences in mean SN-38 parameters between the two age groups were not observed.

(3) Influence of Renal Impairment

The relationship between CPT-11 and SN-38 pharmacokinetic parameters and renal function was evaluated in patients with colorectal cancer who were enrolled in study M/6475/0006. Creatinine clearance (CLcr) was estimated from serum creatinine concentrations and used as a marker of renal function. Creatinine clearance estimates in these patients ranged from 28 to 184 mL/min (mean 90.5 ± 33.5 mL/min). Figure 6 displays the relationship between CPT-11 clearance and estimated creatinine clearance. The relationship between dose-normalized SN-38 $AUC_{0\text{-}24}$ and estimated CLcr is shown in Figure 7. CPT-11 clearance and dose-normalized SN-38 $AUC_{0\text{-}24}$ are independent of CLcr over the range of creatinine clearance values estimated in these patients. Although the pharmacokinetics of CPT-11 have not been formally examined in patients with renal insufficiency, the results of this study are consistent with the hypothesis that alterations in renal function would not be expected to have a major influence on the CPT-11 or SN-38 pharmacokinetics, since renal excretion does not represent a major route of excretion for these compounds.

Figure 6. Relationship Between CPT-11 Clearance and Estimated Creatinine Clearance in Patients with Metastatic Colorectal Cancer (Protocol M/6475/0006)

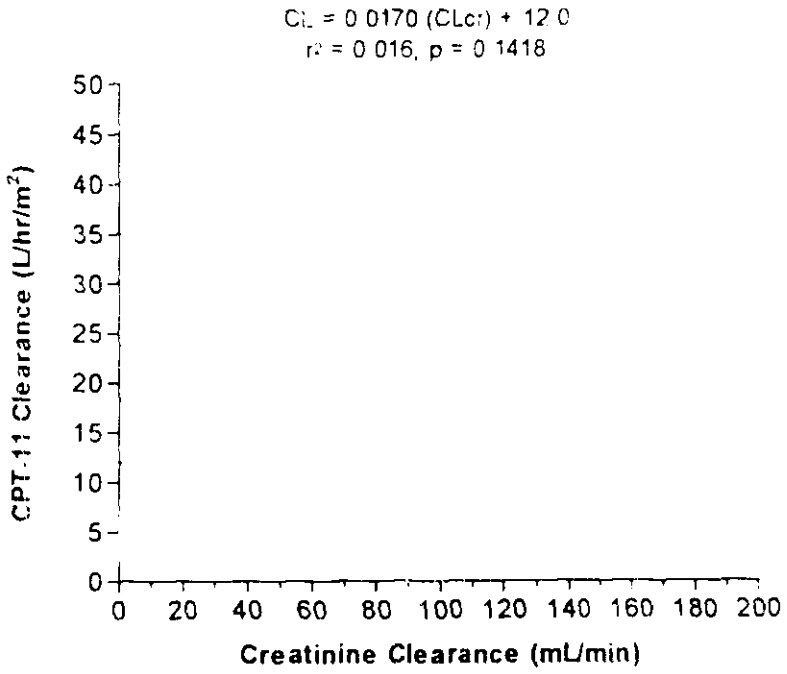
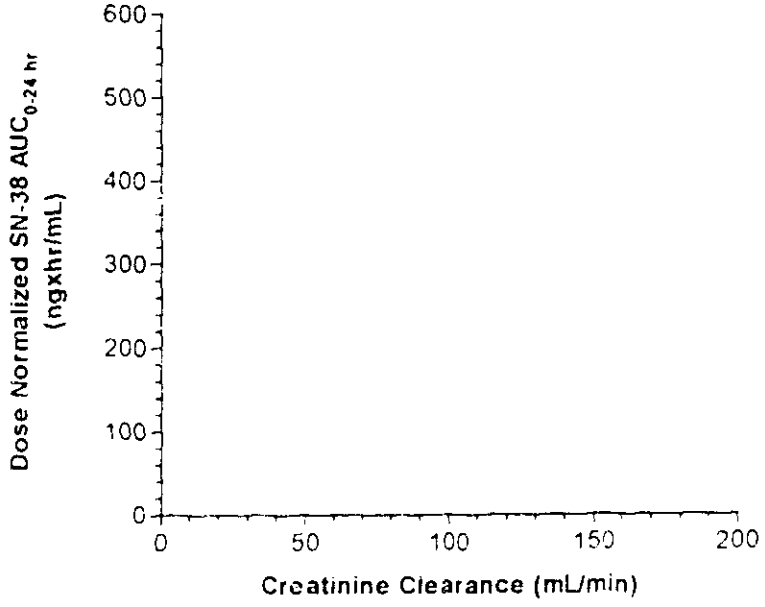


Figure 7. Relationship Between Dose-Normalized SN-38 AUC_{0-24} and Estimated Creatinine Clearance in Patients with Metastatic Colorectal Cancer (Protocol M/6475/0006)



(4) Influence of Hepatic Insufficiency

Since the liver is believed to be a major site for conversion of CPT-11 to SN-38 and for the subsequent conversion of SN-38 to its glucuronide form, the potential exists that hepatic dysfunction could result in altered drug clearance and plasma concentrations of either CPT-11 or SN-38. Formal investigations of CPT-11 and SN-38 pharmacokinetics in patients with severe hepatic impairment have not been undertaken. CPT-11 and SN-38 pharmacokinetics were evaluated in 125 patients with liver metastases and 37 patients without liver metastases in study M/6475/0006. CPT-11 and SN-38 AUC_{0-24} values (dose-normalized) were increased by 21% and 23%, respectively, in patients with liver metastases. A statistically significant, 20% reduction in the clearance of CPT-11 was also observed in these patients. These results are consistent with the hypothesis that hepatic dysfunction may impair the metabolism of both CPT-11 and SN-38. It should be noted that all patients in this study were required to have adequate hepatic function at study entry (i.e., serum total bilirubin $\leq$ 2 mg/dL and SGOT $\leq$ 3 times the upper limit of the normal range, unless the liver was involved with the tumor, in which case the SGOT value must have been $\leq$ 5 times the upper limit of the normal range)

b Drug-drug Interactions

Possible drug-drug interactions of irinotecan hydrochloride with concomitantly administered medications have not been formally investigated. However, the results of studies that describe the pharmacokinetics of CPT-11 and SN-38 in patients with cancer who have been treated with CPT-11 and other anticancer chemotherapeutic agents have been reported in the published literature. Possible interactions with two of these agents, 5-FU and cisplatin, have been suggested.

(1) 5-FU

Japanese investigators reported the results of a dose-escalation and pharmacologic study of CPT-11 in combination with 5-FU in patients with histologically confirmed metastatic colorectal cancer [15,16]. The pharmacokinetics of CPT-11 and SN-38 were determined in 12 patients after CPT-11 in doses ranging from 100 to 150 mg/m^2 was administered as a 90-minute continuous intravenous infusion on day 1. A fixed dose of 5-FU (400 mg/m^2) was given as a continuous infusion over 7 days. Steady-state concentrations of 5-FU were comparable to those reported by other investigators, suggesting that CPT-11 does not influence the pharmacokinetics of 5-FU. However, the area under the plasma concentration-time curve of SN-38 was significantly lower and the CPT-11 AUC was significantly higher during concomitant therapy with 5-FU when compared with historical data in patients who received monotherapy with CPT-11, suggesting that 5-FU might influence the metabolism of CPT-11 to SN-38. In view of the large interpatient variation in the pharmacokinetics of CPT-11 and SN-38 and that this study did not employ a crossover design, The Upjohn Company initiated a study (M/6475/0007) to evaluate the effect of 5-FU and leucovorin (LV) on the metabolism of CPT-11 to its active metabolite SN-38 and to determine the effect of the order of administration of CPT-11, 5-FU, and LV on pharmacokinetics and toxicity, and thereby defining the optimal dose and schedule for this three-drug combination. Pharmacokinetic analysis of plasma concentration data for the first 21 patients demonstrated that administration of CPT-11 immediately before or immediately after 5-FU/LV resulted in mean Cmax and AUC values for CPT-11 and SN-38 which were within 10% of corresponding values determined after the drugs were separated by 24 hours (i.e., CPT-11 alone) [17]. Concomitant administration of 5-FU/LV does not appear to alter the conversion of CPT-11 to SN-38 metabolite.

(2) Cisplatin

In a Japanese Phase I study [18], 14 patients with previously untreated lung cancer were treated with CPT-11 (60 to 90 mg/m^2) in combination with cisplatin (60 mg/m^2). Plasma pharmacokinetics of CPT-11 and SN-38 were determined in 10 patients, 7 received 80 mg/m^2 and 3 received 90 mg/m^2 CPT-11. A 57% increase in SN-38 AUC was observed after only a 12.5% (10 mg/m^2) increase in the CPT-11 dose. A pharmacokinetic interaction between CPT-11 and cisplatin was suggested since SN-38 AUCs tended to increase proportionately with dose intensification of CPT-11 from 50 to 125 mg/m^2 in a previous study conducted by the same investigators [19]. The pharmacokinetic interaction between these two agents is being investigated by Upjohn in study M/6475/0028.

3 Population Pharmacokinetics

CPT-11 plasma concentration data collected from patients enrolled in two Phase II clinical efficacy/safety studies (M/6475/0001 and M/6475/0006) were analyzed. Patients in both studies received CPT-11 administered as a 90-minute infusion once weekly for 4 consecutive weeks, followed by a 2-week rest period (one course). In protocol M/6475/0001, nine patients received a starting dose of 150 mg/m^2,

while the remaining 39 patients received a starting dose of 125 mg/m^2. In protocol M/6475/0006, the first 64 enrolled patients received a starting dose of 125 mg/m^2. The subsequently enrolled 102 patients received a 100-mg/m^2 starting dose. Dosage adjustments after the initial starting dose were made for each patient based on toxicity. Up to six blood specimens were collected from each patient on Week 1 and Week 3 of the first course of therapy. CPT-11 plasma concentration data were fit to a two-compartment model using the NONMEM computer program, version IV.

CPT-11 concentration data (1581 plasma concentrations) from 197 patients were used in the analysis. The patient population was 50.3% male and 49.7% female, with a mean age of 59.2 ± 12.4 years (range 25 to 84 years) and a mean weight of 75.7 ± 16.6 kg (range 43.1 to 121.7 kg). Systemic clearance (CL) of CPT-11 was 13.8 L/hr/m^2 (% SEM = 4.5%), volume of the central compartment (Vc) was 33.2 L/m^2 (% SEM = 7.7%), and volume of the peripheral compartment (V_p) was 60.7 L/m^2 (% SEM = 4.7%). The magnitude of interindividual variability (CV%) was 37.9%, 72.2%, and 28.8% for CL, Vc, and V_p, respectively. Residual variability of the plasma CPT-11 concentration data was 25.7%. The population pharmacokinetic parameter estimates were similar to those determined using non-compartmental analyses.

4 Pharmacodynamics

a Pharmacokinetics-Toxicity Relationships

The principal side effects observed with the administration of CPT-11 are neutropenia, leukopenia, and late (> 24 hours after administration of CPT-11) diarrhea. This section summarizes investigations to examine potential relationships between CPT-11 and/or SN-38 pharmacokinetic parameters and principal toxicities (i.e., late diarrhea or neutropenia) and antitumor response.

Evaluation of the relationship between CPT-11 and SN-38 pharmacokinetic parameters and late diarrhea, leukopenia, or neutropenia was carried out in three studies (M/6475/0001, M/6475/0006, and M/6475/0008).

In study M/6575/0001 patients were treated at a starting dose of 125 or 150 mg/m^2 intravenously over 90 minutes once weekly for 4 weeks, followed by a 2-week rest (one course) Dosage adjustments were made for each patient based on toxicity The maximum concentration and area under the concentration-time curve of CPT-11 did not reach statistical significance for either the intensity (i e , grade) of late diarrhea or neutropenia Both SN-38 C_{max} and AUC_{0-24} values correlated statistically with the intensity of neutropenia Similar positive correlations between these parameters and the intensity of late diarrhea were also observed, but only the correlations between pharmacokinetic parameters determined on Week 3 were statistically significant While correlations between SN-38 C_{max} and AUC_{0-24} and major toxicities were observed, there was considerable overlap in these parameters for patients experiencing grade 0 (none) to grade 4 (severe) late diarrhea and neutropenia Because of this variability, identification of patients who are at risk of experiencing severe diarrhea and neutropenia using pharmacokinetic endpoints appears impractical

In study M/6575/0006 patients were treated at a starting dose of 100 mg/m^2 or 125 mg/m^2 intravenously over 90 minutes once weekly for 4 weeks, followed by a 2-week rest (one course) Dosage adjustments were made for each patient based on toxicity The correlation between maximum concentration of CPT-11 and either the intensity (i e , grade) of late diarrhea or neutropenia did not reach statistical significance CPT-11 AUC_{0-24}, SN-38 C_{max}, and SN-38 AUC_{0-24} values demonstrated a positive correlation with both the intensity of late diarrhea and neutropenia during course 1 Although correlations between CPT-11 and SN-38 exposure (i e , C_{max} and AUC_{0-24}) and toxicity were observed, there was considerable overlap in exposure among patients who experienced grades 0 to 4 late diarrhea and neutropenia as depicted in Figures 8 and 9 As a result, these correlations are of limited value in predicting patients who are at risk of experiencing severe diarrhea and neutropenia

Figure 8. Relationship Between CPT-11 and SN-38 $AUC_{0\text{-}24}$ Values and Worst Grade of Late Diarrhea During the First Course of Therapy (Protocol M/6475/0006)

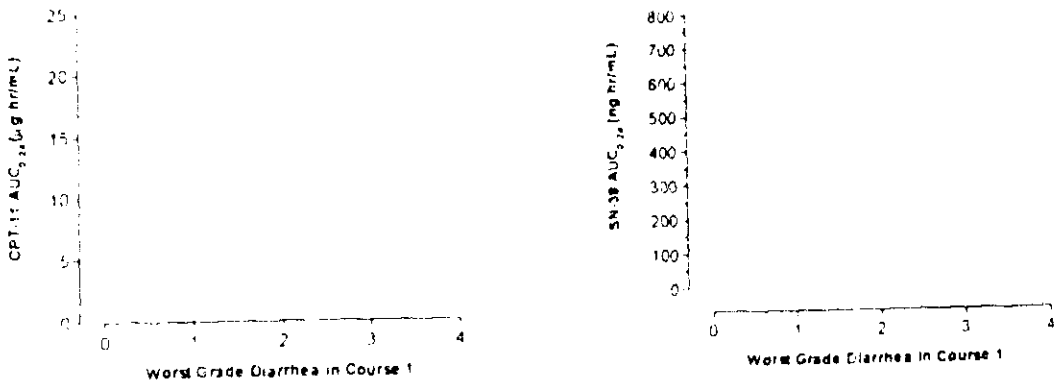
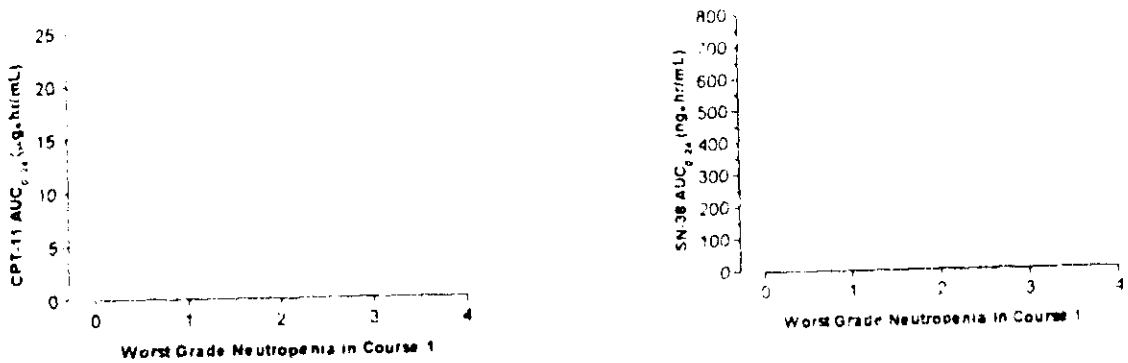


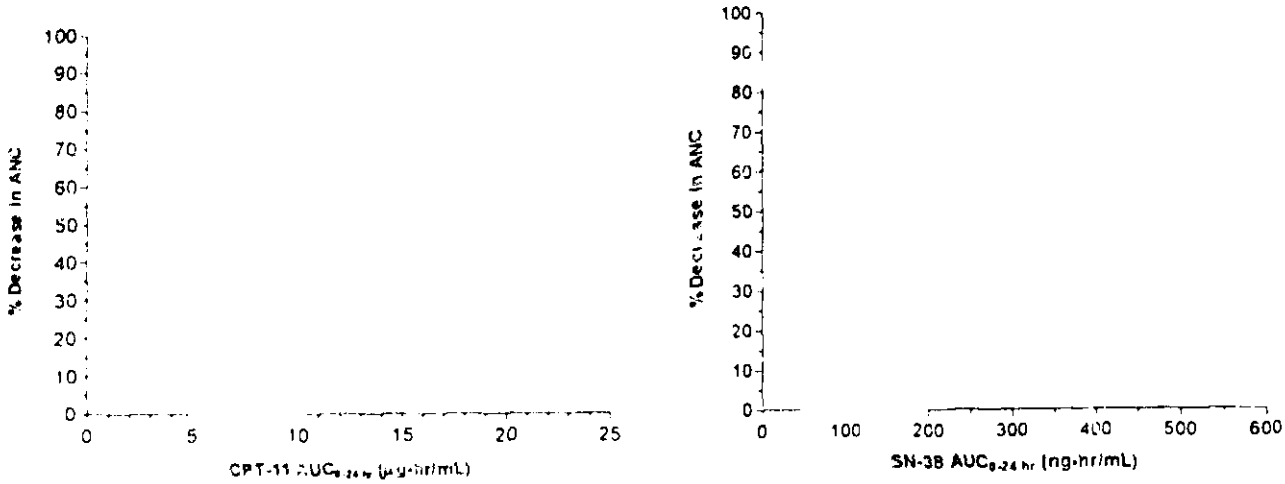
Figure 9. Relationship Between CPT-11 and SN-38 $AUC_{0\text{-}24}$ Values and Worst Grade of Neutropenia During the First Course of Therapy (Protocol M/6475/0006)



The percentage decrease in absolute neutrophil count versus $AUC_{0\text{-}24}$ for CPT-11 and SN-38 during course one were fitted to a sigmoidal E_{max} model. The model predicted that a CPT-11 $AUC_{0\text{-}24}$ of 6.64 µg•hr/mL and a SN-38 $AUC_{0\text{-}24}$ of 145 ng•hr/mL would result in a 50% decrease in absolute neutrophil count (see Figure 10). However, r^2 values were low (CPT-11: r^2=0.19, SN-38: r^2=0.24), demonstrating that greater than 75% of the variance in percentage decrease in neutrophil count appears to be due to factors other than variation in CPT-11 $AUC_{0\text{-}24}$ or SN-38 $AUC_{0\text{-}24}$.

Figure 19. Relationship Between CPT-11 and SN-38 AUC_{0-24} and Percentage Decrease in Absolute Neutrophil Count (ANC) During the First Course of Therapy in Patients with Metastatic Colorectal Cancer (Protocol M/6475/0006).

The dashed line represents the fit to a sigmoidal E_{max} model.



Gupta et al [26] have hypothesized that late diarrhea is associated with intestinal accumulation of SN-38 and that biliary concentrations of SN-38 may be predictive of gastrointestinal toxicity induced by CPT-11. An empiric pharmacokinetic parameter called the SN-38 "biliary index" was used as a measure of the extent of SN-38 secretion into the bile. Biliary index values, which were calculated by multiplying the relative AUC ratio of SN-38 to SN-38G by the CPT-11 AUC, were significantly greater in patients experiencing grade 3 to 4 diarrhea. Since glucuronidation represents the major detoxification pathway of SN-38, patients deficient in this enzyme activity may have a greater susceptibility to diarrhea. Additional studies to further evaluate the relationship between glucuronidation and CPT-11-induced gastrointestinal toxicity are in progress in larger patient populations.

b. Pharmacokinetics-Antitumor Response Relationships

CPT-11 and SN-38 pharmacokinetic parameters in responders (i.e., patients who demonstrated a partial or complete tumor response) and non-responders have been compared in two studies of patients with metastatic colorectal cancer that progressed or recurred after one previous 5-FU-based chemotherapeutic regimen. Eight of 35 patients with pharmacokinetic assessments in the first study (M/6475/0001) and 16 of 162 patients with pharmacokinetic assessment in the second study (M/6475/0006) demonstrated an objective antitumor response. In both studies, CPT-11 pharmacokinetic parameters were similar in the two groups of patients. Mean SN-38 AUC_{0-24} values were 30% (M/6475/0001) and 25% (M/6475/0006) higher in patients who demonstrated an antitumor response in these studies. While these results are consistent with the hypothesis that higher exposure (AUC_{0-24}) to SN-38 is more likely to produce an anticancer effect, the differences between the two groups were not statistically significant in either study.

Table 6. Summary of Pharmacokinetic Par[illegible] for CPT-11 in Clinical Pharmacokinetic Studies
Mean (St[illegible] Deviation)[a]

Protocol Number	CPT-11 Dose (mg/m^2)[b]	No. of Doses	No. of Evaluable Patients	AUC_{0-24} (µg•hr/mL)	Cmax (µg/mL)	Tmax (hr)	Half-life (hr)	CL (L/hr/m^2)	V_z (L/m^2)	Urinary Recovery[c] (% Dose)
Phase I Studies in Patients with Cancer										
M/6475/0026	100	1	3	4.70 (0.63)[d]	1.22 (0.24)	—[e]	3.9	21.5 (2.7)	104 (13)[f]	22 (6)[g]
	150	1	3	7.60 (2.01)[d]	1.42 (0.12)	—[e]	5.8	20.8 (6.0)	132 (20)[f]	26 (5)[g]
	200	1	3	10.6 (10.3)[d]	1.56 (0.59)	—[e]	3.9	27.7 (27.0)	151 (58)[f]	24 (3)[g]
	240	1	11	15.2 (7.41)[d]	2.57 (0.90)	—[e]	5.5	20.9 (17.5)	123 (16)[f]	37 (5)[g]
	290	1	8	17.0 (5.20)[d]	2.3[illegible] 0.96)	—[e]	6.7	21.1 (19.5)	209 (62)[f]	59 (15)[g]
	345	1	3	24.4 (16.1)[d]	3.05 (1.41)	—[e]	3.6	16.5 (10.9)	141 (79)[f]	72 (0)[g]
M/6475/0027	50	1	2	2.79 (0.11)[d]	0.89 (0.18)	—[e]	5.7 (0.4)	18.0 (0.7)	—[e]	9.70 (10.2)[h]
	80	1	2	7.18 (0.53)[d]	1.12 (0.36)	—[e]	8.3 (1.3)	11.2 (0.8)	—[e]	9.50 (0.85)[h]
	100	1	4	6.83 (0.42)[d]	1.29 (0.19)	—[e]	11.5 (6.0)	14.7 (0.9)[i]	—[e]	14.8 (6.50)[h,i]
	125	1	2	12.5 (6.80)[d]	1.70 (0.28)	—[e]	9.3 (5.9)	11.8 (6.4)	—[e]	21.3 (0.28)[h]
	150	1	4	8.44 (1.60)[d]	1.56 (0.27)	—[e]	9.0 (3.5)	18.4 (3.2)	—[e]	20.5 (13.0)[h]
	180	1	3	11.8 (0.94)[d]	1.97 (0.11)	—[e]	9.1 (3.0)	15.4 (1.2)	—[e]	—[e]

[a] Mean value used if no. patients >1
[b] Doses are based on irinotecan hydrochloride (CPT-11); drug was administered intravenously
[c] Urine collected for 48 hrs following dosing
[d] $AUC_{0-\infty}$
[e] Not calculated or reported
[f] Steady-state volume of distribution (mean ± SEM)
[g] Mean ± SEM
[h] Mean (±SD) determined from individual patient data in study report
[i] N = 3

Table 6. Summary of Pharmacokinetic Para[illegible] for CPT-11 in Clinical Pharmacokinetic Studies Mean (St[illegible] Deviation)[a]

Protocol Number	CPT-11 Dose (mg/m^2)[b]	No. of Doses	No. of Evaluable Patients	AUC_{0-24} (µg•hr/mL)	Cmax (µg/mL)	Tmax (hr)	Half-life (hr)	CL (L/hr/m^2)	V_z (L/m^2)	Urinary Recovery[c] (% Dose)
Phase I Studies in Patients with Cancer (continued)										
M/6475/0008	100	1	3	5.60 (0.967)[d]	—[e]	—[e]	—[e]	20.3 (4.37)	—[e]	—[e]
	120	1	6	5.03 (1.11)[d]	—[e]	—[e]	—[e]	24.9 (5.98)	—[e]	—[e]
	145	1	10	12.0 (6.79)[d]	—[e]	—[e]	—[e]	13.9 (5.98)	—[e]	—[e]
	175	1	2	14.5 (5.22)[d]	—[e]	—[e]	—[e]	12.9 (4.62)	—[e]	—[e]
DM111	50	1	3	3.55 (1.68)[d]	0.72 (0.26)	—[e]	5.8 (1.0)	—[e]	—[e]	—[e]
	100	1	4	14.2 (7.52)[d]	1.87 (0.51)	—[e]	7.2 (5.2)	—[e]	—[e]	—[e]
	165	1	5	21.46 (5.33)[d]	4.67 (2.38)	—[e]	5.0 (2.1)	—[e]	—[e]	16.9[f,h]
	250	1	5	27.86 (9.98)[d]	7.57 (6.85)	—[e]	5.0 (0.4)	—[e]	—[e]	17.1[g,h]
	350	1	1	44.7[d]	7.09	—[e]	6.1	—[e]	—[e]	—[e]
Phase II Studies in Patients with Colorectal Cancer										
M/6475/0001	125	1	26[i]	13.5 (3.66)	1.38 (0.304)	1.59 (0.099)	5.0	9.90 (3.91)	73.8 (36.5)	—[e]
	150	1	9[i]	17.1 (2.64)	1.73 (0.392)	1.59 (0.076)	5.3	8.60 (1.19)	68.6 (20.3)	—[e]
M/6475/0006	100	1	98[i]	8.20 (3.19)[j]	1.29 (0.488)	1.61 (0.223)	5.7[j]	13.2 (4.32)[j]	107 (29.4)[j]	—[e]
	125	1	64[i]	10.2 (3.27)[k]	1.66 (0.797)	1.68 (0.352)	5.7[k]	13.3 (6.01)[k]	110 (48.5)[k]	—[e]
M/6475/0010	125	1	18[i]	6.66 (1.89)[l]	1.38 (0.428)	1.54 (0.059)	6.4			

[a] Mean value used if no. patients >1
[b] Doses are based on irinotecan hydrochloride (CPT-11); drug was administered intravenously
[c] Urine collected for 48 hrs following dosing
[d] $AUC_{0-\infty}$
[e] Not calculated or reported
[f] N = 2
[g] N = 1
[h] Urine collected for 24 hrs following dosing
[i] Patients with pharmacokinetic assessment on week 1 of therapy
[j] N = 90
[k] N = 61
[l] N = 8

Table 7. Summary of Pharmacokinetic Parameters for S Clinical Pharmacokinetic Studies of CPT-11 Mean (Standard ı on)

Protocol Number	CPT-11 Dose[b] (mg/m²)	No. of Doses	No. of Evaluable Patients	AUC$_{0-\infty}$ (ng•hr/mL)	Cmax (ng/mL)	Tmax (hr)	Half-life (hr)	Metabolic Ratio (%)	Urinary Recovery[c] (% Dose)
Phase 1 Studies in Patients with Cancer									
M 6475 0026	100	1	3	163 (11.8)[d]	30.8 (10.0)	2.8 (0.2)	2.8	2.19[e]	—[f]
	150	1	3	239 (190)[d]	19.3 (13.5)	1.6 (0.1)	11.6	3.14[e]	—[f]
	200	1	3	253 (47.4)[d]	23.0 (13.5)	2.1 (0.5)	6.1	2.39[e]	—[f]
	240	1	11	274 (159)[d]	32.8 (12.3)	2.2 (0.2)	6.9	1.80[e]	—[f]
	290	1	8	404 (329)[d]	48.8 (39.5)	2.2 (0.2)	3.8	2.38[e]	—[f]
	345	1	3	664 (474)[d]	78.4 (66.8)	2.3 (0.03)	14.0	2.72[e]	—[f]
M 6475 0027	50	1	2	215 (35.6)[d]	26.4 (3.3)	—[f]	8.6 (2.8)	7.71 (0.98)[g]	0.21 (0.11)[g]
	80	1	2	322 (140)[d]	31.6 (18.5)	—[f]	16.1 (7.0)	4.42 (1.62)[g]	0.12 (0.04)[g]
	100	1	4	370 (234)[d]	34.4 (16.7)	[f]	17.0 (5.8)[h]	5.46 (3.65)[g]	0.26 (0.29)[g,h]
	125	1	2	450 (192)[d]	39.3 (4.7)	—[f]	12.6 (4.8)	3.74 (0.50)[g]	0.44 (0.11)[g]
	150	1	4	410 (282)[d]	36.7 (18.4)	[f]	15.4 (5.6)	4.56 (2.19)[g]	0.25 (0.18)[g]
	180	1	3	368 (83.8)[d]	26.2 (4.9)	[f]	28.0 (15.4)	3.11 (0.50)[g]	—[f]

[a] Mean value used if no. patients >1
[b] Doses are based on irinotecan hydrochloride (CPT-11); drug was administered intravenously
[c] Urine collected for 48 hrs following dosing
[d] AUC$_{0-\infty}$
[e] Calculated from mean CPT-11 and SN-38 AUC$_{0-\infty}$ values
[f] Not calculated or reported
[g] Mean (±SD) determined from individual patient data in study report
[h] N = 3

continued

Table 7. Summary of Pharmacokinetic Parameters for S Mean (Standard L ...) Clinical Pharmacokinetic Studies of CPT-11

Protocol Number	CPT-11 Dose[b] (mg/m²)	No. of Doses	No. of Evaluable Patients	$AUC_{0-\infty}$ (ng•hr/mL)	Cmax (ng/mL)	Tmax (hr)	Half-life (hr)	Metabolic Ratio (%)	Urinary Recovery[c] (% Dose)
Phase I Studies in Patients with Cancer (continued)									
M 6475 0008	100	1	3	102 (28)[d]	[e]	[e]	[e]	1.82	Mean 0.25[g]
	120	1	6	127 (45)[d]	[e]	[e]	[e]	2.52	
	5	1	10	271 (119)[d]	[e]	[e]	[e]	2.26	
	175	1	2	376 (6.29)[d]	[e]	[e]	[e]	2.59	
DM111	50	1	3	173 (92)[d]	21.0 (8.84)	[e]	11.4 (7.7)	4.87[f]	[e]
	100	1	4	581 (473)[d]	33.5 (13.3)	[e]	18.5 (9.6)	4.10[f]	[e]
	165	1	5	667 (484)[d]	49.0 (17.6)	[e]	12.2 (5.4)	3.11[f]	0.13[g,h]
	250	1	5	876 (672)[d]	72.3 (40.9)	[e]	13.9 (7.6)	3.14[f]	0.14[g,h]
	350	1	1	1120[d]	139	[e]	14.8	2.51[f]	[e]
Phase II Studies in Patients with Colorectal Cancer									
M 6475 0001	125	1	26	459 (218)	34.4 (15.0)	2.31 (0.960)	[e]	3.74 (2.37)[j]	[e]
	150	1	9	359 (112)	29.1 (13.6)	2.20 (0.892)	[e]	2.16 (0.781)	[e]
M 6475 0006	100	1	98	206 (104)[k]	21.8 (10.1)	2.17 (0.742)	9.8[l]	2.58 (1.10)[k]	[e]
	125	1	64	229 (108)[m]	26.3 (11.9)	2.21 (0.718)	9.8[n]	2.25 (0.799)[m]	[e]
M 6475 0010	125	1	18	90.8 (36.9)[o]	17.1 (7.18)	1.97 (0.811)	9.4[o]	1.31 (0.336)[p]	[e]

[a] Mean value used if no. patients >1
[b] Doses are based on irinotecan hydrochloride (CPT-11); drug was administered intravenously
[c] Urine collected for 48 hrs following dosing
[d] $AUC_{0-\infty}$
[e] Not calculated or reported
[f] Calculated from mean CPT-11 and SN-38 $AUC_{0-\infty}$ values
[g] Urine collected for 24 hrs following dosing
[h] N = 2
[i] N = 1
[j] N = 25
[k] N = 90
[l] N = 87
[m] N = 61
[n] N = 60
[o] N = 8
[p] N = 7

VI Phase IV Commitments and Labeling Revisions

1. Biliary index should be determined in patients with severe hepatic compromise.

The sponsor has submitted a protocol for the study of CPT-11, SN-38 and SN-38G disposition in individuals with severe hepatic compromise. This comment is to indicate why study of individuals with severe hepatic compromise is essential and to assure that such study is performed in a way that allows proper dosage and administration labeling to be constructed should the study results warrant such labeling.

Study M/6475/0008 shows a correlation between increasing biliary index and development of severe late diarrhea (p. 28 of this review). Biliary index is calculated as follows:

$$\text{AUC SN-38} \div \text{AUC SN-38G} \times \text{AUC CPT-11}$$

Changes in hepatic function have either been demonstrated to, or would be predicted to, impact on all three parameters used to determine biliary index:

A AUC SN-38 -- AUC SN-38 increases by 23% in patients with liver metasteses relative to patients without liver metasteses (study M\6475\0006, p. 23 of this review).

B AUC SN-38G -- The tissue responsible for formation of SN-38G has not been determined. However, since glucuronidation is most frequently accomplished hepatically, and the liver is likely the primary site of conversion of CPT-11 to SN-38 (see C. below), glucuronidation is likely accomplished in the liver. Thus, changes in liver function potentially alter SN-38G formation and thus AUC SN-38G.

C AUC CPT-11 -- Studies using *in vitro* tissue homogenates show that the liver is more effective at converting CPT-11 than any other tissue (p.15 of this review). Based on these data, the sponsor concludes that the liver is the primary site of conversion of CPT-11 to SN-38 (p.15 of this review, Sponsor's Proposed Labeling -- p. 3 of Appendix I of this review).

The population that will receive irinotecan post-approval is patients with colorectal cancer whose disease is refractory to 5-FU treatment. Individuals with severe hepatic compromise constitute part of this population, but no data on patients with compromised hepatic function appear in the NDA. Because changes in hepatic function either have been shown to or are predicted to impact disposition of CPT-11, SN-38 and SN-38G, and because changes in disposition (biliary index) appear to correlate with toxicity, the sponsor should determine the biliary index in patients with severe hepatic compromise.

Investigation of patients with severe hepatic compromise need not be accomplished by initiating a separate study. The sponsor might choose to modify the patient population of the planned phase III (accelerated approval commitment) study to include a sufficient number of individuals with severe hepatic compromise. Whatever plan is developed, it is important that patients be sampled with sufficient intensity that it will be possible to write detailed dosage and administration recommendations should the study results warrant such.

2. A mass balance study should be performed in humans, and an attempt to identify the chemical structure of the predominant metabolites of irinotecan present in urine and feces should be made. An attempt to characterize the ability of each predominant irinotecan metabolite to cause tumor regression, late diarrhea or neutropenia should be made.

Minimal mass balance information is contained in the NDA: two individuals had urine and bile measured for 48 hrs. -- 25 and 50% of the dose was recovered, respectively (p. 15 of this review). No attempt to identify species other than CPT-11, SN-38 and SN-38G in human plasma, urine or bile appears in the NDA. No sampling of human feces appears in the NDA. Thus, it is possibile that an undescribed molecular entity is present in high concentrations in circulating plasma. The following data is consistent with the presence of an unknown active metabolite:

i. In rodents, piperidinopiperidine is formed when CPT-11 is metabolized to SN-38 (pp. 14 - 15 of this review). CPT-11 is much more potent than SN-38 in inhibiting acetylcholinesterase (Upjohn study # 7256-94-145), leading to the speculation that the piperidinopiperidine moiety may have anti-cholinesterase activity and, if present in humans, cause diarrhea.

ii. Late diarrhea occurs with greater frequency and severity following doses late in a course than after the first dose of a course (see clinical review of this NDA). It is unlikely that this is due to CPT-11 or SN-38 accumulation, as no accumulation was noted in multiple dose studies M/6475/0006 and M/6475/0001 and the half-lives of CPT-11 and SN-38 are approximately 6 hrs and approximately 10 hrs, respectively. A tenable explanation of the observed effect is that an unknown metabolite accumulates and causes toxicity with later doses.

iii. The sponsor believes that it may be possible to increase dose intensity by dosing biweekly rather than weekly, and has submitted a protocol to investigate a biweekly dosage regimen. If the proposed study confirms the putative ability to increase dose intensity by using a biweekly regimen, the result could be explained by the presence of an unknown toxic metabolite that accumulates when irinotecan is dosed weekly but does not accumulate when irinotecan is dosed biweekly.

Acquisition of mass balance information would rule out the following:

i. The reason why a better correlation between PK and PD does not exist is because an undescribed active species is responsible for efficacy, toxicity or both. Dosage adjustment based upon concentration of this metabolite increases the safety or effectiveness or both of irinotecan.

ii. Dosage adjustment for patients with renal compromise may be necessary because toxicity from a unknown renally eliminated toxic metabolite may occur if such patients are dosed per the current dosage and administration labeling.

iii. Drug interactions between irinotecan and certain other concommittantly administered medications occur because an unknown metabolite of irinotecan and the concomittantly administered medications share the same metabolic path.

3. The ability of irinotecan, and predominant irinotecan metabolites, to act as substrate or inhibitor for human cytochromes P450 should be studied *in vitro*.

While there is no evidence to suggest that the conversion of irinotecan to SN-38 is mediated by the cytochrome P450 system, no investigation of the ability of CPT-11 to be metabolized to a species other than SN-38 was performed. No studies examining the ability of irinotecan metabolites to act as substrates or inhibitors of human cytochromes P450 were performed. The ability of irinotecan and predominant irinotecan metabolites to act as substrates or inhibitors of human cytochromes P450 should be studied *in vitro*. The information acquired will be useful in identifying potential drug interactions.

4. A search for protein binding interactions between SN-38 and medications frequently co-administered with irinotecan should be performed *in vitro*. A similar *in vitro* search for protein binding interactions between any highly protein bound metabolites identified in the recommended mass balance study (2. above) and medications frequently co-administered with irinotecan should also be performed.

SN-38 is highly (~95%) bound to plasma protein (p. 12 of this review). Performance of these protein binding studies will identify potential drug interactions.

Pharmacokinetics

After intravenous infusion of CAMPTOSAR in humans, irinotecan plasma concentrations decline in a multiexponential manner with a mean terminal elimination half-life of about 6 hours

(insert new sentences) Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of CAMPTOSAR

SN-38 area under the curve values are about 2 to 8% of those observed for irinotecan.

Pharmacokinetics

After intravenous infusion of CAMPTOSAR in humans, irinotecan plasma concentrations decline in a multiexponential manner with a mean terminal elimination half-life of about 6 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 hrs. The half-lives of the lactone (active) forms of irinotecan and SN-38 are similar to those of total irinotecan and SN-38, as the lactone and hydroxy acid forms are in equilibrium. Over the dose range of 50 to 350 mg·m^2, AUC of irinotecan increases linearly with dose. AUC of SN-38 increase less than proportionally with dose. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of CAMPTOSAR. SN-38 AUC values are about 2 to 8% of those observed for irinotecan.

original

Summary of Mean (± Standard Deviation) Irinotecan and SN-38 Pharmacokinetic Parameters in Patients With Metastatic Carcinoma of the Colon and Rectum

Dose (mg/m^2)	Irinotecan					SN-38		
	C_{max} (µg/mL)	AUC_{0-24} (µg•hr/mL)	$t_{½}$ (hr)	Varea (L/m^2)	CL ($L/hr/m^2$)	C_{max} (ng/mL)	AUC_{0-24} (ng•hr/mL)	$t_{½}$ (hr)
125 (N=64)	1 66 ± 0 797	10 2 ± 3 27	~~5-7~~	110 ± 48 5	13.3 ± 6.01	26 3 ± 11 9	229 ± 108	~~9-8~~

C_{max} - Maximum plasma concentration
AUC_{0-24} - Area under the plasma concentration-time curve from time 0 to 24 hours after the end of the 90-minute infusion
$t_{½}$ - half-life
Varea -
CL - Total systemic clearance

revised

Summary of Mean (± Standard Deviation) Irinotecan and SN-38 Pharmacokinetic Parameters in Patients With Metastatic Carcinoma of the Colon and Rectum

Dose (mg/m^2)	Irinotecan					SN-38		
	C_{max} (µg/mL)	AUC_{0-24} (µg•hr/mL)	$t_{½}$ (hr)	Varea (L/m^2)	CL ($L/hr/m^2$)	C_{max} (ng/mL)	AUC_{0-24} (ng•hr/mL)	$t_{½}$ (hr)
125 (N=64)	1 66 ± 0 797	10 2 ± 3 27	X ± s d	110 ± 48 5	13 3 ± 6 01	26 3 ± 11 9	229 ± 108	X ± s d

C_{max} - Maximum plasma concentration
AUC_{0-24} - Area under the plasma concentration-time curve from time 0 to 24 hours after the end of the 90-minute infusion
$t_{½}$ - terminal elimination half-life
Varea - Volume of distribution of terminal elimination phase
CL - Total systemic clearance

Distribution Irinotecan is extensively distributed to body tissues, estimates of the mean steady-state volume of distribution range from 105 L/m^2 to 266 L/m^2. Irinotecan exhibits moderate plasma protein binding (30 to 68% bound)

SN-38 is highly bound to human plasma proteins (approximately 95% bound) The major plasma protein to which irinotecan and SN-38 bind is albumin [4]

Metabolism The metabolic conversion of irinotecan to [insert phrase] SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver SN-38 subsequently undergoes conjugation to form a glucuronide metabolite

The disposition of irinotecan has not been fully elucidated in humans

Distribution Irinotecan is extensively distributed to body tissues, estimates of the mean steady-state volume of distribution range from 105 L/m^2 to 266 L/m^2. Irinotecan exhibits moderate plasma protein binding (30 to 68% bound) SN-38 is highly bound to human plasma proteins (approximately 95% bound) The major plasma protein to which irinotecan and SN-38 bind is albumin [4]

Metabolism and Excretion The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver SN-38 subsequently undergoes conjugation to form a glucuronide metabolite SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines in vitro

The disposition of irinotecan has not been fully elucidated in humans. The urinary excretion of irinotecan is 11 - 20%, SN-38 - 1%, and SN-38 glucuronide 3% The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of CAMPTOSAR in two patients ranged from approximately 25% (100 mg/m^2) to 50% (300 mg/m^2)

Pharmacokinetics in Special Populations

Geriatric

The terminal half life of irinotecan was 6 0 hours in patients who were 65 years or older and 5 5 hours in patients younger than 65 years [insert sentence]

Pediatric The pharmacokinetics of irinotecan have not been studied in the pediatric population

Gender The pharmacokinetics of irinotecan do not appear to be influenced by gender

Race The ~~potential~~ influence of race on the pharmacokinetics of irinotecan has not been evaluated

Hepatic Insufficiency The influence of hepatic insufficiency on the pharmacokinetic characteristics of irinotecan and its metabolites has not been formally studied

Renal Insufficiency

Drug-Drug Interactions

Possible pharmacokinetic interactions of CAMPTOSAR with other concomitantly administered medications have not been formally investigated

Pharmacokinetics in Special Populations

Geriatric The terminal half life of irinotecan was 6 0 hours in patients who were 65 years or older and 5 5 hours in patients younger than 65 years Dose-normalized $AUC_{0\text{-}24}$ for SN-38 in patients who were at least 65 years of age was 11% higher than in patients younger than 65 years No change in dosage and administration is recommended for geriatric patients

Pediatric The pharmacokinetics of irinotecan have not been studied in the pediatric population

Gender The pharmacokinetics of irinotecan do not appear to be influenced by gender

Race The influence of race on the pharmacokinetics of irinotecan has not been evaluated

Hepatic Insufficiency The influence of hepatic insufficiency on the pharmacokinetic characteristics of irinotecan and its metabolites has not been formally studied Among patients with known hepatic tumor involvement, irinotecan and SN-38 AUC values were approximately 20% higher than values for patients without liver metastases For patients having liver metastases without decreased hepatic function, no change in dosage and administration is recommended

Renal Insufficiency The influence of renal insufficiency on the pharmacokinetics of irinotecan has not been evaluated

Drug-Drug Interactions

Possible pharmacokinetic interactions of CAMPTOSAR with other concomitantly administered medications have not been formally investigated

NO FURTHER CHANGES

VII REFERENCES

The references cited are listed below, along with their location in the NDA. Publications included in the Upjohn Technical Reports are listed in italicized type beneath the corresponding report.

		VOL.	PAGE
1	Rivory LP, Chatelut E, Canal P, Mathieu Boue A, Robert J. Kinetics of the in vivo interconversion of the carboxylate and lactone forms of irinotecan (CPT-11) and of its metabolite SN-38 in patients. Cancer Res 1994;54(24):6330-3	1.37	6/2/231
2	Sasaki Y, Yoshida Y, Sudoh K, Hakusui H, Fujii H, Ohtsu T et al. Pharmacological correlation between total drug concentration and lactones of CPT-11 and SN-38 in patients treated with CPT-11. Jpn J Cancer Res 1995; 86(1):111-6	1.37	6/2/235
3	Fujii H, Sudo K, Yoshida H, Hakumizu H, Otsu M, Wakita H, Igarishi T, Ito K, Sasaki Y. Blood kinetics of the lactone form of CPT-11 and SN-38. Jpn J Clin Phamacol Ther 1994;25(1):55-6	1.37	6/2/241
4	Hakusui H, Atsumi R. Submitted by: Sindelar LB, Slatter JG. Metabolic fate of CPT-11: the chemical structure of the main metabolites in rat bile after a single intravenous dose. **Upjohn Technical Report 7256-94-114**, December 20, 1994 *Atsumi R, Suzuki W, Hakusui H. Identification of the metabolites of irinotecan, a new derivative of camptothecin, in rat bile and its biliary excretion. Xenobiotica 1991;21(9):1159-69*	1.38	6/3/7
5	Hakusui H, Suzuki W, Fujimaki M, Atsumi R. Submitted by: Guth D, Slatter JG. Metabolite profiles in bile and enterohepatic recirculation of [^{14}C]CPT-11 (U-101440E) following a single intravenous administration to male Wistar rats. **Upjohn Technical Report 7256-94-106**, November 15, 1994 *Atsumi R, Suzuki W, Hakusui H. Identification of the metabolites of irinotecan, a new derivative of camptothecin, in rat bile and its biliary excretion. Xenobiotica 1991;21(9):1159-69.*	1.38	6/3/44
6	Rivory LP, Robert J. Identification and kinetics of a β-glucuronide metabolite of SN-38 in human plasma after administration of the camptothecin derivative irinotecan. Cancer Chemother Pharmacol 1995;36:176-9	1.38	6/3/77

7 Kuhn JG Submitted by Schaaf LJ Pharmacokinetic evaluation of CPT-11 and SN-38 (protocol M/6475/0027, Besselaar protocol GfHBA-393B)
Upjohn Technical Report 7215-95-030,
September 29, 1995 — 1.39 — 6/4/7

Rothenberg ML, Kuhn JG, Burris HA, Nelson J, Eckardt JR, Tristan Morales M, et al Phase I and pharmacokinetic trial of weekly CPT-11 J Clin Oncol 1993;11(11):2194-204 — 1.37 — 6/2/210

8 Suzuki W, Hakusui H Submitted by Guth D, Yancey M In vitro human protein binding of CPT-11 (DQ-2805)
Upjohn Technical Report 7256-94-129,
January 23, 1995 — 1.41 — 6/6/373

9 Burke TG Submitted by Slatter JG Protein binding studies on CPT-11 (U-101440E) and SN-38 (U-101503)
Upjohn Technical Report 7256-94-138,
February 2, 1995 — 1.37 — 6/2/170

Burke TG, Munshi CB, Mi Z, Jiang Y The important role of albumin in determining the relative human blood stabilities of the camptothecin anticancer drugs J Pharm Sci 1995, 84(4):518-9

Burke TG, Mi Z The structural basis of camptothecin interactions with human serum albumin impact on drug stability J Med Chem 1994,37(1):40-6

Burke TG, Mi ZH Ethyl substitution at the 7 position extends the half-life of 10-hydroxycamptothecin in the presence of human serum albumin J Med Chem 1993,36:2580-2

10 Tsuji T, Kaneda N, Dado K, Yokokura T, Yoshimoto T Tsuru D Submitted by Slatter JG CPT-11 converting enzyme from rat serum purification and some properties
Upjohn Technical Report 7256-94-149,
February 7, 1995 — 1.38 — 6/3/169

Tsuji T, Kaneda N, Kado K, Yokokura T, Yoshimoto T, Tsuru D CPT-11 converting enzyme from rat serum purification and some properties J Pharmacobiodyn 1991;14(6):341-9

11	Kono A, Hara Y. Submitted by: Guth D, Slatter JG. Conversion of CPT-11 (CPT-101440E) into SN-38 in human tissues. **Upjohn Technical Report 7256-94-121**, January 18, 1995 *Kono A, Hara Y. Conversion of CPT-11 into SN-38 in human tissues. Jpn J Cancer Chemother 1991;18(12):2175-8*	1.37	6/2/123
12	Kawato Y, Aonuma M, Matsumoto K, Sato K. Submitted by: Slatter JG. Bioactivation of CPT-11 (IL-101440E) to the active metabolite SN-38 in vitro: Comparison of rat, dog and human tissues. **Upjohn Technical Report 7256-94-147**, February 15, 1995 *Kawato Y, Aonuma M, Matsumoto K, Sato K. Production of SN-38, a main metabolite of the camptothecin derivative CPT-11, and its species and tissue specificities. Yakubutsu Dotai 1991;6(6):899-907*	1.37	6/2/97
13	Lokiec F, Canal P, Gieschen C, Chatelut E, Armand JP, Roche H et al. Pharmacokinetics of irinotecan and its metabolites in human blood, bile, and urine. Cancer Chemother Pharmacol 1995;36(1):79-82	1.38	6/3/199
14	de Forni M, Bugat R, Chabot GG, Culine S, Extra JM, Gouvette A, et al. Phase I and pharmacokinetic study of the camptothecin derivative irinotecan, administered on a weekly schedule in cancer patients. Cancer Res 1994;54(16):4347-54	1.38	6/3/129
15	Sasaki Y, Ohtsu A, Shimada Y, Ono K, Saijo N. Simultaneous administration of CPT-11 and fluorouracil: alteration of the pharmacokinetics of CPT-11 and SN-38 in patients with advanced colorectal cancer. J Natl Cancer Inst 1994;86(14):1096-8	1.38	6/3/203
16	Shimada Y, Sasaki Y, Sugano K, Shirao K, Kondo H, Yokota T, et al. Combination Phase I study of CPT-11 (Irinotecan) combined with continuous infusion of 5-fluorouracil (5FU) in metastatic colorectal cancer. Proc Annu Meet Am Soc Clin Oncol, Abstract No. 575, 1993;12:196	1.38	6/3/206
17	Saltz L, Kanowitz J, Kemeny N, Kelsen D, Conti J, Batano D et al. Phase I trial of irinotecan (CPT-11), 5-fluorouracil (5FU), and leucovorin (LV) in patients with advanced solid tumors. Proc Am Soc Clin Oncol, Abstract No. 1546, 1995;14:476	1.38	6/3/207
18	Masuda N, Fukuoka M, Kudoh S, Kusunoki Y, Matsui K, Takifuji N, et al. Phase I and pharmacologic study of irinotecan in combination with cisplatin for advanced lung cancer. Br J Cancer 1993;68(4):777-82	1.38	6/3/137

19 Negoro S, Fukuoka M, Masuda N, Takada M, Kusunoki Y, Matsui K, et al. Phase I study of weekly intravenous infusions of CPT-11, a new derivative of camptothecin, in the treatment of advanced non-small cell lung cancer. J Natl Cancer Inst 1991;83(16):1164-8 . . . 1.38 6/3/208

20 Gupta E, Lestingi TM, Mick R, Ramirez J, EE, Ratain MJ Submitted by: Schaaf LJ. Metabolic fate of irinotecan in humans: correlation of glucuronidation with diarrhea (protocol M/6475/0008)
Upjohn Technical Report 7215-95-032,
September 25, 1995 . . . 1.39 6/4/1

Gupta E, Lestingi TM, Mick R, Ramirez J, Vokes EE, Ratain MJ. Metabolic fate of irinotecan in humans: Correlationof glucuronidation with diarrhea. Cancer Res 1994;54(14):3723-5 . . . 1.37 6/2/207

21 Kaneda N, Yokokura T. Submitted by: Guth D, Yancey MF. Pharmacokinetic study of CPT-11 (U-101440E) in male Wistar rats following single intravenous administration of 1 to 40 mg/kg
Upjohn Technical Report 7256-94-128,
April 12, 1995 . . . 1.37 6/2/34

Kaneda N, Yokokura T. Nonlinear pharmacokinetics of CPT-11 in rats [published erratum appears in Cancer Res 1990;50(14):4451]. Cancer Res 1990;50(6):1721-5

22 Staton BA. Determination of total U-101440 and total U-101503 in human plasma by HPLC with fluorescence detection. Upjohn Test/Assay 7256/101440-/01.1.
September 22, 1994 . . . 1.42 6/7/1

23 Bartlero I, Gandia D, Armand J-P, Mathieu-Boué A, Ré M, Gouyette A, et al. Submitted by: Yancey MF, Cohen DW Simultaneous determination of the camptothecin analogue CPT-11 and its active metabolite SN-38 by high-performance liquid chromatography: application to plasma pharmacokinetic studies in cancer patients
Upjohn Technical Report 7256-94-153,
February 6, 1995 . . . 1.38 6/3/81

Bartlero I, Gandia D, Armand JP, Mathieu-Boué A, Ré M, Gouyette A, et al. Simultaneous determination of the camptothecin analogue CPT-11 and its active metabolite SN-38 by high-performance liquid chromatography: application to plasma pharmacokinetic studies in cancer patients. J Chromatogr 1992;575(2):275-80

24	Kaneda N, Hagata H, Furuta T, Yokokura T Submitted by: Cohen DW, Slatter JG. Pharmacokinetics and metabolism of CPT-11 and metabolite SN-38 in mice following single intravenous administration **Upjohn Technical Report 7256-94-111,** December 29, 1994	1.37	6/2/22
	Kaneda N, Nagata H, Furuta T, Yokokura T. Metabolism and pharmacokinetics of the camptothecin analogue CPT-11 in the mouse [published erratum appears in Cancer Res 1990;50(14):4451]. Cancer Res 1990; 50(6):1715-20.		
25	Beijnen JH, Smith BR, Keijer WJ, Van Glijn R, tenBokkel Huinink WW, et al. High-performance liquid chromatographic analysis of the new antitumor drug SK&F 104864-A (NSC 609-699) in plasma. J Pharm Biomed Anal 1990;8:789-794	1.38	6/3/223
26	Hakusui H, Suzuki W. Submitted by: Yancey MF, Cohen DW. HPLC Method for the determination of CPT-11 and SN-38 in plasma. **Upjohn Technical Report 7256-94-150,** January 31, 1995	1.42	6/7/237
27	Yancey MF, Shobe EM. Stability of U-101440 (Irinotecan, CPT-11) and U-101503 (SN-38) under physiological and storage conditions encountered during lactone-specific assays. **Upjohn Technical Report 7256-95-053,** August 29, 1995	1.42	6/7/254
28	Hakusui H, Suzuki W, Atsumi R. Submitted by: Schaaf LJ Metabolic fate of CPT-11: phase I study of CPT-11 in cancer patients (study report DM111) **Upjohn Technical Report 7215-95-031,** September 25, 1995	1.39	6/4/172
	Taguchi T, Wakaui A, Hasegawa K, Nutani H, Furue H, Ohta K, et al. Phase I clinical study of CPT-11. Jpn J Cancer Chemother 1990;17(1):115-20	1.38	6/3/1
29	Bombardt PA. Interim report on the stability of total (ring-opened plus hydroxy-acid forms) irinotecan and its metabolite (U-101503) in human plasma under long term storage conditions at -20°C Upjohn memo to Schaaf LJ. September 12, 1995	1.42	6/7/383
30	Staton BA. Possible interference from co-administered drugs in irinotecan protocols. Upjohn Memo to PA Bombardt. April 28, 1995	1.42	6/7/392
31	Knuth DW. Irinotecan (CPT-11) method cross-validation data. Dr. Ross Donehower, Johns Hopkins. Protocol M/6475/0026 (GHBA - 392, JHOC - 9105) Upjohn memo to LJ Schaaf. October 25, 1995	1.42	6/7/394

32	Knuth DW. Irinotecan (CPT-11) method procedure and cross-validation data. Dr. John Kuhn, University of Texas Health Science Center - San Antonio (UTHSC-SA) Upjohn memo to LJ Schaaf. October 26, 1995	1.42	6/7/233
33	Schaaf LJ, Knuth DW, Antal EJ. A pharmacokinetic addendum to the phase II, open-label study of irinotecan hydrochloride (CPT-11) in patients with metastatic colorectal cancer not previously treated with chemotherapy or radiotherapy (M/6475/0010) **Upjohn Technical Report TR 7215-95-042**, October 20, 1995	1.42	6/7/18
34	Rowinsky E, Grochow L, Hendricks C, Sartorius S, ettinger D, McGuire W, et al. Phase I and pharmacologic study of topotecan (SK&F 104864): a novel topoisomerase I inhibitor. J Clin Oncol 10:647-656, 1992	1.38	6/3/213
35	Schaaf LJ, Knuth DW, Elfring GL. Pharmacokinetics of CPT-11 and SN-38: a multicenter, phase II study of irinotecan hydrochloride (CPT-11) in metastatic colorectal carcinoma refractory to previous 5-fluorouracil (5-FU)-based chemotherapy (M/6475/0001) **Upjohn Technical Report 7215-95-034**, October 23, 1995	1.39	6/4/198
36	Schaaf LJ, Ichhpurani AK, Elfring GL. Pharmacokinetics of CPT-11 and SN-38: a multicenter, open-label, phase II study of irinotecan hydrochloride (CPT-11) in patients with 5-fluorouracil (5-FU)-refractory colorectal cancer (M/6475/0006) **Upjohn Technical Report 7215-95-035**, October 24, 1995	1.40	6/5/1
37	Donehower RC. Submitted by: Schaaf LJ. Pharmacokinetics of CPT-11 and SN-38: phase I study of irinotecan hydrochloride administered every three weeks in selected patients with carcinoma (protocol M/6475/0026; Besselaar protocol GIIBA392B) **Upjohn Technical Report 7215-95-033**, September 29, 1995	1.39	6/4/69
	Rowinsky EK, Grochow LB, Ettinger DS, Sartorius SE, Lubejko BG, Chen TL, et al. Phase I and pharmacological study of the novel topoisomerase I inhibitor 7-ethyl-10-(4-(1-piperidino)-1-piperidino) carbonyloxycamptothecin (CPT-11) administered as a ninety-minute infusion every 3 weeks. Cancer Res 1994, 54(2):427-36	1.37	6/2/221

Interstitial chemotherapy with drug polymer implants for the treatment of recurrent gliomas

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✓ Malignant gliomas have been difficult to treat with chemotherapy. The most effective agent, BCNU (carmustine), has considerable systemic toxicity and a short half-life in serum. To obviate these problems, a method has been developed for the local sustained release of chemotherapeutic agents by their incorporation into biodegradable polymers. Implantation of the drug-impregnated polymer at the tumor site allows prolonged local exposure with minimal systemic exposure. In this Phase I-II study, 21 patients with recurrent malignant glioma were treated with BCNU released interstitially by means of a polyanhydride biodegradable polymer implant. Up to eight polymer wafers were placed in the resection cavity intraoperatively, upon completion of tumor debulking. The polymer releases the therapeutic drug for approximately 3 weeks.

Three increasing concentrations of BCNU were studied; the treatment was well tolerated at all three levels. There were no adverse reactions to the BCNU-wafer treatment itself. The average survival period after reoperation was 65 weeks for the first dose group, 64 weeks for the second dose group, and 32 weeks for the highest dose group. The overall mean survival time was 48 weeks from reoperation and 94 weeks from the original operation. The overall median survival times were 46 weeks postimplant and 87 weeks from initial surgery. Eighteen (86%) of 21 patients lived more than 1 year from the time of their initial diagnosis and eight (38%) of 21 patients lived more than 1 year after intracranial implantation of the polymer. Frequent hematology, blood chemistry, and urinalysis tests did not reveal any systemic effect from this interstitial chemotherapy.

Since the therapy is well tolerated and safe, a placebo-controlled clinical trial has been started. This trial will measure the effect of the second treatment dose on survival of patients with recurrent malignant gliomas.

KEY WORDS · **chemotherapy** · **brain neoplasm** · **glioma** · **BCNU** · **biodegradable polymer** · **drug delivery**

MALIGNANT gliomas, which account for about one-half of the 9000 new cases of primary brain tumors reported in the United States each year, remain refractory to treatment despite numerous attempts to provide effective forms of therapy.[3] The tumors progress rapidly and resection followed by external beam irradiation, the standard treatment, provides median survival times of less than 1 year after surgery.[20] Although some improvement in the number of long-term survivors has been obtained by administration of the nitrosourea BCNU (carmustine), its use has been limited by the systemic toxicity of the drug. Moreover, BCNU has a serum half-life ($t_{1/2}$) of only 15 minutes, further limiting its usefulness.[1] For these reasons, we sought a different means of supplying the drug more directly to the tumor. In this regard, we took advantage of the observation that recurrence of these tumors is usually observed within 2 cm of the initial tumor margin.[2] We therefore developed a biodegradable polymer as a suitable vehicle for incorporating various chemotherapeutic agents and delivering them directly to the site of the tumor.

[illegible] carboxyphenoxypropane (PCPP) and sebacic acid (SA) in a ratio of 20:80 [illegible] can be produced in a variety of forms including wafers, microspheres, and rods[illegible] The BCNU can be incorporated into the matrix, which is biodegradable, and hence the active agent is protected from hydrolysis. In preclinical studies we showed: first, that PCPP:SA was biocompatible and could be implanted safely in the brain of rodents and primates;[illegible] second, that BCNU could be released in a sustained and controlled manner;[illegible] and third, that there is significant diffusion of "active BCNU" released from polymers[illegible] and that this form of delivery could inhibit the growth of an experimental malignant glioma in rats.[illegible] Based on these results, we proceeded with a Phase I trial.

We describe here our first study of the administration of BCNU, incorporated into biodegradable polymer wafers, to patients with recurrent tumors. The drug/polymer wafers were implanted at the tumor site after resection of the tumor. The objectives of the study were to determine the safety of increasing doses of BCNU with the polymer in such patients and to establish the feasibility of this novel form of treatment.

Clinical Material and Methods

Patient Population

Patients with recurrent malignant glioma, verified by imaging scans and clinical evaluation, were candidates for enrollment in the study. The inclusion criteria were: an indication for reoperation, that is, the presence of a unilateral single focus of tumor in the cerebrum showing at least a 1.5-cu cm enhancing volume on computerized tomography (CT) scanning; a Karnofsky Performance Scale (KPS)[illegible] score of at least 60 (indicating ability to function independently) at the time of enrollment; one course of external beam radiation therapy; and no chemotherapy during the 6 weeks before enrollment. In addition, each surgeon had independently determined that another resection would be in the patient's best interest.

Written informed consent was obtained from all patients. The treatment protocol was approved by the Food and Drug Administration and the appropriate institutional review boards at each study center.

BCNU Wafers

The polyanhydride polymer used in this study was Biodel polymer, a copolymer of PCPP:SA, prepared [illegible] methods described elsewhere.[illegible] The polymer and BCNU were co-dissolved in [illegible] and spray-dried into microspheres [illegible]. The microspheres were pressed into [illegible] and 3.0 mm thick by compression molding [illegible] aluminum foil pouches [illegible] and sterilized by 2.2 megarad [illegible].

Trial Design

All patients underwent baseline examination, KPS score determination, and CT with and without contrast enhancement. A craniotomy was then performed for maximum resection of tumor. A fresh-frozen or squash sample of suspected tumor was sent for histological examination; the pathologist's report of malignant glioma was the final admission criterion for the study. Formalin-sized paraffin-embedded blocks were prepared for formal pathological evaluation and slides were sent to the referee neuropathologist (P.C.B.).

After removal of the tumor, wafers were placed on the resection surface to cover as much tissue as possible. Up to eight wafers were used according to the size of the resection cavity, and overlapping was permitted. Sheets of oxidized regenerated cellulose (Surgicel) were occasionally used to secure the polymers against the brain. After wafer placement, the dura was closed, the craniotomy bone was replaced, and the scalp was closed in a conventional manner.

For assessing toxic effects (local and systemic) of interstitial BCNU release, patients were followed for the first 7 weeks by neurological examination, KPS score determination, hematological and blood chemistry testing, and urinalysis. Contrast-enhanced and noncontrast CT scans or magnetic resonance (MR) images were obtained within 1 to 2 days postoperatively and again at 14 and 49 days.

All brain imaging studies (CT for all but one patient who underwent MR imaging) were reviewed by a referee neuroradiologist. They were analyzed to evaluate tumor size and possible local reactions to the treatment.

Dosages and Administration

The three groups with increasing amounts of BCNU were studied sequentially; when one treatment group had demonstrated tolerance of the treatment, the next drug dosage group was started. A modified Fibonacci scale was used to determine the appropriate increase in dose.[illegible] For Group 1, 25 μg BCNU/sq mm of polymer (1.93% BCNU loading) yielded 3.85 mg of BCNU/wafer for a maximum dose of 31 mg. For Group 2, 50 μg BCNU/sq mm of polymer (3.85% of BCNU loading) yielded 7.7 mg of BCNU/wafer for a maximum dose of 62 mg. For Group 3, 82.5 μg BCNU/sq mm of polymer (6.35% of BCNU loading) was utilized to yield 12.7 mg BCNU/wafer for a maximum patient dose of 102 mg.

Statistical Methods

Dosage groups were compared with respect to the demographic variables of patient age, weight, and height by use of the Kruskal-Wallis test. The groups were also compared with regard to sex and race, by use of a chi-square contingency table analysis.[illegible]

The dosage groups were compared by the Kruskal-Wallis test at baseline and at each subsequent visit with respect to a standardized detailed neurological exami-

and the KPS score. At each visit the change baseline was computed for each patient. Within each treatment group, the significance of this change was determined by the Wilcoxon paired-sample test while the treatment groups were compared by the Kruskal-Wallis test. Survival curves were determined for each treatment group by the Kaplan-Meier method while the treatment groups were compared by the log rank test (Mantel-Cox) and the generalized Wilcoxon test (Breslow).

The change from baseline data of hematology, blood chemistry, and urinalysis results was computed for each patient. For each treatment group, the significance of the change from baseline at each visit was determined by the Wilcoxon paired-sample test. The treatment groups were compared using the Kruskal-Wallis test. The results were considered to be statistically significant if the two-sided p value was 0.05 or less.

Results

Patients

Twenty-one patients entered the study between September, 1987, and July, 1988. Five patients were treated with 3.85 mg of BCNU/wafer (Group 1), five with 7.7 mg of BCNU/wafer (Group 2), and 11 with 12.7 mg BCNU/wafer (Group 3). Most of the patients received all eight polymer implants.

significant differences were found among treatgroups for age (average 48.6 years), body weight and height, sex, race, baseline KPS score, or interval since initial surgery (average 46 weeks). In the first two treatment groups, 60% had glioblastomas, whereas all of the patients in the third treatment group initially had glioblastomas. Tumor volumes were not significantly different among treatment groups.

Ten patients had previously received various types of chemotherapy including BCNU, CCNU (lomustine), cisplatin, and alpha-interferon. In addition, one patient from treatment Group 3 had received ^{125}I implants.

Neurological and Karnofsky Examinations

Patients were generally in good condition on enrollment. The mean KPS scores for Groups 1 to 3 were 82, 86, and 82, respectively. Immediately following surgery, most patients showed a drop in both neurological function and KPS score, reflecting the immediate consequences of craniotomy and tumor removal. Within 2 weeks, however, most had improved their neurological and KPS scores to preoperative values and these remained stable through Day 49 of the study, with mean KPS scores for Groups 1 to 3 of 84, 86, and 72, respectively.

A significant difference among treatment groups was found for changes in visual acuity at 14, 28, and 49 days after surgery. Three patients in Group 3, with tumors located in the occipital lobe, had disturbances on at baseline examination. These disturbances ed after surgery, contributing largely to the statistically significant differences observed. No other neurological component and no KPS showed statistically significant differences either within a group (change from baseline values) or between groups.

Laboratory Tests

No patients had a significant reduction in blood cell counts that would indicate systemic exposure to BCNU. Moreover, blood chemistry and urinalysis did not show evidence of renal or hepatic toxicity. Hyperglycemia and glycosuria were observed, but these could be attributed to the large amounts of corticosteroid used in treating these patients.

Tumor Response

In 13 of the 21 patients evenly distributed among treatment groups, scans obtained on Days 14 and 49 of the study revealed a distinct thin ring and areas of contrast enhancement. In about one-half of these patients, most of the enhancing effect resolved within 7 weeks; in the other patients it persisted or increased. Clinical and neurological evaluation did not reveal any correlation between the occurrence or development of contrast enhancement and any sign or symptom of toxicity. Thus, despite sometimes marked increases in enhancement, there was minimal net mass effect. Vague outlines of wafers in or near the original placement sites could be seen on noncontrast and contrast-enhanced CT scans obtained postoperatively (Fig. 1) and, in some patients, at intervals up to 49 days following surgery.

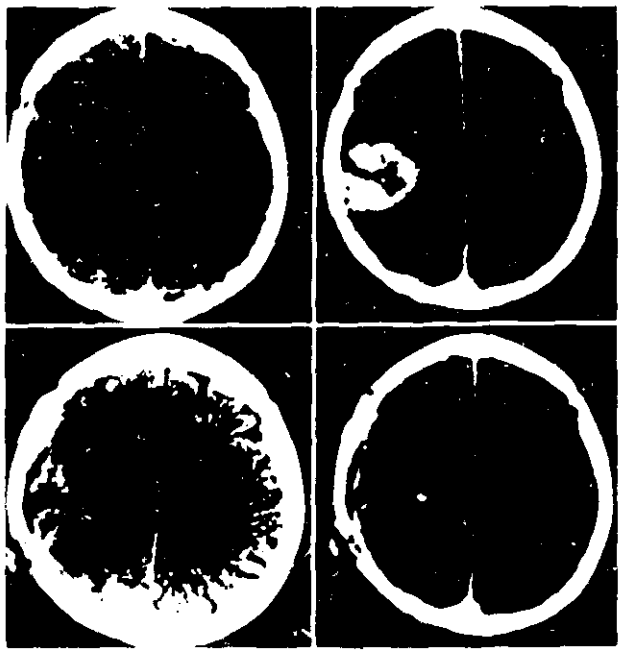

FIG. 1. *Upper*: Preoperative computerized tomography (CT) scans, without (*left*) and with (*right*) contrast enhancement. *Lower*: Postoperative CT scans, without (*left*) and with (*right*) contrast enhancement. Polymer wafers appear as bright white lines along the resected tumor-bed surface.

[illegible] implant survival times for Groups 1–3 were [illegible] of [illegible] 64, and 32 weeks, respectively, [illegible] survival times of 65, 47, and 23 weeks, [illegible]. The overall mean period of survival was [illegible] weeks from implantation and 94 weeks from the [illegible] operation. The overall median survival times [illegible] weeks from implant surgery and 87 weeks from [illegible] surgery. Clinically and radiologically, patients in this series who died had recurrence of tumor or other tumor-related events. At last evaluation (March 1, [illegible]) two patients were still alive after surviving 109 and 125 weeks. There were no significant differences in period of survival of the four patients with anaplastic astrocytoma as compared to the overall group.

[illegible]

The expected course of events for postoperative neurosurgical patients was observed and no medical occurrences appeared to result from the polymer implants. *Ten patients underwent reoperations during the course of this study:* two patients in Group 1; three patients in Group 2, an average of 21 weeks postimplant; and five patients in Group 3, an average of 17 weeks postimplant. Interstitial radioactive seeds were implanted in one Group 1 patient at 68 weeks and in one Group 3 patient at 23 weeks. One patient in Group 1 underwent a contralateral craniotomy for placement of interleukin-2 (IL-2) at 50 weeks after polymer implantation.

The principal finding at reexploration was necrotic tissue, similar to that reported following interstitial radiation treatment. Removal of the necrotic tissue generally proved beneficial.

Eight patients had seizures during the study; all of these had a preexisting tumor-related seizure disorder. Six patients experienced cerebral edema during the study, as is typical for postoperative craniotomy patients, *and all received postsurgical corticosteroid treatment.* There were no significant differences between the three groups regarding steroid requirements of patients. At baseline examination, the average steroid (dexamethasone) dose was 21 mg 1 day prior to implantation, [illegible] mg on Day 7, and 7 mg on Day 49.

[illegible]

The opportunity was taken at autopsy or at reoperation to examine resection sites for the presence of wafer remnants. Small, amorphous, semi-solid fragments of *polymer were found at reoperation in Group 2 patients.* One patient from Group 3, who died 6 weeks after implantation, was found at autopsy to have [illegible] with discs similar in size but flexible [illegible] than the original wafers. Three other [illegible] underwent autopsy or reoperation [illegible] weeks after implantation had persistent [illegible]. No BCNU was detected in any of the [illegible] that did not yet [illegible] anhydride bonds present. It is likely that this material was a degraded remnant of the BCNU-polyanhydride complex. Subsequent review did not show any correlation between the persistence of polymer remnants and the occurrence of specific neurological signs in individual patients.

Postmortem Examination

Four brains were examined postmortem. At least one whole-brain histological section taken through the tumor bed was prepared from each case. The cause of death *in each of the four patients could be attributed* to a massive recurrent neoplasm which, in all cases, extended into the opposite cerebral hemisphere via the corpus callosum. In three of the patients, a gliosarcoma was present. This was only a focal finding in two of the lesions but was of sufficient size to exert considerable mass effect in the third case. There was extensive necrosis throughout much of all four neoplasms; however, this did not appear excessive for these malignant neoplasms with their history of radiotherapy. Neither parenchymal necrosis nor vascular fibrinoid necrosis was noted in the surrounding nontumor-bearing brain.

Discussion

Drug Delivery to the Brain

We have demonstrated that a biodegradable polymer implant can be used safely to release a therapeutic drug to treat human brain tumors. This approach goes a step beyond previous attempts to increase exposure of such tumors to BCNU. Examples of these previous approaches include high-dose intravenous BCNU with bone marrow salvage,[25] BCNU infusion after osmotic disruption of the blood-brain barrier,[29] perioperative use of BCNU,[5] and selective intra-arterial infusion of BCNU to the affected hemisphere.[18] Although BCNU is lipid-soluble and readily crosses the blood-brain barrier, it rapidly decomposes in the bloodstream ($T_{1/2}$ 15 minutes), which detracts from the usefulness of these methods. Direct comparison of intracranial and intraperitoneal BCNU polymer implants shows a 113-fold increase in brain exposure to BCNU by using a brain implant.[34]

Wolpert, *et al.*,[33] and Harbaugh, *et al.*,[7] delivered BCNU directly into the tumor resection cavity by a catheter system. This approach is limited by the rapid decomposition of BCNU in aqueous solution. The polyanhydride polymer used for the BCNU wafers is sufficiently hydrophobic to protect the BCNU until it is released into the tumor environment.[14]

Systemic Exposure

A major advantage of local interstitial chemotherapy is the ability to avoid dose-limiting systemic side effects. In this study, patients treated with eight wafers received intracranial doses of about 30 mg, 60 mg, or 100 mg of BCNU, depending on the treatment group. By comparison, the standard single intravenous dose of BCNU is 200 mg. The systemic doses cause enough toxicity so

long recovery intervals are needed between courses limiting the usefulness of systemic treatment. No systemic side effects were attributed to the BCNU wafers nor were there any toxic effects on blood cells electrolytes, or other organs. This high degree of tolerance is remarkable considering the relatively large amounts of drug released directly into the tumor and surrounding central nervous system.

Local Effects in the Brain

Some local effects of the drug were observed. A variable enhancing effect on CT was found in 13 of the 21 patients. The enhancement was similar to that observed with other local treatments (interstitial radiation[1] and intratumoral IL-2[2] and hyperthermia[3]) where a central zone of nonenhancing lucency is located within a ring-shaped area of irregular enhancement. Despite enhancement, mass effect was minimal and spontaneous resolution was observed in some patients about 3 months after surgery. Not surprisingly, local tumor destruction was associated with some localized tissue necrosis; therefore, some patients underwent reoperation because of increasing mass effect (as demonstrated by deterioration in neurological function requiring increasing corticosteroids and by increasing enhancement on CT scanning or MR imaging). Mostly necrotic material was found at reoperation at distances 0 to 1 cm from the tumor resection surface. With removal of the necrotic material, the neurological condition of the patients generally improved.

Survival Times

Survival of patients in the groups with a lower BCNU concentration appeared to be greater than for patients in the highest dose group (Group 3), although definitive conclusions cannot be drawn regarding treatment efficacy because of the small number of patients, differences in tumor type, and lack of cohort control. Harsh, *et al.*,[4] and Ammirati, *et al.*,[5] have reported the median survival time of patients following reoperation for malignant glioma as 36 weeks. In the present study, eight of 10 patients in the first two treatment groups survived beyond 36 weeks; the mean survival times at the cutoff date were 65 and 64 weeks, respectively. In Group 3, which consisted entirely of patients with glioblastomas, only four of 11 patients survived longer than 36 weeks. The overall mean survival time was 48 weeks from implantation and 94 weeks from the original operation. The overall median survival time was 46 weeks from implantation and 87 weeks from initial operation.

Conclusions

This is the first study in a clinical program that explores the intracranial delivery of a chemotherapeutic agent via a biodegradable carrier system. The results show that this novel approach to the treatment of brain tumors is feasible and safe. A placebo-controlled randomized clinical trial is currently under way at 29 centers in the United States and Canada to determine the effect on survival of supplying 3.85% BCNU in biodegradable polymers as treatment for recurrent malignant glioma. Because the treatment is so well tolerated, numerous agents may be incorporated into the polymers. This approach may prove to be a therapeutic advance for a variety of central nervous system diseases.

Acknowledgments

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References

1. Ammirati M, Galicich JH, Arbit E, *et al*: Reoperation in the treatment of recurrent intracranial intraparenchymal tumors. **Neurosurgery 21**:607–613, 1987
2. Barba D, Saris SC, Holder C, *et al*: Intratumoral LAK cell and interleukin-2 therapy of human gliomas. **J Neurosurg 70**:175–182, 1989
3. Bindschnedler C, Leone KW, Marchevsky E, *et al*: Polyanhydride microspheres for implantation by solvent evaporation. **J Pharm Sci 77**:696–698, 1988
4. Brem H: Controlled release polymeric systems for effective delivery to the brain. **Polymer Preprints 31**:[illegible] (Abstract)
5. Brem H: Polymers to treat brain tumors. **Biomaterials** (In press) 1990
6. Brem H, Kader A, Epstein JI, *et al*: Controlled delivery of 1,3-bis(2-chloroethyl)-1-nitrosourea from ethylene-vinyl acetate copolymer. **Select Cancer Ther 5**:55–65, 1989
7. Brem H, Tamargo RJ, Olivi A: Delivery of drugs to the brain by use of a sustained release polymer system. In Salem H (ed): **New Technologies and Concepts for Reducing Drug Toxication**. Caldwell, NJ: Telford Press, 1990 (In press)
8. Butti G, Knerich R, Tanghetti B, *et al*: Perioperative carmustine chemotherapy for malignant brain tumors. **Cancer Treat Rep 68**:1505–1506, 1984
9. Chasin M, Domb A, Ron E, *et al*: Polyanhydrides as drug delivery systems. In Langer R, Chasin M (eds): **Biodegradable Polymers as Drug Delivery Systems**. New York: Marcel Dekker, 1990, pp 43–70
10. Chasin M, Lewis D, Langer R: Polyanhydrides for controlled drug delivery. **Biopharm Manufact 1**:33–46, 1988
11. Domb A, Langer R: Preparation of high molecular weight polyanhydride. **J Polymer Sci 25**:3373–3386, 1987
12. Domb A, Langer R: Polyanhydrides for controlled drug delivery. **Makromol Chem Macromol Symp 19**:189–200, 1988
13. Domb A, Ron E, Langer R: Polyanhydride II: one step polymerization using phosgene or diphosgene as coupling agents. **Macromolecules 12**:1925–1929, 1988
14. Grossman SA, Rienhard CS, Brem H, *et al*: The intracerebral delivery of BCNU with surgically implanted biodegradable polymers: a quantitative autoradiographic study. **Proc Am Soc Clin Oncol 7**:284, 1988 (Abstract)
15. Harbaugh RE, Saunders RL, Reeder RF: Use of implantable pumps for central nervous system drug infusions to

Neurosurgery 2[illegible]

[illegible] *PH, et al. Regenerat[illegible]*

[illegible] *Proc (1989) astrocytoma*

Neurosurgery 21[illegible]

[illegible] *Y. Vasogenicity of radiotherapy*

Neurology 30[illegible] (1980)

[illegible] *PC, Boss DO, et al. The rationale*

[illegible] *intra-arterial chemotherapy with*

[illegible] *glioblastoma. J Neurosurg 63:*

[illegible]

[illegible] *DV, Abramian WH, Craver EE, et al. Nitrogen*

[illegible] *Hodgkins disease. Lancet I:889–901, 1947*

PJ, Walker M. Chemotherapy for malignant

[illegible] **J Neurosurg 68**:[illegible] 1988

PP, Good RR, Jones EO, et al. Contrast-enhance-

[illegible] *computed tomography ring in glioblastoma after*

[illegible] *intraoperative endocurietherapy. Cancer 61*:[illegible]

[illegible]

KW, Brott BC, Langer R. Bioerodible polyanhy-

[illegible] *drides as drug-carrier matrices. I. Characterization, deg-*

[illegible] *radation and release characteristics. J Biomed Mat Res*

19:[illegible] 1985

KW, D'Amore P, Marletta M, et al. Bioerodible

[illegible] *polyanhydrides as drug-carrier matrices. II. Biocompati-*

[illegible] *bility and chemical reactivity. J Biomed Mat Res 20:*

[illegible] 1986

KW, Simonte V, Langer R. Synthesis of polyanhy-

[illegible] *drides: melt-polycondensation, dehydrochlorination, and*

[illegible] *dehydrative coupling. Macromolecules 20*:705–712,

[illegible]

H, Dion RL, Sykes RJ, et al. The antitumor agent

[illegible] *bis(2-chloroethyl)-1-nitrosourea. J Pharm Sci 55:*

[illegible] 1966

Mathiowitz E, Langer R. *Polyanhydride microspheres as*

[illegible] *drug carriers. J Controlled Release 5*:13–22, 1987

Mathiowitz E, Saltzman M, Domb A, et al. Polyanhydride

[illegible] *microspheres as drug carriers. II. Microencapsulation by*

[illegible] *solvent removal. J Appl Polymer Sci 35*:[illegible]

Meredith EK, Selby PJ, Perren TJ, et al. High-dose BC[illegible] *chemotherapy with autologous bone marrow transplantation and full dose radiotherapy for grade IV astrocytoma. Br J Cancer 58*:779–782, 1988

Neuwelt EA, Howieson J, Frenkel EP, et al. *Therapeutic* efficacy of multiagent chemotherapy with drug delivery *enhanced by blood-brain barrier modification in glioblastoma.* **Neurosurgery 19**:573–582, 1986

Penta JS, Rosencweig M, Guarino AM, et al. *Mouse and large-animal toxicology studies of twelve antitumor agents: relevance to starting dose for Phase I clinical trials.* **Cancer Chemother Pharmacol 3**:97–101, 1979

Tamargo RJ, Epstein JI, Reinhard CS, *et al. Brain biocompatibility of a biodegradable controlled release polymer in rats. J Biomed Mat Res 23*:253–266, 1989

Willis BK, Heilbrun MP, Sapozink MD, et al. Stereotactic interstitial brachytherapy of malignant astrocytomas with *remarks on postimplantation computed tomographic appearance.* **Neurosurgery 23**:348–354, 1988

Wolpert SM, Swan ES, Heros D, et al. Selective delivery of chemotherapeutic agents with a new catheter system. **Radiology 166**:547–549, 1988

Yang MB, Tamargo RJ, Brem H. Controlled delivery of 1,3-bis(2-chloroethyl)-1-nitrosourea from ethylene-vinyl acetate copolymer. **Cancer Res 49**:5103–5107, 1989

Zar JH. **Biostatistical Analysis.** *Englewood Cliffs, NJ:* Prentice Hall, 1984

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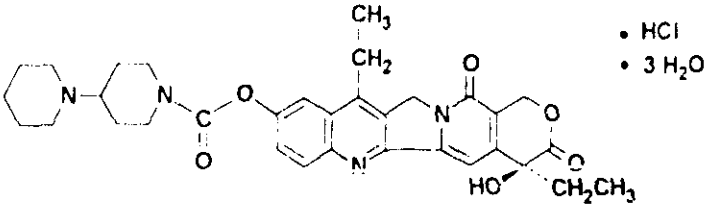
Appendix 1: Sponsor's Proposed Labeling

A. Annotated Proposed Package Insert

The proposed package insert has been annotated to the volume and page number of the specific Item (as identified on FDA form 356h) and the technical sections

DRAFT PACKAGE INSERT	Location in Summary and Technical Sections
CAMPTOSAR™ **brand of irinotecan hydrochloride injection** **DESCRIPTION** CAMPTOSAR Injection (irinotecan hydrochloride injection) is an antineoplastic agent, clinically investigated as CPT-11 CAMPTOSAR is supplied as a sterile, pale yellow, clear, nonaqueous solution. It is available in 100-mg, single-dose, 5-mL vials. Each milliliter of solution contains 20 mg of irinotecan trihydrate, 45 mg of sorbitol NF powder, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.0 to 4.0 with sodium hydroxide and hydrochloric acid. CAMPTOSAR is intended for dilution with 5% Dextrose Injection, USP (D5W) or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion Irinotecan is a semisynthetic derivative of camptothecin, an alkaloid extract from plants such as *Camptotheca acuminata*. The chemical name is (4*S*)-4,11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino)carbonyloxy]-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(4*H*,12*H*)dione hydrochloride trihydrate. Irinotecan hydrochloride is a pale yellow to yellow crystalline powder, with the empirical formula $C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$ and a molecular weight of 677.19. It is soluble in water but sparingly soluble in organic solvents. Its structural formula is as follows	Item 3.II Vol 1.3, pgs 3/2/1 - 35, pg 3.2/64 Item 3.IA Vol 1.2, pgs 3/1/40 - 42
 **Irinotecan Hydrochloride**	Item 3.IA.2 Vol 1.2, pg 3.1/41

CLINICAL PHARMACOLOGY	
Irinotecan is a derivative of camptothecin and belongs to a new class of cytotoxic chemotherapeutic agents with a unique mechanism of action. These drugs interact specifically with the enzyme topoisomerase I and are known as "topoisomerase I inhibitors." The function of topoisomerases is to maintain the proper three-dimensional conformation of DNA by removing supercoils (twists and kinks) during DNA replication and transcription.[1] The cytotoxicity of the camptothecins is due to double-stranded DNA damage produced when, during DNA synthesis (the S-phase), DNA replication enzymes collide with a ternary complex of drug, DNA, and topoisomerase I.[2] This drug-induced damage is not efficiently repaired and apoptosis, a form of programmed cell death, ensues.	Item 5.C.2.b Vol 1.14, pg 5.1.49
The therapeutic effects of irinotecan have been attributed primarily to its active metabolite SN-38. Biochemical studies and in vitro cytotoxicity assays in human and rodent tumor cell lines consistently show SN-38 to be at least 1000-fold more potent as a topoisomerase I inhibitor than irinotecan.[3] SN-38 is formed from irinotecan by carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and the dipiperidino side chain. Thus, irinotecan serves as a water-soluble prodrug of the lipophilic compound SN-38. Both irinotecan and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. A pH-dependent equilibrium exists between the two forms such that an acid pH promotes the formation of the lactone while a more basic pH yields the hydroxy acid anion form.[4]	Item 5.C.4 Vol 1.14, pg 5.1.59 Item 5.E.1.d Vol 1.14, pg 5.1.163
Irinotecan demonstrated marked activity when administered at well-tolerated doses to rodents bearing transplanted malignant tumors. In various models, activity was manifested by growth inhibition, shrinkage, or complete remission of tumors, prolongation of survival, and inhibition of metastasis. Antitumor activity was observed in mice bearing cancers of rodent origin and in human carcinoma xenografts of various histological types. Irinotecan was also active in multidrug-resistant tumor models that respond poorly to various clinically used drugs.	Item 5.C.3 Vol 1.14, pg 5.1.51
Pharmacokinetics	
After intravenous infusion of CAMPTOSAR in humans, irinotecan plasma concentrations decline in a multiexponential manner with a mean terminal elimination half-life of about 6 hours. The average systemic clearance of irinotecan is approximately 13 L/hr·m^2 for total irinotecan and 45 L/hr·m^2 for the lactone form. Although the pharmacokinetics of irinotecan are highly variable among patients, they are linear with respect to the dose of CAMPTOSAR solution over the dose range of 50 to 350 mg/m^2. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of CAMPTOSAR. The mean terminal half-life of the total and lactone forms of SN-38 are slightly longer than corresponding values for irinotecan (13.0 versus 7.9 hr for the total, and 11.5 versus 6.3 hr for the lactone). Maximum plasma SN-38 concentrations are approximately 2 to 5% of peak irinotecan concentrations, while SN-38 area under the curve values are about 2 to 8% of those observed for irinotecan.	Item 6.E.1.b Vol 1.36 pgs 6/1/19 - 23 Item 6.E.1.f Vol 1.36 pgs 6/1/29 - 32 Item 6.E.1.b Vol 1.36 pgs 6/1/19 - 23
Pharmacokinetic parameters for irinotecan and SN-38 following 90-minute infusions of CAMPTOSAR at dose levels of 100 and 125 mg/m^2 were determined in a phase II study in patients with metastatic carcinoma of the colon or rectum and are summarized in the following Table.	Item 6.E.1.b Vol 1.36, pg 6.1.28

Summary of Mean (± Standard Deviation) Irinotecan and SN-38 Pharmacokinetic Parameters in Patients With Metastatic Carcinoma of the Colon and Rectum

Dose (mg/m^2)	Irinotecan					SN-38		
	C_{max} (µg/mL)	AUC_{0-24} (µg·hr/mL)	$t_{½}$ (hr)	V_{area} (L/m^2)	CL ($L/hr/m^2$)	C_{max} (ng/mL)	AUC_{0-24} (ng·hr/mL)	$t_{½}$ (hr)
100 (N=98)	1.29 ± 0.488	8.20 ± 3.19	5.7	107 ± 29.4	13.2 ± 4.32	21.8 ± 10.1	206 ± 104	9.8
125 (N=64)	1.56 ± 0.797	10.2 ± 3.27	5.7	110 ± 48.5	13.3 ± 6.01	26.3 ± 11.9	229 ± 108	9.8

C_{max} - Maximum plasma concentration
AUC_{0-24} - Area under the plasma concentration-time curve from time 0 to 24 hours after the end of the 90-minute infusion
$t_{½}$ - Harmonic mean half-life
V_{area} - Volume of distribution
CL - Total systemic clearance

Distribution Irinotecan is extensively distributed to body tissues; estimates of the mean steady-state volume of distribution range from 105 L/m² to 266 L/m². Irinotecan exhibits moderate plasma protein binding (30 to 68% bound) over the concentration range achieved in clinical studies. SN-38 is highly bound to human plasma proteins (approximately 95% bound). The major plasma protein to which irinotecan and SN-38 bind is albumin.[4]

Metabolism The metabolic conversion of irinotecan to SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver. SN-38 subsequently undergoes conjugation to form a glucuronide metabolite (SN-38 glucuronide). SN-38 was consistently at least 1000 fold more potent than irinotecan and 100-fold more potent than SN-38 glucuronide in cytotoxicity assays using various lines of human and rodent tumor cells cultured in vitro.

Excretion The disposition of irinotecan has not been fully elucidated in humans. The urinary excretion of irinotecan (11 to 20%), SN-38 (< 1%), and SN-38 glucuronide (3%) is low. Thus, renal excretion does not represent a major route of elimination for irinotecan and its known major circulating metabolites.

The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of CAMPTOSAR in two patients ranged from approximately 25% (100 mg/m²) to 50% (300 mg/m²).

Item 6 E.1.c
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Item 6 E.1.d
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Item 5 C.5
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Item 5 C.6
Vol 1.14, pg 5-1.68

Item 6 E.1.e
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Pharmacokinetics in Special Populations	
Geriatric In a clinical trial of CAMPTOSAR in patients with metastatic carcinoma of the colon and rectum, the mean (± SD) systemic clearance of irinotecan was 11.8 ± 3.50 L/hr/m² in 67 patients who were 65 years or older (mean, 71 ± 5 years) and 14.3 ± 5.74 L/hr/m² in 95 patients younger than 65 years (mean, 52 ± 10 years). The terminal half-life of irinotecan was 6.0 hours in patients who were 65 years or older and 5.5 hours in patients younger than 65 years. Dose-normalized area under the curve (AUC_{0-24}) for SN-38 in patients who were at least 65 years of age was 11% higher than the AUC_{0-24} determined in patients younger than 65 years.	Item 6.E.2.a.2 Vol 1.36 pgs 6.1.33 - 34
Pediatric The pharmacokinetics of irinotecan have not been studied in the pediatric population.	
Gender The pharmacokinetics of irinotecan do not appear to be influenced by gender. In clinical trials of CAMPTOSAR in patients with metastatic carcinoma of the colon or rectum who received a dose of 100 mg/m² or 125 mg/m², the mean (± SD) systemic clearance of irinotecan was 13.6 ± 4.76 L/hr/m² in 80 male patients (mean age, 60 ± 11 years) and 12.9 ± 5.33 L/hr/m² in 82 female patients (mean age, 60 ± 13 years). The dose-normalized AUC_{0-24} for SN-38 was 200 ± 95.9 ng•hr/mL in male patients and 194 ± 99.4 ng•hr/mL in female patients.	Item 6.E.2.a.1 Vol 1.36 pgs 6.1.32 - 33
Race The potential influence of race on the pharmacokinetics of irinotecan has not been evaluated.	
Hepatic Insufficiency The influence of severe hepatic insufficiency on the pharmacokinetic characteristics of irinotecan and its metabolites has not been formally studied. All patients in US clinical trials had adequate liver function as measured by serum levels of hepatic enzymes and bilirubin. In a clinical trial in patients with metastatic carcinoma of the colon or rectum, 77.2% of patients had liver metastases and 22.8% did not have liver metastases. Among those patients without known hepatic tumor involvement, irinotecan and SN-38 area-under-the-curve values were approximately 20% lower than values for patients with liver metastases.	Item 6.E.2.a.4 Vol 1.36, pg 6.1.35
Renal Insufficiency Although the pharmacokinetics of irinotecan have not been formally examined in patients with renal insufficiency, alterations in renal function would not be expected to have a major influence on the pharmacokinetics since renal excretion does not represent a major route of elimination for irinotecan or its known major circulating metabolites.	Item 6.E.2.a.3 Vol 1.36, pg 6.1.34
Drug-Drug Interactions	
The effect of the order of administration of CAMPTOSAR either immediately before or after fluorouracil (5-FU) and leucovorin has been studied. Mean irinotecan and SN-38 pharmacokinetic parameters were within 10% of corresponding values observed when CAMPTOSAR was administered alone. Possible pharmacokinetic interactions of CAMPTOSAR with other concomitantly administered medications have not been formally investigated.	Item 6.E.2.b Vol 1.36, pg 6.1.36

CLINICAL STUDIES	
In a phase I study, the maximum tolerated dose of CAMPTOSAR as a single agent in the treatment of patients with various tumors was 150 mg/m^2 when administered once weekly for 4 weeks, followed by a 2-week rest period. The dose-limiting toxicity was diarrhea. In a second phase I study of the same regimen, the maximum tolerated dose of CAMPTOSAR was 120 mg/m^2 without and 145 mg/m^2 with coadministration of G-CSF. The dose-limiting toxicities in this study were diarrhea and neutropenia.	Item 8.G.3 Vol 1.45, pg 8/3/31 TR 7216-95-006 Vol 1.58, pg 8/16/1 TR 7216-95-011 Vol 1.62 , pg 8/20/1
Data from three single-agent clinical studies, involving a total of 304 patients in 59 centers, support the use of CAMPTOSAR in the treatment of patients with metastatic cancer of the colon or rectum that has recurred or progressed following treatment with 5-FU-based therapy. In each study, CAMPTOSAR was administered in repeated 6-week courses comprising 90-minute IV infusions once weekly for 4 weeks, followed by a 2-week rest period. Starting doses of CAMPTOSAR in these trials were 100, 125, or 150 mg/m^2.	Item 8.F.2.a Vol 1.44, pg 8/2/8 Item 8.F.2.b Vol 1.44, pg 8/2/9
In the intent-to-treat analysis of the pooled data across all three studies, 193 of the 304 patients began therapy at the recommended starting dose of 125 mg/m^2. Among these 193 patients, 2 complete and 26 partial responses were observed for an overall response rate of 14.5% (95% Confidence Interval (CI), 9.5 to 19.5%) at this starting dose. The majority of responses were observed within the first two courses of therapy, and all of the responses were observed by the fourth course of therapy. The median duration of response for patients beginning therapy at 125 mg/m^2 was 5.2 months (range, 2.6 to 15.1 months). An additional 53.9% (104/193) of the patients treated at a starting dose of 125 mg/m^2 achieved a best response of stable disease by formal response criteria, but many of these patients experienced substantial reductions in their total tumor burden at some time during the study.	TR 7216-95-007 Vol 1.65, pg 8/23/1 TR 7216-95-008 Vol 1.69, pg 8/27/1 TR 7216-95-010 Vol 1.74, pg 8/32/1 Item 8.F.c (6) - (9), Vol 1.44, pgs 8/2/33 - 48
The individual by-study results for the overall intent-to-treat response rates are as follows: In Study 1 (N=48), the overall response rate was 20.8% (95% CI, 9.3 to 32.3%) for patients receiving a starting dose of 125 or 150 mg/m^2. Only nine patients were treated at the 150-mg/m^2 starting dose due to toxicity concerns. In Study 2 (N=90), the overall response rate was 13.3% (95% CI, 6.3 to 20.4%) for patients receiving a starting dose of 125 mg/m^2. In Study 3, the overall response rate for patients receiving a starting dose of 125 mg/m^2 (N=64) was 12.5% (95% CI, 4.4 to 20.6%); among patients in this study receiving a starting dose of 100 mg/m^2 (N=102), the response rate was somewhat lower at 7.8% (95% CI, 2.6 to 13.1%).	Item 8.F.c (7) Vol 1.44, pg 8/2/34
Response to CAMPTOSAR was observed in males and in females and among patients of all ages. Patients with cancer of the colon or cancer of the rectum responded to CAMPTOSAR, and responses occurred both in patients with single and multiple metastatic sites. Patients responded to CAMPTOSAR regardless of whether prior 5-FU treatment had been given as adjuvant therapy or for metastatic disease. Over half of the patients responding to CAMPTOSAR had not had responses to prior 5-FU-based treatment given for metastatic disease. Response to CAMPTOSAR could be observed in patients who had received more than one prior chemotherapy regimen. Patients who had received previous irradiation to the pelvis also responded to CAMPTOSAR.	Item 8.F.c (7) Vol 1.44, pg 8/2/34
The majority of patients treated with CAMPTOSAR had an increase in or stabilization of body weight and an improvement or maintenance of performance status. Among responding patients with tumor-related symptoms, the majority experienced amelioration of these symptoms during CPT-11 treatment. Moreover, some patients had a longer time to tumor progression after treatment with CAMPTOSAR than they had experienced during their prior 5-FU-based therapy.	Item 8.F.C.(12) (a) and (c), Vol 1.44 pgs 8/2/66 and 78 TR 7216-95-017 Vol 1.84, pg 8/42/1

INDICATIONS AND USAGE CAMPTOSAR is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy.	Item 8.F.1 Vol 1.44, pg 8.2.5
CONTRAINDICATIONS CAMPTOSAR is contraindicated in patients with a known hypersensitivity to the drug	
WARNINGS CAMPTOSAR should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available	Item 8.G.15.b Vol 1.45, pg 8.3/241
CAMPTOSAR can induce both an early and a late form of diarrhea that appear to be mediated by different mechanisms. Early diarrhea (occurring during or within 24 hours of CAMPTOSAR administration) is cholinergic in nature. It can be severe but is usually transient. It may be preceded by complaints of diaphoresis and abdominal cramping. There is evidence that early diarrhea may be ameliorated by administration of atropine (see PRECAUTIONS, General, for dosing recommendations for atropine)	Item 8.G.7.c.(1)(b) Vol 1.45, pg 8.3/210 Item 8.G.15.b.(2)(a) and (b) Vol 1.45, pg 8.3/242
Late diarrhea (occurring more than 24 hours after administration of CAMPTOSAR) may be associated with dehydration and electrolyte imbalance and can be potentially life-threatening. Late diarrhea should be treated promptly with loperamide or other similar antidiarrheal agents (see PRECAUTIONS, Information for Patients, for dosing recommendations for loperamide). Patients with severe diarrhea should be carefully monitored and provided with fluid and electrolyte replacement if dehydration occurs. Administration of CAMPTOSAR should be interrupted in the presence of National Cancer Institute (NCI) grade 3 or 4 late diarrhea. If late diarrhea persists for longer than 3 days despite treatment with loperamide, therapy with CAMPTOSAR should be discontinued and the dose of CAMPTOSAR should be decreased once the patient has recovered (see DOSAGE AND ADMINISTRATION).	Item 8.G.7.c.(2)(a) Vol 1.45, pg 8.3/212 Item 8.G.15.b.(2)(a) Vol 1.45, pg 8.3/242 TR 7216-95-007 Vol 1.65, pg 8.23/1 TR 7216-95-008 Vol 1.69, pg 8.27/1 TR 7216-95-010 Vol 1.74, pg 8.32/1
Deaths due to sepsis following severe myelosuppression have been reported in patients treated with CAMPTOSAR. Therapy with CAMPTOSAR should be temporarily discontinued if neutropenic fever occurs or if the absolute neutrophil count drops below 500/mm^3. The dose of CAMPTOSAR should be reduced if there is a clinically significant decrease in the total white blood cell count (< 2000/mm^3), neutrophil count (< 1000/mm^3), hemoglobin (< 8 gm/dL), or platelet count (< 100,000/mm^3) (see DOSAGE AND ADMINISTRATION). Routine administration of a colony-stimulating factor (CSF) is not necessary, but physicians may wish to consider CSF use in individual patients experiencing problems related to neutropenia.	Item 8.G.4.f.(8) Vol 1.45, pg 8/3/83 Item 8.G.15.b.(3) Vol 1.45, pg 8/3/242
CAMPTOSAR may cause fetal harm when administered to a pregnant woman. CAMPTOSAR has been shown to be teratogenic in rats and rabbits at a dose of 6 mg/kg/day. Treatment-related changes in the fetuses included external and visceral abnormalities, skeletal variations, and skeletal abnormalities. There are no adequate and well-controlled studies in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with CAMPTOSAR.	Item 5.D.5.a Vol 1.14, pg 5.1/138

PRECAUTIONS	
General	
CAMPTOSAR is administered by intravenous infusion. Care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with sterile water and the application of ice are recommended.	Item 8.G.4.g.(8) Vol 1.45, pg 8/3/99
It is recommended that patients receive premedication with antiemetic agents. In clinical studies, premedication has often consisted of 10 mg of dexamethasone given in conjunction with another type of antiemetic agent. Antiemetic agents should be given on the day of treatment, starting at least 30 minutes before administration of CAMPTOSAR. Physicians should also consider providing patients with an antiemetic regimen for subsequent use as needed.	Item 8.G.4.a(6)(c) Vol 1.45, pg 8/3/45 Item 8.G.15.b.(2)(c) Vol 1.45, pg 8/3/244
Administration of 0.25 to 1 mg of intravenous atropine should be considered (unless clinically contraindicated) in patients experiencing diaphoresis, abdominal cramping, or early diarrhea occurring during or within 24 hours following administration of CAMPTOSAR.	Item 8.G.15.b.(2)(b) Vol 1.45, pg 8/3/243
Physicians should exercise caution in treating and monitoring patients older than 65 years and those with the following conditions: active infections, preexisting myelosuppression, preexisting diarrhea, intestinal obstruction, chronic inflammatory bowel disease, compromised pulmonary function, excessive ascites or pleural effusion, diabetes mellitus, or poor performance status.	Item 8.G.11. Vol 1.45, pg 8/3/234 Item 8.G.15.b Vol 1.45, pg 8/3/241
Information for Patients	
Patients and patient caregivers should be informed of the expected toxic effects of CAMPTOSAR, particularly of its gastrointestinal manifestations, such as nausea, vomiting, and diarrhea. Each patient should be instructed to have antidiarrheal medication readily available and begin treatment for late diarrhea (ocurring more than 24 hours after administration of CAMPTOSAR) 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. One dosage regimen for loperamide used in clinical trials consisted of the following (Note: This dosage regimen exceeds the usual dosage recommendations for loperamide.): 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea free for at least 12 hours. During the night, the patient may take 4 mg of loperamide every 4 hours. The patient should also be instructed to notify the physician if diarrhea occurs. Premedication with loperamide is not recommended. While agents other than loperamide may have utility in the treatment of late diarrhea, the experience in US clinical trials with such medications is limited.	Item 8.G.15.b Vol 1.45, pg 8/3/241
The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to discuss any laxative use.	
Patients should consult their physician if vomiting occurs, fever or evidence of infection develop, or if symptoms of dehydration such as fainting, light-headedness, or dizziness are noted following therapy with CAMPTOSAR.	Item 8.G.10.b.(5) Vol 1.45, pg 8/3/232
Patients should be alerted to the possibility of alopecia.	Item 8.G.4.g Vol 1.45, 8/3/85 Item 8.G.4.f.(1) and (2). Vol 1.45, pgs 8/3/55 - 64

Laboratory Tests Careful monitoring of the white blood cell count with differential, hemoglobin, and platelet count is recommended before each dose of CAMPTOSAR.	TR 7216-95-007 Vol 1.65, pg 8/23.1 TR 7216-95-008 Vol 1.69, pg 8/27.1 TR 7216-95-010 Vol 1.74, pg 8/32.1
Drug Interactions Adverse events due to CAMPTOSAR, such as myelosuppression and diarrhea, may be enhanced by combination with other antineoplastic agents having similar adverse events. Data from clinical trials with CAMPTOSAR suggest the potential for an interaction between prior irradiation to major bone-marrow containing areas and CAMPTOSAR in enhancing myelosuppression. Patients receiving CAMPTOSAR and concurrent irradiation may also be at increased risk for myelosuppression, diarrhea, or other toxicities. Lymphocytopenia has been reported in patients receiving CAMPTOSAR, and it is possible that the administration of dexamethasone as antiemetic prophylaxis may have enhanced the likelihood of this effect. However, serious opportunistic infections have not been observed, and no complications have specifically been attributed to lymphocytopenia. Hyperglycemia has also been reported in patients receiving CAMPTOSAR. Usually, this has been observed in patients with a history of diabetes mellitus or evidence of glucose intolerance prior to administration of CAMPTOSAR. It is probable that dexamethasone, given as antiemetic prophylaxis, may have contributed to hyperglycemia in some patients. The incidence of akathisia in clinical trials was somewhat greater (8.5%, 4/47 patients) when prochlorperazine was administered on the same day as CAMPTOSAR than when these drugs were given on separate days (1.3%, 1/80 patients). However, the 8.5% incidence of akathisia is within the range reported for use of prochlorperazine when given as a premedication for other chemotherapies. It is possible that laxative use during therapy with CAMPTOSAR may worsen the incidence or severity of diarrhea. In view of the potential risk of dehydration secondary to vomiting and or diarrhea induced by CAMPTOSAR, the physician may wish to withhold diuretics during dosing with CAMPTOSAR, and certainly during periods of active vomiting or diarrhea. Minor bleeding has infrequently been noted when patients receiving CAMPTOSAR were treated with warfarin. The data do not appear to indicate a propensity for bleeding that is greater than that observed with warfarin alone.	Item 8.G.10.b.(2) Vol 1.45, pg 8.3.231 Item 8.G.10.b.(1) Vol 1.45, pg 8/3.231 Item 8.G.10.b.(3) Vol 1.45, pg 8/3.232 Item 8.G.15.1. (5) Vol 1.45, pg 8.3/246 Item 8.G.10.b.(4) Vol 1.45, pg 8/3.232 Item 8.G.10.b.(5) Vol 1.45, pg 8/3/232 Item 8.G.10.b.(6) Vol 1.45, pg 8/3/232 Item 8.G.10.b.(7) Vol 1.45, pg 8/3/232
Drug-Laboratory Test Interactions There are no known interactions between CAMPTOSAR and laboratory tests.	

Carcinogenesis, Mutagenesis & Impairment of Fertility Irinotecan was not carcinogenic in the rat bioassay when administered at doses of 2 mg/kg or 25 mg/kg once per week for 13 weeks, with a subsequent 91-week observation period Irinotecan was not mutagenic in the in vitro Ames assay. However, in the in vitro Chinese hamster cell chromosomal aberration assay, irinotecan produced a significant increase in the incidence of chromosomal aberrations in a concentration-dependent manner Additionally, in the in vivo mouse micronucleus assay, a single dose of irinotecan over the dosage range of 2.5 to 200 mg/kg, administered intraperitoneally, caused a significant and dose-dependent increase in micronucleated polychromatic erythrocytes and a decrease in the reticulocyte erythrocyte ratio in bone marrow cells. No significant adverse effects on fertility and general reproductive performance were observed after intravenous administration of irinotecan in doses of up to 6 mg/kg/day to rats and rabbits (see WARNINGS)	Item 5.D.4 Vol 1.14, pg 5.1.138 Item 5.D.6. Vol 1.14, pg 5.1.141 Item 5.D.7 Vol 1.14, pg 5.1.141
Pregnancy Pregnancy Category D - see WARNINGS	
Nursing Mothers It is not known whether irinotecan is excreted in human milk Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving therapy with CAMPTOSAR	
Pediatric Use The safety and effectiveness of CAMPTOSAR in the pediatric population have not been established	
ADVERSE REACTIONS **US Clinical Trials** In three clinical studies, 304 patients with metastatic carcinoma of the colon or rectum that had recurred or progress following 5-FU-based therapy were treated with CAMPTOSAR. Seventeen of the patients died within 30 days of the administration of CAMPTOSAR, only one death (due to neutropenic sepsis) was judged to be potentially drug related (0.3%, 1/304). Neutropenic fever, defined as NCI grade 4 neutropenia and grade 2 or greater fever, occurred in nine (3.0%) other patients; these patients recovered with supportive care Thirteen (4.3%) patients discontinued treatment with CAMPTOSAR because of medical events The adverse events in the following Table are based on the experience of the 304 patients enrolled in the three studies	TR 7216-95-007 Vol 1.65, pg 8/23/1 TR 7216-95-008 Vol 1.69, pg 8/27/1 TR 7216-95-010 Vol 1.74, pg 8/32/1 Item 8.G.4.f.(5) and (8), Vol 1.45, pgs 8/3/80 and 83 Item 8.G.4.g (6)(b) Vol 1.45, pg 8/3/96 Item 8.G.4.f.(1) and (3), Vol 1.45, pgs 8/3/55 and 64

Adverse Events Occurring in > 10% of 304 Previously Treated Patients with Metastatic Carcinoma of the Colon or Rectum

Event	% of Patients	% NCI Grade 3 & 4
Gastrointestinal		
Diarrhea (late)*	87.8	30.6
7-9 stools/day (grade 3)	--	16.4
≥10 stools/day (grade 4)	--	14.1
Nausea	86.2	16.8
Vomiting	66.1	12.5
Anorexia	54.6	5.9
Diarrhea (early)†	50.3	7.9
Constipation	29.3	2.0
Flatulence	12.2	0
Stomatitis	11.2	0.7
Dyspepsia	10.5	0
Hematologic		
Leukopenia	62.8	27.6
Anemia	60.5	6.9
Neutropenia	53.3	26.3
500 to <1000/mm³ (grade 3)	--	14.8
<500/mm³ (grade 4)	--	11.5
Body as a Whole		
Asthenia	75.7	12.2
Abdominal pain	56.9	15.8
Fever	45.1	0.7
Pain	23.4	2.3
Headache	16.8	0.7
Back pain	14.5	1.3
Chills	13.8	0.3
Infection	13.8	0
Edema	12.5	1.3
Metabolic & Nutritional		
↓ Body weight	30.3	0.7
Dehydration	14.5	4.3
↑ Alkaline phosphatase	13.2	3.9
↑ SGOT	10.5	1.3
Dermatologic		
Alopecia	60.5	0
Sweating	16.1	0
Rash	12.2	0.7
Respiratory		
Dyspnea	22.0	3.6
↑ Coughing	17.4	0.3
Rhinitis	15.5	0
Neurologic		
Insomnia	19.4	0
Dizziness	14.8	0
Cardiovascular		
Vasodilation	11.2	0

* Occurring > 24 hours after administration of CAMPTOSAR
† Occurring ≤ 24 hours after administration of CAMPTOSAR

Gastrointestinal: Diarrhea, nausea, and vomiting were common adverse events following treatment with CAMPTOSAR and could be severe. These events occurred early (during or within 24 hours of administration of CAMPTOSAR) or late (more than 24 hours after administration of CAMPTOSAR). The median time to onset of late diarrhea was 11 days following administration of CAMPTOSAR	Item 8.G.4.g.(1) - (3) Vol 1.45, pgs 8/3.85 - 92
Hematology: Typical adverse hematologic events of CAMPTOSAR included neutropenia, leukopenia (including lymphocytopenia), and anemia. Serious thrombocytopenia was uncommon. Neutropenic fever (concurrent NCI grade 4 neutropenia and fever of grade 2 or greater) occurred in 3.0% of the patients. Only 5.6% of patients received G-CSF for the treatment of neutropenia. NCI grade 3 or 4 anemia was noted in 6.9% of the patients. Blood transfusions were given to 9.9% of the patients	Item 8.G.4.f.(1) and (3), Vol 1.45, pgs 8/3.55 and 64 Item 8.G.4.g.(6) and (7), Vol 1.45, pgs 8/3.93 - 99
Body as a Whole: Asthenia, fever, and abdominal pain were the most common events of this type	Item 8.G.4.i.(1) Vol 1.45, pg 8/3.100
Hepatic: NCI grade 3 or 4 liver enzyme abnormalities were observed in less than 10% of patients. These events typically occurred in patients with known hepatic metastases.	Item 8.G.4.f.(1) Vol 1.45, pg 8/3.55
Dermatologic: Alopecia, usually transient, was reported during treatment with CAMPTOSAR. Transient rashes have also been reported but did not result in discontinuation of treatment.	Item 8.G.4.i.(2)a.) Vol 1.45, pg 8/3.102
Respiratory: Severe pulmonary events were infrequent; NCI grade 3 or 4 dyspnea was reported in 3.6% of patients with previously treated cancer of the colon or rectum. Over half the patients with dyspnea had lung metastases; the extent to which malignant pulmonary involvement or other preexisting lung disease may have contributed to dyspnea in these patients is unknown.	Item 8.G.4.f.(1) and (5), Vol 1.45, pgs 8/3.55 and 80 Item 8.G.4.g.(5) Vol 1.45, pg 8/3.93
Neurologic: Insomnia and dizziness were observed, but were not usually considered to be directly related to the administration of CAMPTOSAR. Dizziness may sometimes have represented symptomatic evidence of orthostatic hypotension in patients with dehydration.	Item 8.G.4.f.(1) and (2), Vol 1.45, pgs 8/3.55 and 64
Cardiovascular: Vasodilation (flushing) has been observed during administration of CAMPTOSAR but has not required intervention.	Item 8.G.17.(b) Vol 1.45, pg 8/3.269 Item 8.G.4.f.(1) Vol 1.45, pg 8/3.55 Item 8.G.4.h.(1) Vol 1.45, pg 8/3/99
Non-US Clinical Trials Irinotecan has been studied in over 1100 patients in Japan and in over 400 patients in France. Patients in these studies had a variety of tumor types, including cancer of the colon or rectum, and were treated with several different doses and schedules. In general, the clinical activity in patients with previously treated cancer of the colon and rectum, and the types of toxicities observed, were similar to those seen in US trials with CAMPTOSAR. There is some information from Japanese trials that patients with considerable ascites or pleural effusions were at increased risk for neutropenia or diarrhea. A potentially life-threatening pulmonary syndrome, consisting of dyspnea, fever, and a reticulonodular pattern on chest x-ray, was observed in a small percentage of patients in early Japanese studies. The contribution of irinotecan to these preliminary events was difficult to assess because these patients also had lung tumors and some had preexisting nonmalignant pulmonary disease. As a result of these observations, clinical studies in the United States have enrolled limited numbers of patients with compromised pulmonary function, significant ascites, or pleural effusions.	Item 8.G.7. Vol 1.45, pg 8/3.180

OVERDOSAGE

In US phase I trials, single doses of up to 345 mg/m² of CAMPTOSAR were administered to patients with various cancers. Single doses of up to 750 mg/m² of irinotecan have been given in non-US trials. The adverse events in these patients were similar to those reported with the recommended dosage and regimen. There is no known antidote for overdosage of CAMPTOSAR. Maximum supportive care should be instituted to prevent dehydration due to diarrhea and to treat any infectious complications.

Item 8.H
Vol 1.50, pg 8.8/217

Acute toxicity in rodents consists of tremors, convulsions, respiratory distress, and death. Subacute toxicity studies show that irinotecan affects tissues with rapid cell proliferation (bone marrow, intestinal epithelia, thymus, spleen, lymph nodes, and testes). The acute intravenous toxicity of irinotecan in animals is shown below:

Species	LD_{10} (mg/kg)
Mouse	132.4-134.1
Rat	83.6-85.1
Dog	40-80

DOSAGE AND ADMINISTRATION

Starting Dose and Dose Modifications

The recommended starting dose of CAMPTOSAR Injection is 125 mg/m². All doses should be administered as an intravenous infusion over 90 minutes (see Preparation of Infusion Solution below). The recommended treatment regimen (one treatment course) is 125 mg/m² administered once weekly for 4 weeks, followed by a 2-week rest period. Thereafter, additional courses of treatment may be repeated every 6 weeks (4 weeks on therapy followed by 2 weeks off therapy). It is recommended that subsequent doses be adjusted to as high as 150 mg/m² or to as low as 50 mg/m² in 25 to 50 mg/m² increments depending upon individual patient tolerance of treatment (see Table below). Provided intolerable toxicity does not develop, treatment with additional courses of CAMPTOSAR may be continued indefinitely in patients who attain a response or in patients whose disease remains stable. Patients should be carefully monitored for toxicity.

Item 8.G.9.b.(2)
Vol 1.45, pg 8.3.228

The Table below describes the recommended dose modifications during a course of therapy and at the start of each subsequent course of therapy. These recommendations are based on toxicities commonly observed with the administration of CAMPTOSAR. Therapy with CAMPTOSAR should be interrupted when diarrhea persists longer than 3 days despite appropriate treatment with loperamide (see PRECAUTIONS, Information for Patients) or when other intolerable toxicity is observed. Dose modifications for hematologic toxicities other than neutropenia (eg, leukopenia, anemia or thrombocytopenia, and platelets) during a course of therapy and at the start of a subsequent course of therapy are the same as recommended for neutropenia. Dose modifications for nonhematologic toxicities other than diarrhea (nausea, vomiting, etc) during a course of therapy are the same as those recommended for diarrhea. At the start of a subsequent course of therapy, the dose of CAMPTOSAR should be decreased by 25 mg/m² for other NCI grade 2 or by 50 mg/m² for other grade 3 or 4 nonhematologic toxicities. All dose modifications should be based on the worst preceding toxicity.

TR 7216-95-007
Vol 1.65, pg 8/23/1
TR 7216-95-008
Vol 1.69, pg 8/27/1
TR 7216-95-010
Vol 1.74, pg 8/32/1

Recommended Dose Modifications		
Toxicity NCI Grade* (Value)	**During a Course of Therapy**	**At the Start of Subsequent Courses of Therapy**
No toxicity	Maintain dose level	· 25 mg/m² up to a maximum dose of 150 mg/m²
Neutropenia 1 (1500 to 1900/mm³) 2 (1000 to 1400/mm³) 3 (500 to 900/mm³) 4 (< 500/mm³)	Maintain dose level . 25 mg/m² Omit dose, then : 25 mg/m² when resolved to ·. grade 2 Omit dose, then . 50 mg/m² when resolved to ·. grade 2	Maintain dose level Maintain dose level : 25 mg/m² . 50 mg/m²
Neutropenic fever (grade 4 neutropenia & · grade 2 fever)	Omit dose, then . 50 mg/m² when resolved	: 50 mg/m²
Other hematologic toxicities	Dose modifications for leukopenia, thrombocytopenia and anemia during a course of therapy and at the start of subsequent courses of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above	
Diarrhea 1 (2-3 stools/day > pretx†) 2 (4-6 stools/day > pretx) 3 (7-9 stools/day > pretx) 4 (· 10 stools/day > pretx)	Maintain dose level . 25 mg/m² Omit dose, then . 25 mg/m² when resolved to ·. grade 2 Omit dose, then . 50 mg/m² when resolved to ·. grade 2	Maintain dose level Maintain, if the only grade 2 tox‡ . 25 mg/m², if the only grade 3 tox . 50 mg/m²
Other nonhematologic toxicities 1 2 3 4	Maintain dose level . 25 mg/m² Omit dose, then . 25 mg/m² when resolved to ·. grade 2 Omit dose, then : 50 mg/m² when resolved to ·. grade 2	Maintain dose level : 25 mg/m² . 50 mg/m² : 50 mg/m²

*National Cancer Institute Common Toxicity Criteria
†Pretreatment
‡Toxicity

It is recommended that patients receive premedication with antiemetic agents (see PRECAUTIONS, General)	Item 8 G.15 b (2)(c) Vol 1.45, pg 8/3/244
Preparation & Administration Precautions As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions containing CAMPTOSAR. The use of gloves is recommended. If CAMPTOSAR solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If CAMPTOSAR contacts the mucous membranes, flush thoroughly with water. Several published guidelines for handling and disposal of anticancer agents are available.[5-11]	

Preparation of Infusion Solution CAMPTOSAR Injection must be diluted prior to infusion. CAMPTOSAR should be diluted in 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final concentration range of 0.12 to 1.1 mg/mL. In most clinical trials, CAMPTOSAR was administered in 500 mL of 5% Dextrose Injection, USP.	Item 8.F.2.b (2) Vol 1.44, 8/2/11
The solution is physically and chemically stable for up to 24 hours at room temperature (approximately 25°C) and in ambient fluorescent lighting. Solutions diluted in 5% Dextrose Injection, USP and stored at refrigerated temperatures (approximately 2° to 8°C) and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using 0.9% Sodium Chloride Injection, USP, is not recommended due to a low and sporadic incidence of visible particulates. **Freezing CAMPTOSAR and admixtures of CAMPTOSAR may result in precipitation of the drug and should be avoided.** Because of possible microbial contamination during dilution, it is advisable to use the admixture within 24 hours if refrigerated (2° to 8°C, 36° to 46°F) or within 6 hours if kept at room temperature (15° to 30°C, 59° to 86°F). Other drugs should not be added to the infusion solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.	Item 3.II.H Vol 1.4, pg 3.3.112
HOW SUPPLIED Each mL of CAMPTOSAR Injection contains 20 mg irinotecan (on the basis of the trihydrate salt), 45 mg sorbitol, 0.9 mg lactic acid. When necessary, pH has been adjusted to 3.5 with sodium hydroxide and/or hydrochloric acid. CAMPTOSAR Injection is available as single-dose vials in the following package size: 5-mL amber glass vial NDC 0009-7529-01 This is packaged in a foil/plastic blister to protect against inadvertent breakage and leakage. **The vial should be inspected for damage and visible signs of leaks before removing the foil/plastic blister. If damaged, incinerate the unopened package.** Store at controlled room temperature 15° to 30°C (59° to 86°F). Although the product is supplied in an amber glass vial that offers some light protection, it is recommended that the vial (and foil/plastic blister) should remain in the carton until the time of use. **Caution:** Federal law prohibits dispensing without prescription.	Item 3.II.C Vol 1.3, pg 3.2.36 Item 3.[illegible] Vol 1.3, pg 3.[illegible]

REFERENCES

1 Maxwell A, Gellert M Mechanistic aspects of DNA topoisomerases Adv Protein Chem 1986;38:69-107

2 Holm C, Covey JM, Kerrigan D, Pommier Y Differential requirement of DNA replication for the cytotoxicity of DNA topoisomerase I and II inhibitors in Chinese hamster DC3F cells Cancer Res 1989;49:6365-68

3 Kawato Y, Aonuma M, Hirota Y, Kuga H, Sato K Intracellular roles of SN-38, a metabolite of the camptothecin derivative CPT-11, in the antitumor effect of CPT-11 Cancer Res 1991;51(16):4187-91

4 Burke TG, Mi Z The structural basis of camptothecin interactions with human serum albumin impact on drug stability J Med Chem 1994;37(1):40-6

5 Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs NIH Publication No 83-2621 For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402

6 AMA Council Report Guidelines for handling parenteral antineoplastics JAMA 1985;253(11):1590-1592

7 National Study Commission on Cytotoxic Exposure Recommendations for handling cytotoxic agents Available from Louis P Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115

8 Clinical Oncological Society of Australia Guidelines and recommendations for safe handling of antineoplastic agents Med J Australia 1983;1:426-428

9 Jones RB, et al Safe handling of chemotherapeutic agents a report from the Mount Sinai Medical Center CA-A Cancer J for Clinicians, 1983;Sept/Oct:258-263

10 American Society of Hospital Pharmacists Technical Assistance Bulletin on handling cytotoxic and hazardous drugs Am J Hosp Pharm 1990;47:1033-1049

11 OSHA work-practice guidelines for personnel dealing with cytotoxic (antineoplastic) drugs Am J Hosp Pharm 1986;43:1193-1204

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Appendix II: Pharmacokinetic Study Synopses

Study Report DM111
Metabolic Fate of CPT-11: Phase I Study of CPT-11 in Cancer Patients

Technical Report: Hakusui H, Suzuki W, Atsumi R Submitted by Schaaf LJ Metabolic Fate of CPT-11 Phase I Study of CPT-11 in Cancer Patients (Study Report DM111), Upjohn Technical Report 7215-95-031, September 25, 1995

Publication: Taguchi T, Wakui A, Hasegawa K, Nitani H, Furue H, Ohta K, et al Phase I clinical study of CPT-11 Jpn J Cancer Chemother 1990;17(1) 115–120

Investigators & Study Sites: Multiple centers

Clinical Phase Phase I

Sponsor's Stated Objectives Evaluate the safety and pharmacokinetics of irinotecan hydrochloride (CPT-11) administered as a single intravenous infusion

Methodology

Study Design: This was an open-label, multicenter, Phase I study Groups of 3, 4, 5, 5, and 1 patients each were given 50, 100, 165, 250, or 350 mg/m^2 doses of CPT-11, respectively

Number of Patients: Pharmacokinetic assessment was performed in 18 patients (13 male, 5 female) enrolled in this study Patients ranged in age from 31 to 72 years (mean 50 years), in body weight from 39 5 to 69 kg (mean 53 6 kg), and in body surface area from 1 25 to 1 79 m^2 (mean 1 51 m^2)

Selection Criteria: Patients must have been between 15 and 75 years of age with histologically proven malignant tumor, who had not responded to standard chemotherapy and for whom no standard therapy was likely to be of benefit Patients must have been expected to survive throughout the required period of observation and to have a performance status of 0 to 3

Test Product, Dose & Route of Administration: CPT-11 was dissolved in 250 mL of physiological saline solution and administered intravenously over approximately 30 minutes

Sampling Times: Blood samples were collected at the following time points pre-dose and 1, 4, 8, 24, 72, and 168 hours post-infusion Urine samples were collected for 24 hours from the start of the infusion in three patients

Bioanalytical Methods: Total concentrations of CPT-11 and its active metabolite SN-38 were determined using a high-performance liquid chromatographic procedure See comprehensive Bioanalytical Methods section (Appendix 2)

Pharmacokinetic Analysis: The pharmacokinetic parameters for total forms of CPT-11 and SN-38 were calculated using model-independent methods

Statistical Analysis: Summary statistics (mean, standard deviation [SD]) were calculated for pharmacokinetic parameters

Results

Pharmacokinetic Results:

The following two tables summarize the mean (± SD) pharmacokinetic parameters for CPT-11 and SN-38

Summary of CPT-11 Pharmacokinetic Parameters

CPT-11 Dose (mg/m^2)	No. Subjects	AUC (µg•hr/mL)	Cmax (µg/mL)	t½ (hr)
50	3	3 55 (1 68)	0 72 (0 26)	5 8 (1 0)
100	4	14 17 (7 52)	1 87 (0 51)	7 2 (5 2)
165	5	21 46 (5 33)	4 67 (2 36)	5 0 (2 1)
250	5	27 86 (9 98)	7 57 (6 85)	5 0 (0 4)
350	1	44 69	7 09	6 1

Summary of SN-38 Pharmacokinetic Parameters

Dose (mg/m^2)	No. Subjects	AUC (ng•hr/mL)	Cmax (ng/mL)	t½ (hr)
50	3	173 (92)	21 0 (8 84)	11 4 (7 7)
100	4	581 (473)	33 5 (13 3)	18 5 (9 6)
165	5	667 (484)	49 0 (17 6)	12 2 (5 4)
250	5	876 (672)	72 3 (40 9)	13 9 (7 6)
350	1	1120	139	14 8

CPT-11 plasma concentrations exceeded those of SN-38 The ratio of SN-38 to CPT-11 in the plasma was 1/29 to 1/40 and 1/80 to 1/100 for AUC and C_{max}, respectively The plasma concentration of CPT-11 declined with a mean half-life ranging from 5 0 to 7 2 hours The plasma concentration of SN-38 declined more slowly, with mean half-lives ranging from 11 4 to 18 5 hours

The AUC of CPT-11 increased proportionately to the CPT-11 dose, whereas the linearity in SN-38 pharmacokinetics is difficult to assess because of the large interpatient variability in the observed AUC values (mean coefficient of variation = 70%) and the small number of patients examined at each dose level The ratio of the AUC of SN-38 to that of CPT-11 tended to decrease with higher doses of CPT-11, suggesting that the rate of SN-38 formation may be reduced at higher doses

Conclusions:

- Post-infusion CPT-11 plasma concentrations decreased with a mean half-life of 5 0 to 7 2 hours Both the maximum concentration and AUC increased proportionately with the dose of irinotecan
- SN-38, the active metabolite of CPT-11, reached maximum concentrations within 4 hours following the end of infusion and declined thereafter with a mean half-life of 11 4 to 18 5 hours Peak plasma concentrations of SN-38 were approximately 1% to 3% of peak plasma CPT-11 concentrations while SN-38 AUC values were about 2% to 5% of those observed for CPT-11 The increase in AUC of SN-38 was less than proportionate to the increase in irinotecan dose

Protocol M/6475/0001

Pharmacokinetics of Irinotecan Hydrochloride (CPT-11) and it's Metabolite (SN-38) in Patients with Metastatic Colorectal Carcinoma Refractory to Previous 5-Fluorouracil (5-FU)-based Chemotherapy

Technical Report: Schaaf LJ, Knuth DW, and Elfring GL. Pharmacokinetics of CPT-11 and SN-38. A Multicenter, Phase II Study of Irinotecan Hydrochloride (CPT-11) in Metastatic Colorectal Carcinoma Refractory to Previous 5-Fluorouracil (5-FU)-based Chemotherapy (M/6475/0001). Upjohn Technical Report 7215-95-034, October 23, 1995.

See also.

Dietz AJ, Von Hoff DD, Elfring GL, Albert DG, Miller LL. A multicenter, phase II study of irinotecan hydrochloride (CPT-11) in metastatic colorectal carcinoma refractory to previous 5-fluorouracil (5-FU)-based chemotherapy (protocol M/6475/0001). Upjohn Technical Report 7216-95-007, in press.

Schaaf LJ, Ichhpurani AK, and Elfring GL. Population Pharmacokinetic model for analysis of irinotecan hydrochloride (CPT-11) in patients with metastatic colorectal carcinoma refractory to previous 5-fluorouracil (5-FU)-based chemotherapy (M/6475/0001 and M/6475/0006). Upjohn Technical Report. 7215-95-022, October 25,1995.

Publication: None

Investigator & Study Site:

Clinical Phase Phase II

Sponsor's Stated Objectives The primary objective of this study was to estimate the antitumor activity (response rate) of irinotecan hydrochloride (CPT-11) in patients with metastatic colorectal carcinoma that progressed or recurred after one previous 5-fluorouracil (5-FU)-based chemotherapeutic regimen. The secondary objectives were to evaluate the time to and duration of antitumor response and to evaluate the toxicities of CPT-11. The objectives of the pharmacokinetic portion of the study were to determine the pharmacokinetics of CPT-11 and SN-38 in metastatic colorectal carcinoma patients and to investigate potential correlations between CPT-11 and/or SN-38 plasma concentrations and response or toxicity after treatment with irinotecan hydrochloride.

Methodology

Study Design: This was an open-label study that was conducted by one principal investigator at four regional institutions. CPT-11 was administered as a 90-minute intravenous (IV) infusion once weekly for 4 consecutive weeks, followed by a 2-week rest period (one course). The initial starting dose was 150 mg/m^2, however, this was reduced to 125 mg/m^2 after four of the first nine patients who were treated with the 150 mg/m^2 dose developed grade 4 diarrhea with dehydration and were hospitalized for supportive care (all four recovered without sequelae). Dosage adjustments were made for each patient based on toxicity. Blood specimens for pharmacokinetic evaluation were obtained during the first course of therapy after the weeks 1 and 3 doses.

Number of Patients: Plasma concentration data were available from 35 of the 48 patients enrolled in this phase II study. Patients (19 male, 16 female) ranged in age from 29 to 74 years (mean 56.4 years) and in weight from 45.9 to 121.7 kg (mean 76.7 kg). On week 1, plasma specimens were collected from nine patients who received a dose of 150 mg/m^2 while the remaining 26 patients received a 125-mg/m^2 dose. Specimen collection was repeated following dosing on week 3 in 27 patients. One of these patients had specimens collected on week 4 (patient 8911) rather than on week 3 as scheduled. For pharmacokinetic analyses, the period (i.e., week) designation for specimens collected on this week were set equal to period 3. Since dosage adjustments after the initial starting dose were made for each patient based on toxicity, the doses administered to these patients on week 3 were often less than doses administered on week 1. One of the 9 patients who initially received the 150-mg/m^2 starting dose and 15 of the 26 patients who initially received the 125-mg/m^2 starting dose received the same dose on both week 1 and week 3.

Selection Criteria: Patients with metastatic colorectal carcinoma that progressed or recurred after one previous 5-FU-based chemotherapeutic regimen participated in this study.

Test Product, Dose & Route of Administration: The dose of CPT-11 was based on the trihydrate and was calculated using body surface area, as determined from actual body weight. The appropriate dose of CPT-11 was diluted and mixed in 500 mL of 5% Dextrose Injection (D5W) and infused IV over 90 minutes once weekly for 4 consecutive weeks.

Sampling Times: Blood samples were scheduled to be obtained as follows: immediately before CPT-11 administration (baseline), at the end of the infusion, and at 2 and 24 hours after the end of the infusion.

Bioanalytical Methods: Plasma concentrations of total CPT-11 and total SN-38 were determined by a high-performance liquid chromatographic (HPLC) method. See Analytical Methods (Appendix IV).

Pharmacokinetic Analysis: The plasma concentration-time data of CPT-11 and SN-38 were analyzed by noncompartmental analysis using SAS. To assess the extent of metabolism in patients, a metabolic ratio value, defined as SN-38 AUC divided by CPT-11 AUC (expressed as a percentage), was calculated.

Pharmacodynamic Analyses: The principal side effects observed with the administration of CPT-11 are neutropenia, leukopenia, and late (> 24 hours after administration of CPT-11) diarrhea. In order to examine any relationships between CPT-11 and/or SN-38 pharmacokinetics with principal toxicities (i.e., late diarrhea or neutropenia), pharmacokinetic-pharmacodynamic analyses were performed. For these analyses, the worst grade toxicity (National Cancer Institute [NCI] Common Toxicity Criteria) listed as a medical event during the first course of therapy only was used because of the possible influence of previous CPT-11 administration on the pharmacodynamic effects of either the parent drug or metabolite SN-38.

Statistical Analyses: Comparisons of pharmacokinetic parameters determined on week 1 and week 3 in patients receiving the same dose (125 mg/m^2) of CPT-11 on both weeks were performed using the Wilcoxon Signed Rank test, a nonparametric analogue to the paired-difference t-test. Statistical comparisons of CPT-11 and SN-38 pharmacokinetic parameters (week 1) between responders (i.e., patients who demonstrated a partial or complete tumor response) and non-responders, and between patients < 65 years and patients ≥ 65 years were performed using the Wilcoxon Rank Sum test (NPAR1WAY procedure in SAS). This non-parametric analogue to the two-sample t-test was used since distributional analysis, using the Shapiro-Wilk test, demonstrated that several of the parameters were not normally distributed. The non-parametric Spearman rank order correlation test was used to assess possible correlations between CPT-11 or SN-38 pharmacokinetic parameters and principal toxicities (NCI grade late diarrhea and neutropenia). All statistical evaluations were conducted using SAS. For all evaluations, statistical significance was defined by $p<0.05$.

Results

Pharmacokinetic Results: Mean (± SD) pharmacokinetic parameters for CPT-11 and SN-38 following a 90-minute infusion of 125 or 150 mg/m^2 CPT-11 on week 1 are in Table 1. The interpatient variability, based on coefficients of variation, in CPT-11 C_{max} and AUC_{0-24} parameters was approximately half of that observed for SN-38. CPT-11 C_{max} and AUC_{0-24} increased proportionately with starting dose. The clearance and volume of distribution at the 125- and 150-mg/m^2 dose levels were not statistically different. In contrast, SN-38 C_{max} and AUC_{0-24} values in patients receiving the 150-mg/m^2 dose were lower (15% and 22%, respectively) than the same values determined in patients receiving the 125-mg/m^2 starting dose. The metabolic ratio decreased from 3.74% in patients receiving a 125-mg/m^2 dose to 2.16% in patients receiving the 150-mg/m^2 dose. CPT-11 and SN-38 pharmacokinetic parameters in 15 (7 male; 8 female) patients < 65 years of age and in 11 (6 male; 5 female) patients ≥ 65 years of age who received 125 mg/m^2 CPT-11 were compared after administration on week 1. While mean SN-38 C_{max} and AUC_{0-24} values were 25% and 21% greater in patients ≥ 65 years than in patients < 65 years, these differences were not statistically significant.

Among the small number of patients (N=15) who received 125-mg/m^2 irinotecan on both week 1 and week 3, mean CPT-11 parameters were similar. Mean SN-38 C_{max} and AUC_{0-24} values on week 3 were 22 and 27% lower, respectively, than those determined on week 1. While these differences were statistically significant, there was considerable interpatient variability on these two occasions.

Table 1. Mean (± SD) CPT-11 and SN-38 Pharmacokinetic Parameters Following Infusion (90-minute) of 125 or 150 mg/m^2 CPT-11 in Patients with Colorectal Cancer on Week 1 of Therapy

Parameter	125 mg/m^2 [N=26]	150 mg/m^2 [N=9]	p Value[a]
CPT-11:			
T_{max} (hr)	1.59 (0.099)	1.59 (0.076)	0.7622
C_{max} (µg/mL)	1.38 (0.304)	1.73 (0.392)	0.0235
AUC_{0-24} (µg•hr/mL)	13.5 (3.66)	17.1 (2.64)	0.0097
CL (L/hr/m^2)	9.90 (3.91)	8.60 (1.19)	0.4850
V_z (L/m^2)	73.8 (36.5)	68.6 (20.3)	0.8949
$t_{½}$ (hr)[b]	5.03	5.31	—
SN-38:			
T_{max} (hr)	2.31 (0.960)	2.20 (0.892)	0.8649
C_{max} (ng/mL)	34.4 (15.0)	29.1 (13.5)	0.4391
AUC_{0-24} (ng•hr/mL)	459 (218)[c]	359 (112)	0.1976
Metabolic Ratio (%) [d]	3.74 (2.37)[c]	2.16 (0.781)	0.0236

[a] Wilcoxon Rank Sum test
[b] Harmonic mean half-life
[c] N=25
[d] Ratio of SN-38 to CPT-11 AUC_{0-24} expressed as a percent

Overall, 62 pharmacokinetic data sets were obtained in the 35 patients. Model-independent analyses of all data sets yielded the following pharmacokinetic parameters for CPT-11: a terminal half-life of 5.0 hr, a volume of distribution (V_z) of 73.0 L/m^2, and a total body clearance of 9.8 L/hr/m^2. The metabolic ratio (percentage SN-38 AUC_{0-24}/CPT-11 AUC_{0-24}) represented a mean value of 3.2% of the parent AUC_{0-24}. A population pharmacokinetic analysis of all data available from this study and a second study in a similar patient population (M/6475/0006) utilizing the NONMEM computer program generated similar parameters.

Drug Effect and Safety Results:

CPT-11 pharmacokinetic parameters were similar in responders and non-responders. Mean SN-38 C_{max} and AUC_{0-24} values were 25% and 30% higher, respectively, in patients who demonstrated an antitumor response. While these results are consistent with the hypothesis that higher exposure (AUC) to SN-38 is more likely to produce an anticancer effect, the number of patients enrolled in this study was small, and these differences in SN-38 pharmacokinetic parameters were not statistically significant.

The maximum concentration and area under the concentration-time curve of CPT-11 did not correlate with either the intensity (i.e., grade) of late diarrhea or neutropenia. Both SN-38 C_{max} and AUC_{0-24} values correlated statistically with the intensity of neutropenia. A similar positive correlation between these parameters and the intensity of late diarrhea was also observed, but only the correlations between parameters determined on week 3 were statistically significant. Although correlations between SN-38 C_{max} and AUC_{0-24} were observed, there was considerable overlap in these parameters for patients who experienced grades 0 to 4 late diarrhea and neutropenia. This variability is reflected in correlation coefficients which only ranged from 0.27 to 0.53. Thus, identification of patients who are at risk of experiencing severe diarrhea and neutropenia cannot be predicted based upon the relative magnitude of pharmacokinetic indices of exposure to CPT-11 or SN-38.

Conclusions:

- CPT-11 C_{max} and AUC_{0-24} increased proportionately with starting dose
- The clearance and volume of distribution at the 125- and 150-mg/m^2 dose levels were not statistically different
- SN-38 C_{max} and AUC_{0-24} values in patients who received the 150-mg/m^2 dose were lower than the same values determined in patients who received the 125-mg/m^2 starting dose
- Statistically significant differences in CPT-11 and SN-38 pharmacokinetics between patients $\geq$ 65 years and $<$ 65 years were not observed
- There was considerable overlap in CPT-11 and SN-38 pharmacokinetic parameters in patients who experienced grade 0 to 4 late diarrhea and neutropenia

Protocol M/6475/0006
Pharmacokinetics of Irinotecan Hydrochloride (CPT-11) and it's Metabolite (SN-38) in Patients with 5-Fluorouracil-Refractory Colorectal Cancer

Technical Report: Schaaf LJ, Ichhpurani AK, and Elfring GL. Pharmacokinetics of CPT-11 and SN-38: a multicenter, open-label, phase II study of irinotecan hydrochloride (CPT-11) in patients with 5-fluorouracil (5-FU)-refractory colorectal cancer (M/6475/0006). Upjohn Technical Report 7215-95-035, October 24, 1995.

See also:

Dietz AJ, Von Hoff DD, Elfring GL, Albert DG, Wolf DL, Locker PK, et al. A multicenter, open-label, phase II study of irinotecan hydrochloride (CPT-11) in patients with 5-fluorouracil (5-FU)-refractory colorectal cancer (protocol M/6475/0006). Upjohn Technical Report 7216-95-010, in press.

Schaaf LJ, Ichhpurani AK, and Elfring GL. Population pharmacokinetic model for analysis of irinotecan hydrochloride (CPT-11) in patients with metastatic colorectal carcinoma refractory to previous 5-fluorouracil (5-FU)-based chemotherapy (M/6475/0001 and M/6475/0006). Upjohn Technical Report, 7215-95-022, October 25, 1995.

Publication: None

Investigators & Study Sites:

Clinical Phase Phase II

Sponsor's Stated Objectives 1) To assess the antitumor activity of irinotecan hydrochloride (CPT-11) in patients with metastatic colorectal cancer that had progressed within 6 months of one prior 5-fluorouracil (5-FU)-based chemotherapeutic regimen, 2) to evaluate the qualitative and quantitative toxicities of CPT-11 in this patient population, and 3) to study the pharmacokinetics of CPT-11 and its active metabolite SN-38 in metastatic colorectal carcinoma patients and to investigate potential correlations between CPT-11 and/or SN-38 plasma concentrations and response or toxicity.

Methodology

Study Design: This was a multicenter (nine principal investigators), open-label study. CPT-11 was administered as a 90-minute intravenous (IV) infusion once weekly for 4 consecutive weeks, followed by a 2-week rest period (one course). The starting dose of CPT-11 was originally 125 mg/m^2, and this dose was administered to the first 64 patients who were enrolled. The starting dose was reduced to 100 mg/m^2 in an effort to reduce the perceived toxicity associated with the drug. Dosage adjustments were made for each patient based on toxicity. Blood specimens for pharmacokinetic evaluation were obtained during the first course of therapy after the week 1 and week 3 doses.

Number of Patients: Plasma concentration data were available from 162 of the 166 patients who received irinotecan hydrochloride in this Phase II study. Patients (80 male, 82 female) ranged in age from 25 to 84 years (mean 59.8 years) and in weight from 43.1 to 113.9 kg (mean 75.5 kg). On week 1 plasma specimens were collected from 64 patients who received a dose of 125 mg/m^2, while the remaining 98 patients received a 100-mg/m^2 dose. Specimen collection was repeated following dosing on week 3 in 127 patients. Four of these patients had specimens collected on week 4 or week 6 rather than week 3 as scheduled. For pharmacokinetic analysis, the period (i.e., week) designation of specimens collected on these weeks were set equal to 3. Since dosage adjustments after the initial starting dose were made for each patient based on toxicity, the doses administered to these patients on week 3 were often less than doses administered on week 1. Thirty four of the 64 patients who initially received the 125-mg/m^2 starting dose and 59 of the 98 patients who initially received the 100-mg/m^2 received the same dose on both week 1 and week 3.

Selection Criteria: Patients with metastatic colorectal carcinoma that progressed or recurred after one previous 5-FU-based chemotherapeutic regimen or recurred within 6 months after completion of adjuvant therapy participated in this study.

Test Product, Dose & Route of Administration: The dose of CPT-11 was based on the trihydrate and was calculated using body surface area, as determined from actual body weight. The appropriate dose of CPT-11 was diluted and mixed in 500 mL of 5% Dextrose Injection (D5W) and infused IV over 90 minutes once weekly for 4 consecutive weeks.

Sampling Times: Blood samples were scheduled to be obtained as follows: immediately before CPT-11 administration (baseline), at the end of the infusion, and at 2, 4, and 24 hours after the end of the infusion.

Bioanalytical Methods: Plasma concentrations of total CPT-11 and total SN-38 were determined by a high-performance liquid chromatographic (HPLC) method.

Pharmacokinetic Analysis: The plasma concentration-time data of CPT-11 and SN-38 were analyzed by noncompartmental analysis using SAS. To assess the extent of metabolism in patients, a metabolic ratio value, defined as SN-38 AUC divided by CPT-11 AUC (expressed as a percentage), was calculated.

Pharmacodynamic Analyses: The principal side effects observed with the administration of CPT-11 are neutropenia, leukopenia, and late (> 24 hours after administration of CPT-11) diarrhea. In order to examine any relationships between CPT-11 and/or SN-38 pharmacokinetics with principal toxicities (i.e., late diarrhea or neutropenia), pharmacokinetic-pharmacodynamic analyses were performed. For these analyses, the worst grade toxicity (National Cancer Institute [NCI] Common Toxicity Criteria) listed as a medical event during the first course of therapy only was used because of the possible influence of previous CPT-11 administration on the pharmacodynamic effects of either the parent drug or metabolite SN-38.

Statistical Analyses: Statistical comparisons of CPT-11 and SN-38 pharmacokinetic parameters (week 1) between males and females, between patients < 65 years and patients ≥ 65 years, and between responders (ie patients who demonstrated a partial or complete tumor response) and non-responders were performed using the Wilcoxon Rank Sum test (NPAR1WAY procedure in SAS). This non-parametric analogue to the two-sample t-test was used, since distributional analysis using the Shapiro-Wilk test demonstrated that several of the parameters were not normally distributed. Comparisons of pharmacokinetic parameters as a function of CPT-11 dose were performed using a one-way analysis of variance. Scatterplots and linear regression analyses were used to examine the relationship between CPT-11 and SN-38 pharmacokinetic parameters and dose or age. The non-parametric Spearman rank order correlation test was used to assess possible correlations between CPT-11 or SN-38 pharmacokinetic parameters and principal toxicities (NCI grade late diarrhea and neutropenia). Possible relationships between CPT-11 or SN-38 $AUC_{0\text{-}24}$ and toxicities were also explored by examining scatterplots of these parameters as a function of toxicity grade. The relationship between myelosuppression (neutropenia) and systemic exposure was also evaluated by examining scatterplots of percent decrease in absolute neutrophil count (ANC) versus CPT-11 $AUC_{0\text{-}24}$ or SN-38 $AUC_{0\text{-}24}$. The relationship between percent decrease in neutrophils at nadir (first course only) and CPT-11 $AUC_{0\text{-}24}$ or SN-38 $AUC_{0\text{-}24}$ were fit using a sigmoidal maximum effect (sigmoidal E_{max}) model using the PCNONLIN computer program. All statistical comparisons were conducted using the Statistical Analysis System. For all evaluations, statistical significance was defined by $p<0.05$.

Results

Pharmacokinetic Results: Mean (± SD) pharmacokinetic parameters for CPT-11 and SN-38 following a 90-minute infusion of 100 or 125 mg/m^2 CPT-11 on week 1 can be found in Table 1.

CPT-11 C_{max} and AUC_{0-24} increased proportionately with starting dose. The 25% larger starting dose of 125 mg/m^2 resulted in mean CPT-11 C_{max} and AUC_{0-24} values which were 24.4% and 23.6% greater, respectively, than the corresponding values determined in patients receiving the 100-mg/m^2 starting dose. The clearance and volume of distribution at the 100- and 125-mg/m^2 dose levels were not statistically different. In contrast, SN-38 C_{max} and AUC_{0-24} values in patients treated with the 125-mg/m^2 dose were only 20.6% and 11.2% greater, respectively, than the corresponding values determined in patients treated with the lower starting dose. Among patients who received the same dose of CPT-11, either 100 mg/m^2 (N=59) or 125 mg/m^2 (N=34), on both week 1 and week 3, mean CPT-11 parameters were similar. At the 125-mg/m^2 dose, mean SN-38 C_{max} and AUC_{0-24} values on week 3 were 17% and 7% lower, respectively, than those determined on week 1. While these differences approached statistical significance, there was considerable interpatient variability on these two occasions.

Table 1. Mean (± SD) CPT-11 and SN-38 Pharmacokinetic Parameters Following Infusion of 100 mg/m^2 or 125 mg/m^2 CPT-11 in Patients with Colorectal Cancer on Week 1 of Therapy

Parameter	Dose (mg/m^2)		% Difference	p-Value[a]
	100 [N=98]	125 [N=64]		
Age (yr):	59.0 (13.4)	61.1 (9.90)	--	0.7773
CPT-11:				
T_{max} (hr)	1.61 (0.223)	1.68 (0.352)	+ 4.3 %	0.2622
C_{max} (µg/mL)[b]	1.29 (0.486)	1.66 (0.797)	+ 28.7 %	0.0001
AUC_{0-24} (µg•hr/mL)[c]	8.20 (3.19)[d]	10.2 (3.27)[e]	+ 24.4 %	0.0001
CL (L/hr/m^2)	13.2 (4.32)[d]	13.3 (6.01)[e]	+ 0.8 %	0.3578
V_z (L/m^2)	107 (29.4)[d]	110 (48.5)[e]	+ 2.8 %	0.4539
$t_{½}$ (hr)[f]	5.68[g]	5.70[e]	+ 0.4 %	0.7059[g]
SN-38:				
T_{max} (hr)	2.17 (0.742)	2.21 (0.718)	+ 1.8 %	0.6485
C_{max} (ng/mL)[b]	21.8 (10.1)	26.3 (11.9)	+ 20.6 %	0.0087
AUC_{0-24} (ng•hr/mL)[c]	206 (104)[d]	229 (108)[e]	+ 11.2 %	0.0862
$t_{½}$ (hr)[f]	9.79[h]	9.77[i]	- 0.2 %	0.8438[g]
Metabolic Ratio (%):[j]	2.58 (1.10)[d]	2.25 (0.799)[e]	- 12.8 %	0.1214

[a] Wilcoxon Rank Sum test
[b] Peak plasma concentration
[c] Area under the concentration-time curve from time zero to 24 after the end of the infusion
[d] N=90
[e] N=61
[f] Harmonic mean half-life
[g] Comparison of elimination rate constant values
[h] N=87
[i] N=60
[j] Ratio of SN-38 to CPT-11 AUC_{0-24} expressed as a percent

CPT-11 and SN-38 pharmacokinetic parameters in 80 male and 82 female patients who received 100-mg/m^2 or 125-mg/m^2 CPT-11 were compared after administration on week 1. Female patients demonstrated a small (16.7%), but statistically significant, increase in dose-normalized CPT-11 C_{max} compared with males. All other CPT-11 and SN-38 parameter values were within 10% of corresponding values determined in males.

CPT-11 and SN-38 pharmacokinetic parameters in 95 (46 male, 49 female) patients < 65 years of age and in 67 (34 male, 33 female) patients ≥ 65 years of age who received 100-mg/m^2 or 125-mg/m^2 CPT-11 on week 1 were compared. Although statistically significant differences in mean CPT-11 dose-normalized C_{max}, dose-normalized AUC_{0-24}, CL, and λ_z parameters were observed between patients < 65 years and ≥ 65 years, the magnitude of differences was less than 18%. Statistically significant differences in mean SN-38 parameters between the two age groups were not observed.

Overall, 288 pharmacokinetic data sets were obtained in the 162 patients with metastatic colorectal cancer. Model-independent analyses of all data sets yielded the following pharmacokinetic parameters for CPT-11: a terminal half-life of 5.64 hr, a volume of distribution (V_z) of 131 L/m^2, and a total body clearance of 15.6 L/hr/m^2. The terminal half-life of SN-38 was 9.83 hr. The metabolic ratio (percentage SN-38 AUC_{0-24} / CPT-11 AUC_{0-24}) represented a

mean value of 2.41% of the parent AUC_{0-24}. A population pharmacokinetic analysis of all data available from this study and a second study in a similar patient population (M6475/0001) utilizing the NONMEM computer program generated similar parameters for CPT-11.

Drug Effect and Safety Results:

CPT-11 pharmacokinetic parameters were similar in responders and non-responders. Mean SN-38 AUC_{0-24} was 25% higher in patients who demonstrated an antitumor response. While these results are consistent with the hypothesis that higher exposure (AUC_{0-24}) to SN-38 is more likely to produce an anticancer effect, the difference between the two groups was not statistically significant. Maximum concentration of CPT-11 did not correlate with either the intensity (i.e., grade) of late diarrhea or neutropenia. CPT-11 AUC_{0-24} values demonstrated a positive correlation with the intensity of late diarrhea and neutropenia. SN-38 C_{max} and AUC_{0-24} values correlated statistically with the both the intensity of late diarrhea and neutropenia during course 1. Although correlations between CPT-11 and SN-38 pharmacokinetic parameters and toxicity were observed, there was considerable overlap in these parameters for patients experiencing grades 0 to 4 late diarrhea and neutropenia. This variability is reflected in correlation coefficients which only ranged from . Thus, these results indicate that identification of patients who are at risk of experiencing severe diarrhea and neutropenia cannot be predicted based upon the relative magnitude of pharmacokinetic indices of exposure to CPT-11 or SN-38.

Conclusions:

- Maximum CPT-11 plasma concentrations (C_{max}) and area under the concentration time curve (AUC_{0-24}) values increased in a dose-proportionate manner. Although SN-38 C_{max} and AUC_{0-24} values increased with dose, the increase was less than dose proportionate.

- Female patients demonstrated a small (16.7%), but statistically significant, increase in dose-normalized CPT-11 C_{max} compared with males. All other CPT-11 and SN-38 parameter values were within 10% of corresponding values determined in males.

- Small (<18%), but statistically significant, differences in mean CPT-11 dose-normalized C_{max}, dose-normalized AUC_{0-24}, CL, and λ_z parameters were observed between patients < 65 years and patients ≥ 65 years. Statistically significant differences in mean SN-38 parameters between the two age groups were not observed.

- There was considerable overlap in CPT-11 and SN-38 pharmacokinetic parameters in patients who experienced grade 0 to 4 late diarrhea and neutropenia.

Protocol M/6475/0008
Metabolic Fate of Irinotecan in Humans: Correlation of Glucuronidation with Diarrhea

Technical Report: Gupta E, Lestingi TM, Mick R, Ramirez J, Vokes EE, Ratain MJ. Submitted by: Schaaf LJ. Metabolic Fate of Irinotecan in Humans: Correlation of Glucuronidation with Diarrhea (Protocol M/6475/0008). Upjohn Technical Report 7215-95-032, September 25, 1995.

See also

Miller LL, Dietz AJ, Kinney MI. A phase I dose-escalation study of once weekly dosing with irinotecan hydrochloride (CPT-11) for 4-weeks (Protocol M/6475/0008). Upjohn Technical Report 7216-95-011, in press.

Publication: Gupta E, Lestingi TM, Mick R, Ramirez J, Vokes EE, Ratain MJ. Metabolic fate of irinotecan in humans: correlation of glucuronidation with diarrhea. Cancer Res 1994;54:3723-3725.

Investigator & Study Site:

Clinical Phase: Phase I.

Objectives: Determine the maximum tolerated dose (MTD) of irinotecan hydrochloride (CPT-11) when administered to patients with solid tumors or lymphomas. The pharmacokinetic goals of this study were to determine the pharmacokinetics of CPT-11 and its two metabolites, SN-38 and SN-38 glucuronide (SN-38G), and to assess the relationship between gastrointestinal toxicity and the pharmacokinetics of CPT-11 and its metabolites.

Methodology

Study Design: This was a single-center, open-label, dose-escalation study. CPT-11 was administered as weekly doses for 4 consecutive weeks, followed by a 2-week rest period. The dose of CPT-11 was sequentially increased in each group of 3 patients until the MTD was reached. The planned dose levels were 100, 120, 145, 175, and 210 mg/m^2.

Number of Patients: Pharmacokinetic assessment was reported for 21 (12 male, 9 female) of 26 patients enrolled in this study. Patients ranged in age from 39 to 69 years (mean 53 years) and in body weight from 40 to 94 kg (mean 73.4 kg).

Selection Criteria: Patients had either measurable or evaluable disease, were at least 18 years of age, had a Karnofsky's performance status of at least 70%, and had a life expectancy of at least 3 months. All patients met the standard laboratory criteria including criteria for adequate organ function.

Test Product, Dose & Route of Administration: The dose of CPT-11 was based on the trihydrate and was administered intravenously in 500 mL of normal saline solution over 90 minutes.

Sampling Times: Blood samples were obtained at 0, 30, 60, 90 minutes during infusion and at 10, 20, 30, 45, minutes and 1, 1.5, 2, 4, 6, 8, 12, and 24 hours post-dose. Urine samples were obtained for the first 24 hours after infusion.

Bioanalytical Methods: Total CPT-11 and SN-38 concentrations in the plasma were determined using a high performance liquid chromatographic method. SN-38 glucuronide (SN-38G) concentrations were determined as the increase in SN-38 concentrations following incubation of plasma with β-glucuronidase.

Pharmacokinetic Analysis: The plasma concentration-time data of CPT-11, SN-38, and SN-38G were analyzed by noncompartmental analysis using PCNONLIN. The investigators hypothesized that diarrhea is associated with intestinal accumulation of SN-38 and that biliary concentrations of SN-38 may be predictive of gastrointestinal toxicity induced by irinotecan hydrochloride. To assess the relationship between gastrointestinal toxicity and pharmacokinetics of CPT-11 and its metabolites, an empiric pharmacokinetic parameter called the SN-38 "biliary

index" (BI) was defined. This parameter was calculated by multiplying the relative AUC ratio of SN-38 to SN-38G (defined as the "biliary ratio") by the AUC of CPT-11 and represents a measure of the extent of SN-38 secreted into the bile.

Statistical Analysis: Summary statistics (mean, standard deviation [SD]) were calculated for pharmacokinetic parameters. The nonparametric Mann-Whitney test was used to test for differences in pharmacokinetic parameters between patients experiencing grade 0 to 2 or grade 3 to 4 diarrhea.

Results

Pharmacokinetic Results: A summary of the mean (± SD) pharmacokinetic parameters for CPT-11 and its metabolites at each of the four dose levels is listed in Table 1. A summary of the correlation of pharmacokinetic parameters to CPT-11 induced diarrhea is presented in Table 2.

Table 1. Mean (SD) Pharmacokinetic Parameters for CPT-11, SN-38, and SN-38G by Dose Level

Dose Level (mg/m^2)	Number of Patients	CPT-11 AUC (µg•hr/mL)	SN-38 AUC (ng•hr/mL)	SN-38G AUC (ng•hr/mL)	CPT-11 CL ($L/hr/m^2$)
100	3	5.60 (0.967)	102 (28)	399 (344)	20.3 (4.37)
120	6	5.03 (1.11)	127 (45)	269 (233)	24.9 (5.98)
145	10	12.0 (6.79)	271 (119)	1,152 (1,199)	13.9 (5.93)
175	2	14.5 (5.22)	376 (6.29)	1,058 (622)	12.9 (4.62)

Table 2. Comparison of Pharmacokinetic Parameters in Patients Experiencing Grade 0 to 2 or Grade 3 to 4 Diarrhea[a]

Pharmacokinetic Estimates	Grade 0-2 (n=5)	Grade 3-4 (n=5)	p-Value[b]
CPT-11 AUC (µg•hr/mL)	9.16 (8.39-17.9)	14.9 (6.29-23.4)	0.75
SN-38 AUC (ng•hr/mL)	212 (170-283)	269 (162-545)	0.35
SN-38G AUC (ng•hr/mL)	890 (413-2135)	762 (242-4206)	0.46
Biliary ratio	0.27 (0.12-0.41)	0.53 (0.13-0.87)	0.25
Biliary index (ng•hr/mL)	2,276 (1,812-3,812)	4,747 (3,028-7,856)	0.03

a Patients receiving a dose of 145 mg/m^2 were classified according to the worst grade of diarrhea in treatment cycle 1 or 2. Values are represented as median values with the range in parentheses.

b Mann-Whitney test p-value

A 2.6-fold increase in CPT-11 AUC was observed as the dose was increased from 100 mg/m^2 to 175 mg/m^2. Across the four dose levels, variability in CPT-11 AUC as measured by the percentage coefficient of variation ranged from 17% to 57%. AUC estimations for SN-38 and SN-38G demonstrated a 3.7- and 2.7-fold increase, respectively, over the 1.75-fold dose range. The variability in SN-38 AUC, estimated by the percentage coefficient of variation, ranged from 2% to 44% across the four dose levels.

There appeared to be no increase in the SN-38G AUC between the 145-mg/m^2 and the 175-mg/m^2 dose levels, suggesting possible saturation of glucuronidation of SN-38 to SN-38G. The increase in the SN-38 AUC irrespective of decreasing clearance of CPT-11 could be due to the capacity limitation of the glucuronidation pathway for conversion of SN-38 to SN-38G. The interpatient variability (coefficient of variation) in SN-38 glucuronide AUC ranged from 59% to 104%.

A secondary peak in the plasma profile of SN-38 was observed in several patients. This finding is suggestive of hydrolysis of SN-38G by β-glucuronidase in the intestine resulting in enterohepatic circulation of SN-38.

An average of 0.25% and 3% of the dose was excreted in the urine as SN-38 and SN-38G.

At the MTD, median CPT-11 AUC, SN-38 AUC, and biliary ratio values were 62%, 27%, and 96% higher, respectively, in the group of patients who experienced grade 3 to 4 diarrhea than in patients who experienced grade 0 to 2 diarrhea. However, comparison of median values of CPT-11 AUC, SN-38 AUC, SN-38G AUC, and "biliary ratios" between the grade 0 to 2 and grade 3 to 4 group at the 145-mg/m^2 dose level showed no statistically significant differences. The only statistically significant difference in pharmacokinetic parameters between two groups was the "biliary index" with median values of 2276 and 4747 in the grade 0 to 2 and grade 3 to 4 groups, respectively ($p=0.03$). There was also a significant difference in biliary index values between the two groups when patient data was pooled across all dose levels ($p=0.0004$). There was an obvious division of patients based on this index, with about 90% of the patients with grade 3 to 4 diarrhea having index estimates above 4000. In 4 of 5 patients with grade 3 to 4 diarrhea in the 145 mg/m^2 dose level, the biliary index was >4000.

Conclusions:

- Individual patient differences as well as dose-dependency in the SN-38 glucuronidation pathway may have a major influence on SN-38 disposition.
- Biliary index values were greater in patients who experienced grade 3 to 4 diarrhea than in patients who experienced grade 0 to 2 diarrhea.
- The investigators concluded that the relatively higher biliary index values, suggestive of higher biliary concentrations of SN-38, were possibly due to low glucuronidation rates. Since glucuronidation represents the major detoxification pathway of SN-38, patients deficient in this enzyme activity may have a greater susceptibility to diarrhea.

Protocol M/6475/0010

Pharmacokinetics of Irinotecan (CPT-11) and it's Metabolite (SN-38) in Patients with Metastatic Colorectal Cancer Not Previously Treated with Chemotherapy or Radiotherapy

Technical Report: Schaaf LJ, Knuth DW, and Antal EJ. A Pharmacokinetic Addendum to the Phase II, Open-Label Study of Irinotecan Hydrochloride (CPT-11) in Patients with Metastatic Colorectal Cancer Not Previously Treated with Chemotherapy or Radiotherapy (Protocol M/6475/0010). Upjohn Technical Report 7215-95-042, October 20, 1995

See also

Dietz AJ, Von Hoff DD, Albert DG, Wolf DL, Locker PK, Miller LL. Phase II, open label study of irinotecan hydrochloride (CPT-11) in patients with metastatic colorectal cancer not previously treated with chemotherapy or radiotherapy (Protocol M/6475/0010). Upjohn Technical Report, 7216-95-012, in press

Publication: None

Investigator & Study Site:

Clinical Phase Phase II

Sponsor's Stated Objectives The primary objective of this study was to estimate the antitumor activity (response rate) of irinotecan hydrochloride (CPT-11) in patients with metastatic colorectal carcinoma not previously treated with chemotherapy or radiotherapy and to characterize the toxicities of CPT-11 in this patient population. The objectives of the pharmacokinetic portion of the study were to determine the pharmacokinetics of CPT-11 and SN-38 in patients with metastatic colorectal carcinoma who had not previously been treated with chemotherapy or radiotherapy.

Methodology

Study Design: This was a single-center, open-label study of CPT-11 in patients with metastatic colorectal carcinoma that had not been previously treated with chemotherapy or radiotherapy. CPT-11 was administered as a 90-minute intravenous infusion (IV) once weekly for 4 consecutive weeks, followed by a 2-week rest period (one course). The initial starting dose of CPT-11 was 125 mg/m^2. Dosage adjustments were made for each patient based on toxicity. Blood specimens for pharmacokinetic evaluation were obtained during therapy. The course and week number of collection varied from patient to patient.

Number of Patients: Plasma concentration data were available from 22 of the 41 patients. Patients (10 male, 12 female) ranged in age from 26 to 84 years (mean 60.4 years) and in weight from 48 to 100 kg (mean 70.3 kg). Pharmacokinetic assessments were performed in 18 patients after receiving CPT-11 125 mg/m^2, 1 after receiving 100 mg/m^2, 1 after receiving 94 mg/m^2, 1 after receiving 92 mg/m^2, and 1 after receiving 87.5 mg/m^2.

Selection Criteria: Patients had histologically confirmed colorectal carcinoma, with a Karnofsky's performance status of at least 60%, and had a life expectancy of at least 3 months. They had no prior chemotherapy or radiotherapy.

Test Product, Dose & Route of Administration: The dose of CPT-11 was based on the trihydrate and was administered IV in 500 mL of normal saline or 5% dextrose solution over 90 minutes.

Sampling Times: Blood samples were scheduled to be obtained as follows: immediately at the end of the infusion (time 0) and at 5, 10, 15, 30, 60, 90 minutes and 2, 3, 4, 5, 6, and 24 hours after the end of the infusion.

Bioanalytical Methods: Plasma concentrations of total CPT-11 and total SN-38 were determined using a high performance liquid chromatographic method.

Pharmacokinetic Analysis: The plasma concentration-time data of CPT-11 and SN-38 were analyzed by noncompartmental analysis using SAS. To assess the extent of metabolism in patients, a metabolic ratio value, defined as SN-38 AUC divided by CPT-11 AUC (expressed as a percentage), was calculated.

Statistical Analysis: Summary statistics (mean, standard deviation [SD]) were calculated for pharmacokinetic parameters.

Results

Pharmacokinetic Results: A summary of mean (± SD) CPT-11 and SN-38 pharmacokinetic parameters for the 18 patients after administration of a 125-mg/m^2 dose of CPT-11 are listed in Table 1. The 24-hour post-infusion specimen was only collected in 10 patients. Eight of these patients received a dose of 125 mg/m^2. The calculation of all planned pharmacokinetic parameters could only be done on these patients' data.

Table 1. Summary of Mean (S.D.) Pharmacokinetic Parameters Following the Administration of 125 mg/m^2 Doses of CPT-11 in Patients Who Had Not Previously Been Treated with Chemotherapy or Radiotherapy

Parameter	Number of Patients	CPT-11	SN-38
C_{max}	18	1.38 ± 0.428 µg/mL	17.1 ± 7.18 ng/mL
T_{max}	18	1.54 ± 0.059 hr	1.97 ± 0.811 hr
AUC_{0-24}	8	6.66 ± 1.89 µg•hr/mL	90.8 ± 36.9 ng•hr/mL
CL	8	18.3 ± 4.44 L/hr/m^2	-
V_z	8	195 ± 121 L/m^2	-
λ_z	8 (CPT-11) 7 (SN-38)	0.109 ± 0.030 hr^{-1}	0.075 ± 0.042 hr^{-1}
$t_{½}$[a]	8 (CPT-11) 7 (SN-38)	6.4 hr	9.4 hr
Metabolic Ratio	7	-	1.31 ± 0.336%

[a] Harmonic Mean

In comparison to the mean parameter values from two other clinical trials (M/6475/0001 and M/6475/0006), which involved patients possessed similar demographic characteristics but had been treated previously with chemotherapy or radiotherapy, AUC_{0-24} hr values were notably smaller in the patients from this current trial. This was particularly true for SN-38, which was also characterized by a reduced C_{max} from previous studies. Although differing patient characteristics and small sample sizes could have influenced the resulting parameter values, assay performance might have also contributed.

Conclusions:

- The pharmacokinetics of CPT-11 and SN-38 were determined in this addendum to clinical study M/6475/0010 in patients with metastatic colorectal carcinoma who had not previously been treated with chemotherapy or radiotherapy. Overall the area under the curves for both CPT-11 and SN-38 were less then those observed in patients receiving 125 mg/m^2 CPT-11 in other Phase II trials. The difference might be attributable to assay performance.

Protocol M/6475/0026

An Open-Label Clinical Trial to Assess the Safety, Tolerance and Pharmacokinetics of Single Intravenous Doses of CPT-11 Administered Every 3 Weeks

Technical Report: Donehower RC. Submitted by: Schaaf LJ. Pharmacokinetics of CPT-11 and SN-38: Phase I Study of Irinotecan Hydrochloride Administered Every Three Weeks in Selected Patients with Carcinoma (Protocol M/6475/0026; Besselaar Protocol GHBA392B) Upjohn Technical Report 7215-95-033, September 29, 1995

See also

Rock MK. Submitted by: Dietz AJ, Elfring GL, Locker PK. An open-label clinical trial to assess the safety, tolerance and pharmacokinetics of single intravenous doses of CPT-11 administered every three weeks in selected patients with carcinoma (Protocol M/6475/0026, Besselaar Protocol GHBA392B), Upjohn Technical Report 7216-95-005, May 9, 1995

Publication: Rowinsky EK, Grace LB, Ettinger DS, Sartorius SE, Lubejko BG, Chen T, et al. Phase I and pharmacological study of the novel topoisomerase I inhibitor 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin (CPT-11) administered as a ninety-minute infusion every 3 weeks. Cancer Res 1994;54:427–436

Investigators & Study Sites:

Clinical Phase: Phase I

Sponsor's Stated Objectives: This study was conducted to: determine maximum-tolerated dose (MTD) and dose-limiting toxicity (DLT) of irinotecan hydrochloride trihydrate (CPT-11), determine the toxicity profile of CPT-11, characterize the pharmacokinetic parameters of CPT-11, and collect information about antitumor effects of CPT-11 in patients with solid tumors

Methodology

Study Design: This was a single-center, open-label, dose-escalation study

Number of Patients: Pharmacokinetic assessment was performed in 31 (17 male, 14 female) patients enrolled in this study. Patients ranged from 20 to 75 years of age (median 49 years)

Selection Criteria: Patients had histologically proven malignant solid tumor for which no curative treatment existed, were at least 18 years of age, and had a performance status of 2 or better and a life expectancy of at least 3 months. All patients met the standard laboratory criteria including criteria for adequate organ function

Test Product, Dose & Route of Administration: CPT-11 was diluted in 500 mL of 5% dextrose solution and administered as a 90-minute intravenous infusion every 21 days with the following dose levels being studied: 100, 150, 200, 240, 290, or 345 mg/m^2. Doses were based on the trihydrate. Dose modifications were made based on toxicity

Sampling Times: Blood samples were obtained at pre-dose, 5, 10, 20, 30, 45, 60, and 90 minutes and 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours after the end of infusion. Urine was collected continuously for 48 hours in the following divided periods: 0-6 hours, 6-12 hours, 12-24 hours, and 24-48 hours post-treatment

Bioanalytical Methods: Total and lactone CPT-11 and SN-38 concentrations in plasma were determined using high performance liquid chromatographic methods

Pharmacokinetic Analysis: Pharmacokinetic parameters pertaining to the plasma disposition of total CPT-11 and SN-38 were derived for 31 and 25 patients, respectively. The disposition of the lactone forms of CPT-11 and SN-38 were derived for 22 and 29 patients, respectively. Pharmacokinetic modeling and parameter estimation was performed by the non-linear regression program PCNONLIN

Statistical Analysis: Summary statistics (mean, standard deviation [SD]) were calculated for pharmacokinetic parameters. Relationships between pharmacokinetic parameters and categorical gastrointestinal or hematological toxicity were assessed using Spearman's rank-order correlation statistic.

Results

Pharmacokinetic Results: The following tables summarize the mean (± SD) pharmacokinetic parameters for both the total and lactone forms of CPT-11 (Table 1) and SN-38 (Table 2).

Table 1. Summary of Mean (SD) CPT-11 Pharmacokinetic Parameters

CPT-11 Dose (mg/m^2)	No. Subjects	$AUC_{0-\infty}$ (μg•hr/mL)		Cmax (μg/mL)		$t_{½}$[a] (hr)		CL ($L/hr/m^2$)	
		Lactone	Total	Lactone	Total	Lactone	Total	Lactone	Total
100	3	--	4.70 (0.63)	--	1.22 (0.24)	--	3.9	--	21.5 (2.7)
150	3	--	7.60 (2.01)	--	1.42 (0.12)	--	5.8	--	20.8 (6.0)
200	3	--	10.6 (10.3)	--	1.56 (0.59)	--	3.9	--	27.7 (27.0)
240	11	6.83 (5.24)	15.2 (7.41)	1.42 (0.67)	2.57 (0.90)	6.4	5.5	55.9 (33.2)	20.8 (17.5)
290	8	7.78 (3.67)	17.0 (5.20)	1.35 (0.77)	2.37 (0.96)	4.3	6.7	45.1 (19.9)	21.1 (19.8)
345	3	7.71 (6.06)	24.4 (16.1)	1.56 (0.82)	3.05 (1.41)	3.9	3.6	67.0 (46.2)	16.5 (10.9)

[a] Harmonic mean half-life

Table 2. Summary of Mean ± (SD) SN-38 Pharmacokinetic Parameters

CPT-11 Dose (mg/m^2)	No. Subjects	$AUC_{0-\infty}$ (ng•hr/mL)		Cmax (ng/mL)		$t_{1/2}$ (hr)[a]	
		Lactone	Total	Lactone	Total	Lactone	Total
100	3	64.3 (4.7)	103 (11.8)	21.3 (3.6)	30.8 (10.0)	--	2.8
150	3	68.4 (47.4)	239 (190)	8.6 (3.6)	19.3 (13.5)	--	11.6
200	3	123 (35.5)	253 (47.4)	13.1 (4.3)	23.0 (13.5)	--	6.1
240	11	144 (90.8)	274 (158.8)	19.3 (8.2)	32.8 (12.3)	--	6.9
290	8	185 (194)	404 (329)	22.2 (11.6)	48.8 (39.5)	--	3.8
345	3	383 (308)	664 (474)	36.5 (36.3)	78.4 (66.8)	--	14.0

[a] Harmonic mean half-life

Large interindividual differences in C_{max} values were observed for both total CPT-11 and CPT-11 lactone at each dose level; however, the relationship between C_{max} for total CPT-11 and dose was linear.

For total CPT-11, there was significant interindividual variability in $AUC_{0-\infty}$ values at all dose levels, but the correlation with dose appeared to be linear. In addition, clearance (CL), steady-state volume of distribution (V_{ss}), and terminal elimination half-life ($t_{1/2}$) values for CPT-11 did not change with dose, indicating linear pharmacokinetic behavior over the dose range studied. Across all dose levels, mean (± SE) for total CPT-11 were CL = 352 ± 34 mL/min/m^2 (21.1 ± 2.0 L/hr/m^2), volume of distribution of the central compartment (V_c) = 88 ± 27 L/m^2, V_{ss} = 148 ± 20 L/m^2, and harmonic mean $t_{1/2}$ = 5.2 hours.

The $AUC_{0-\infty}$ for CPT-11 lactone represented 44 ± 4% (range, 21 to 83%) of the total $AUC_{0-\infty}$ for CPT-11. The mean clearance and $t_{1/2}$ for CPT-11 lactone was 891 ± 20 mL/min/m^2 (53.5 ± 1.2 L/hr/m^2) and 5.0 hr.

There was also significant overlap in the magnitude of individual C_{max} and $AUC_{0-\infty}$ values for both total SN-38 and SN-38 lactone at all dose levels. Maximum plasma concentrations of SN-38 were observed at 2.2 ± 0.1 hr (range hr) after the end of the infusion. Mean C_{max} values for both total SN-38 and the SN-38 lactone at each dose level were 25- to 47-fold lower than compared with respective values for CPT-11. Similarly, mean $AUC_{0-\infty}$ values were 12- to 34-fold lower for both total SN-38 and the SN-38 lactone compared with the respective values for CPT-11. The $AUC_{0-\infty}$ for SN-38 lactone represented 51 ± 4% (range 7 to 75%) of the total $AUC_{0-\infty}$ for SN-38. The relationship between irinotecan hydrochloride dose and total SN-38 $AUC_{0-\infty}$ or SN-38 lactone $AUC_{0-\infty}$ appeared linear. The harmonic mean $t_{1/2}$ of total SN-38 was 5.9 hours.

The percentage of the administered dose excreted as CPT-11 in the urine over 48 hours was 37.4 ± 4.3% (range 15.4 to 94%). Urinary excretion of SN-38 was not reported.

Conclusions:

- CPT-11 and SN-38 pharmacokinetic parameters appear to increase linearly with dose over the dosage range studied.

- Large interindividual variability in the pharmacokinetic behavior of CPT-11 and SN-38 was observed. Pharmacokinetic variability may be accentuated at higher doses which could increase the likelihood for toxicity in susceptible individuals.

- Neither the symptom complex consisting of diarrhea and abdominal cramps nor the symptom complex of nausea, vomiting, and anorexia could be related to C_{max} or $AUC_{0-\infty}$ values for total or lactone forms of either CPT-11 or SN-38.

- No relationship was observed between hematologic toxicity and either C_{max} or $AUC_{0-\infty}$ values for total or lactone forms of CPT-11.

Protocol M/6475/0027
A Phase I, Open-Label Trial to Assess the Safety, Tolerance and Pharmacokinetics of Weekly Intravenous Doses of CPT-11

Technical Report: Kuhn JG. Submitted by: Schaaf LJ. Pharmacokinetic Evaluation of CPT-11 and SN-38 (Protocol M/6475/0027, Besselaar Protocol GHBA-393B). Upjohn Technical Report 7215-95-030, September 29, 1995.

See also

Rock MK. Submitted by: Dietz AJ, Elfring GL, Locker PK. An open-label clinical trial to assess the safety, tolerance and pharmacokinetics of weekly intravenous doses of CPT-11 in selected patients with carcinoma (protocol M/6475/0027, Besselaar protocol GHBA-393B). Upjohn Technical Report 7216-95-006, May 9, 1995.

Publication: Rothenberg ML, Kuhn JG, Burris III HA, Nelson J, Eckardt JR, Tristan-Morales M, et al. Phase I and pharmacokinetic trial of weekly CPT-11. J Clin Oncol 1993;11(11):2194–2204.

Investigator & Study Site:

Clinical Phase: Phase I

Sponsor's Stated Objectives: Characterize the maximum-tolerated dose (MTD), toxicities, pharmacokinetic profile, and antitumor effects of irinotecan hydrochloride (CPT-11) in patients with refractory solid malignancies.

Methodology

Study Design: Open-label, single-center, dose-escalation study.

Number of Patients: Pharmacokinetic assessment was performed in 17 patients, (12 male, 5 female) enrolled in this study. Patients ranged in age from 19 to 78 years (mean 55 years), in body weight from 52.0 to 102.8 kg (mean 76.0 kg), and in body surface area from 1.47 to 2.22 m^2 (mean 1.90 m^2).

Selection Criteria: Patients must have been at least 18 years of age with a histologically proven malignant tumor for which no curative treatment existed and for which no standard therapy was likely to be of benefit to the patient. Only patients with solid tumors and measurable disease were eligible. Patients must have had a predicted life expectancy of at least 12 weeks and a performance status of 2 or better. Patients must have been off previous anticancer therapy (eg, chemotherapy, radiation, surgery) for at least 4 weeks (6 weeks if prior therapy with nitrosourea or mitomycin C) and have recovered from the toxic effects of that treatment, pretreatment granulocyte count ≥ 3500 cells/mm^3 and a platelet count $\geq 100{,}000$/mm^3 and a hemoglobin ≥ 10 gm/dL, adequate liver function (total bilirubin ≤ 2.0 mg/dL, SGOT <3x the institution upper limit of normal and a prothrombin time within the normal range) and adequate renal function (serum creatinine ≤ 2.0 mg/dL or creatinine clearance ≥ 60 mL/min and normal urinalysis).

Test Product, Dose & Route of Administration: CPT-11 was administered as weekly doses (based on the trihydrate) for 4 consecutive weeks, followed by a 2-week rest period (one course). The initial dose of CPT-11 was 50 mg/m^2 with escalation in separate groups of patients to a maximum dose of 180 mg/m^2. The dose was diluted in 500 mL 5% Dextrose Injection (D5W) and infused over 90 minutes by drip infusion.

Sampling Times: Blood samples were obtained during the first cycle of therapy from at least two patients treated at each dose level. Blood samples were collected at the following time points: 0 min, 15 min, and 45 min into infusion, end of infusion, and at 5, 10, 20, 30, 45, 60, 90 min, and 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours post-infusion.

Urine samples were collected at baseline and every 6 hours for 12 hours, then every 12 hours up to 48 hours.

Bioanalytical Methods: A reverse phase HPLC assay was used to analyze both lactone and total plasma concentrations of CPT-11 and SN-38.

Pharmacokinetic Analysis: The pharmacokinetic parameters were calculated using model-independent methods.

Statistical Analysis: Summary statistics (mean, standard deviation [SD]) were calculated for pharmacokinetic parameters.

Results

Pharmacokinetic Results: The following tables summarize mean (± SD) pharmacokinetic parameters for both the total and lactone forms of CPT-11 (Table 1) and SN-38 (Table 2).

The mean terminal half-life of total CPT-11 was 7.9 ± 2.8 hours while the lactone form of CPT-11 had a terminal half-life of 6.3 ± 2.2 hours. The mean terminal half-life of the active metabolite SN-38 was longer (13.0 ± 5.8 hours and 11.5 ± 3.8 hours for the total and lactone ring forms, respectively). The peak plasma concentrations for CPT-11 occurred at the end of the 90-minute infusion, while the peak concentration of SN-38 occurred at more variable time points ranging from 30 to 90 minutes after the end of the infusion. Plasma clearance of CPT-11 was independent of dose, with a mean clearance of 15.3 ± 3.5 L/hr/m^2 for the total and 45.6 ± 10.8 L/hr/m^2 for the lactone form.

Over the dose range tested (50 to 180 mg/m^2), linear relationships were identified between CPT-11 dose and both the peak plasma concentration and AUC of CPT-11. The relationship between irinotecan dose and SN-38 AUC appeared to be linear at doses less than 150 mg/m^2.

The $AUC_{lactone}$ to AUC_{total} ratio remained relatively constant over the entire dosage range for both CPT-11 (mean 33.9 ± 5.2%) and SN-38 (mean 44.7 ± 10.2%).

Table 1. Summary of Mean (SD) CPT-11 Pharmacokinetic Parameters

CPT-11 Dose (mg/m^2)	No. Subjects	AUC (µg•hr/mL)		Cmax (µg/mL)		t½ (hr)		CL ($L/hr/m^2$)	
		Lactone	Total	Lactone	Total	Lactone	Total	Lactone	Total
50	2	1 13	2 79 (0 11)	0 45	0 89 (0 18)	5 4	5 7 (0 4)	44 3[a]	18 0 (0 7)
80	2	2 12 (0 61)	7 18 (0 53)	0 49 (0.36)	1 12 (0 36)	6 6 (0 1)	8 3 (1 3)	39 3 (11 2)	11 2 (0.8)
100	4	2.23[b] (0.33)	6 83[b] (0 42)	0 69 (0 10)	1 29 (0 19)	7 3 (3 8)	11 5 (6 0)	45 5 (7 4)	14.7[b] (0 9)
125	2	4 58 (2 27)	12 48 (6.80)	0 94 (0 01)	1 70 (0 28)	9 0 (6 7)	9 3 (5 9)	31 2 (15 5)	11.8 (6 4)
150[c]	4	2 81 (0 46)	8 44 (1 60)	0 66 (0 16)	1 56 (0 27)	6 2 (1 6)	9 0 (3 5)	54 5 (8 4)	18 4 (3 2)
180	3	3 83 (0.63)	11 75 (0 94)	0 83 (0 12)	1 97 (0 11)	8 3 (2 7)	9 1 (3.0)	47 8 (7.3)	15 4 (1.2)

[a] n=1
[b] n=3
[c] Parameters determined during week 1 of dosing

Table 2. Summary of Mean (SD) SN-38 Pharmacokinetic Parameters

CPT-11 Dose (mg/m^2)	No. Subjects	AUC (ng•hr/mL)		Cmax (ng/mL)		t½ (hr)	
		Lactone	Total	Lactone	Total	Lactone	Total
50	2	62 3 (3 70)	215 (35 60)	13 3 (9 5)	26 4 (3 3)	9 0 (1 5)	8 6 (2 8)
80	2	162 (75 5)	322 (140)	12 4 (8 1)	31 6 (18 5)	11 6 (4 4)	16 1 (7 0)
100	4	215[a] (97 7)	370[b] (234)	15.3 (9 2)	34 4 (16 7)	13 4[a] (8 1)	17 0[b] (5 8)
125	2	196 (35 7)	450 (192)	16 1 (3 3)	39 3 (4 7)	14 4 (5 3)	12 6 (4 8)
150[c]	4	123[b] (68 2)	410 (282)	13 1 (7 6)	36 7 (18 4)	12 2[b] (0 2)	15 4 (5 6)
180	3	232 (45 0)	368 (83 8)	11 8 (5 0)	26 2 (4 9)	32 9 (16 8)	26 0 (15 4)

[a] n=2
[b] n=3
[c] Parameters determined during week 1 of dosing

Urinary excretion of both CPT-11 and SN-38 in 48-hour urine collections was low (1to 0 ± 0.1% and 0.26 ± 0.18%, of the administered dose for CPT-11 and SN-38, respectively)

In vitro plasma protein binding of both CPT-11 and SN-38 was concentration independent over the concentration ranges tested (CPT-11 50 to 1000 ng/mL, SN-38 10 to 160 ng/mL). A mean of 68.2 ± 2.1% of CPT-11 and 95.6 ± 0.8% of SN-38 was protein bound

Conclusions:

- The clearance of CPT-11 was independent of dose. The relationship between CPT-11 dose and SN-38 AUC appeared to be linear at doses less than 150 mg/m^2
- The mean half-life of total CPT-11 was approximately 8 hours, while the half-life of the active metabolite SN-38, was about 13 hours
- The ratio of the lactone AUC to total AUC remained relatively constant over the entire dose range for both CPT-11 and SN-38
- Renal excretion is not a major route of elimination for either CPT-11 or SN-38
- Plasma protein binding was independent of concentration with about 68% of CPT-11 and 96% of SN-38 bound to protein

Clinical Pharmacology and Biopharmaceutics

NDA: 20,571 **Submission Date**: December 28, 1995

RE: information request to sponsor

Generic Name: irinotecan HCl

Formulation: injection

Sponsor: The Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001-0199

Reviewer: Gene M. Williams, Ph.D.

Background

The NDA for irinotecan was filed without submission of the raw data in item 6 in electronic format. At the pre-NDA meeting with the sponsor, a request for electronic submission was conveyed by Dr. Mehta of our Division

Information request to sponsor

1. We ask that all raw data contained in item 6 be submitted in electronic format (ASCII or Microsoft EXCEL 5.0 for Windows 3.1, or formats readily converted to ASCII or EXCEL 5.0 by tools possessed by the Agency).

Patient/subject data for the 300+ individuals with PK should include a number that uniquely identifies each subject, study number, site number, absolute dose administered, infusion rate, actual sampling time, concentrations, pharmacodynamic/toxicodynamic measurements and demographic data that might influence parameters (i.e., age, weight, body surface area, gender, ethnicity, co-medications, smoking status, etc.).

We also ask that the actual code used in modeling be submitted in electronic format (ASCII or WP6.0a for Windows 3.1 or formats readily converted to ASCII or WP6.0a for Windows 3.1 by tools possessed by the Agency).

2. Electronic submission of as much of the text and figures of item 6 as possible would be helpful (ASCII or WP6.0a for Windows 3.1 or formats readily converted to ASCII or WP6.0a for Windows 3.1 by tools possessed by the Agency). The desire for electronic submission of text and figures is distinct from the request in 1. above, and solely for the convenience of the reviewer. Since any electronic submission of text and figures is a

convenience for the reviewer, mixed electronic formats or submission of only selected studies or portions of selected studies is encouraged. Absence of electronic submission of text and figures will not adversely affect review of the submission.

JAN 31 1996

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-571 **Submission Date**: December 28, 1995

Generic Name, Dose, And Formulation: Irinotecan HCl Injection, 125 mg/m^2, 20 mg/mL

Brand Name: Camptosar

Sponsor: The UpJohn Company
Kalamazoo, MI 49001

Reviewer: N.A.M. Atiqur Rahman

Submission: New Drug Application (original)

Filling Issues

Irinotecan hydrochloride (CPT-11) is a water soluble, semi-synthetic derivative of the plant alkaloid camptothecin. The drug represents "topoisomerase I inhibitors" class of cytotoxic chemotherapeutic agents. CPT-11 is a prodrug which is converted by carboxyesterases to the metabolite SN-38 (7-ethyl-10-hydroxycamptothecin). The cytotoxic and antitumor activities of CPT-11 are principally mediated by the metabolite SN-38. The drug is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy. The recommended starting dose of CPT-11 injection is 125 mg/m^2 administered over 90 minutes. Each cycle of therapy will consist of 125 mg/m^2 administered once weekly for 4 weeks, followed by a 2-week rest period.

The sponsor has submitted a list of four Phase I and three Phase II studies where the pharmacokinetics of the drug were evaluated (**appendix**). The studies appear to provide descriptive pharmacokinetics, dose proportionality, drug metabolism, pharmacokinetics in special population, drug-drug interaction, population pharmacokinetics, pharmacokinetic /pharmacodynamic assessment of irinotecan hydrochloride. The sponsor has also submitted a list of other ongoing clinical studies which include pharmacokinetic assessment (**appendix**).

The sponsor has provided adequate assay description and validation for the NDA review to begin.

The Biopharmaceutics section of the NDA is indexed and paginated and organized in a manner to allow substantive review to begin.

Recommendation:

The NDA 20-571 (irinotecan hydrochloride injection) is acceptable for filing from the clinical pharmacology and biopharmaceutics perspective.

N.A.M. Atiqur Rahman, Ph. D. 1/31/96
Team Leader, Oncology Drug Products
Division of Pharmaceutical Evaluation I

Mehul U. Mehta, Ph.D. 1/31/96
Deputy Director
Division of Pharmaceutical Evaluation I

cc: NDA 20-571
HFD-150/Vaccari
HFD-150/Division file
HFD-860 (Malinowski, Mehta, Rahman)
HFD-850 (Drug, Chron, Reviewer's files)

APPENDIX

Table 6.B-2. Location of Study Documents
Phase I Clinical Pharmacokinetic Studies of Irinotecan Hydrochloride (CPT-11)

Protocol No Sponsor Investigator(s)	Study Design/Regimen	Location of Study Synopsis	Location of Study Report	Reference No.
M/6475/0026[a] Donehower	Single-center, open-label, single dose, dose-escalation study to determine the maximum-tolerated dose (MTD) of CPT-11 when administered as a 90-min IV infusion once every 3 wk to patients with various solid tumors	Vol. - 1.36 Page - 6/1/71	TR 7215 95 033 Vol. - 1.39 Page - 6/4/69	11
M/6475/0027[a] Rothenberg & Von Hoff	Single center, open-label, multiple-dose dose-escalation study to determine the MTD of CPT-11 when administered as a 90-min IV infusion 1X/wk for 4 wk, followed by a 2-wk rest period, to patients with various solid tumors	Vol. - 1.36 Page - 6/1/75	TR 7215 95 030 Vol. - 1.39 Page - 6/4/7	10
M/6475/0008[b] NCI Vokes	Single-center, open-label, multiple-dose, dose-escalation study to determine the MTD of CPT-11 when administered as a 90-min infusion 1X/wk for 4 wk, followed by a 2-wk rest period, to patients with various solid tumors or lymphomas refractory to previous chemotherapy	Vol. - 1.36 Page - 6/1/64	TR 7215 95 032 Vol. - 1.39 Page - 6/4/1	9
Study Report DM111[c]	Multi-center, open-label, dose-escalation study to determine the MTD, safety, and pharmacokinetics of CPT-11 when administered as a single intravenous infusion over 30 min to patients with various solid tumors refractory to previous chemotherapy	Vol. - 1.36 Page - 6/1/51	TR 7215-95-031 Vol. - 1.39 Page - 6/4/172	15

[a] Conducted when IND was held by
[b] Conducted under IND held by the investigators in a published manuscript. The protocol was subsequently amended to include an additional 24 patients to study the effects of sex and race on CPT-11 pharmacokinetics. This phase of the study was ongoing as of the 03/31/95 data cut-off date for the NDA.
[c] Study was conducted in and submitted to IND when it was held by the study was monitored by GH Besselaar Associates (Princeton, NJ). This phase of the study is complete

Table 6.B-3. Location of Study Documents
Phase II Clinical Pharmacokinetic Studies of Irinotecan Hydrochloride (CPT-11) in Patients with Colorectal Cancer

Protocol No. Sponsor Investigator(s)	Study Design/Regimen	Location of Study Synopsis	Location of Study Report	Reference No.
M/6475/0001[a] Upjohn San Antonio Regional[b]	Open-label, US Phase II study in patients with metastatic colorectal carcinoma that recurred or progressed after one prior treatment with a 5-FU-based chemotherapeutic regimen.	Vol. - 1.36 Page - 6/1/54	TR 7215-95-034 Vol. - 1.39 Page - 6/4/196	16
M/6475/0006 Upjohn CPT-11 Study Group[b]	Multicenter, open-label, US Phase II study in patients with metastatic colorectal carcinoma that recurred or progressed after one prior treatment with a 5-FU-based chemotherapeutic regimen.	Vol. - 1.36 Page - 6/1/59	TR 7215-95-035 Vol. - 1.40 thru 1.41 Page - 6/5/1 thru 6/6/372	17
M/6475/0010	Single-center, open-label, US Phase II study in patients metastatic colorectal cancer not previously treated with chemotherapy or radiotherapy.	Vol. - 1.36 Page - 6/1/68	TR 7215-95-042 Vol. - 1.42 Page - 6/7/18	41

[a] The US development of CPT-11 was initially undertaken by
acting as their agent. US development of CPT-11 was licensed to The Upjohn Company in November, 1993. Pharmacokinetic specimens were collected between January 8 and July 2, 1993.

[b] A list of study centers is included in the clinical study report.

[c] Conducted under IND [redacted] held by the

F. ONGOING STUDIES

As of the data cut-off date for this submission, nine clinical studies which included pharmacokinetic assessment, were ongoing in the United States. Included in these nine studies were six phase I studies of different dosing regimens and/or combination therapy and three phase II studies of CPT-11 in patients with lung cancer. A description of these studies is provided in Tables 6.F-1 and 6.F-2. An in vitro assessment of CPT-11 and SN-38 partitioning into human RBCs is ongoing.

Table 6.F-1. Ongoing US Phase I Studies of CPT-11 with Pharmacokinetic Assessment

Protocol No. Investigator(s)	Study Design	Drug	Regimen		No. of Pts[a]
M6475/0007 Saltz	Open-label, non-comparative, dose-escalating study to determine the maximum-tolerated dose (MTD), dose-limiting toxicity (DLT) & pharmacokinetics of combination therapy of CPT-11, leucovorn & 5-fluorouracil (5-FU) in patients with various malignancies.	CPT-11	100, 125, or 150 mg/m² intravenously (IV)	1X/wk for 4 wk followed by 2-wk rest	24
		Leucovorn	20 mg/m² IV		
		5-FU	210, 285, 340, 425 or 500 mg/m² IV		
M6475/0008[b] (Amendment) Vokes	Open-label, multiple-dose study at the MTD to evaluate the effects of gender & race on pharmacokinetics in 24 patients with various solid tumors or lymphomas.	CPT-11	145 mg/m² IV 1X/wk for 4 wk, followed by a 2-wk rest		22
M6475/0009[b] Parnes	Open-label, non-comparative, dose-escalating study to determine the MTD, DLT & pharmacokinetics of combination therapy with CPT-11, 5-FU & leucovorn in patients with various malignancies.	5-FU	500 mg/m² IV 1X/wk (on day 3) for 4 wk, followed by 2-wk rest		9
		Leucovorn	500 mg/m² IV 1X/wk (on day 3) for 4 wk, followed by 2-wk rest		
		CPT-11	Escalating doses, 25, 50, ... mg/m² IV on wk 1 & 4		
		5-FU	Escalating doses, 250, 300, 350, ... mg/m²/d IV x 4 d (days 2-5) q 8 wk		8
		Leucovorn	20 mg/m²/d IV x 4 d (days 2-5) q 8 wk		
		CPT-11	100 mg/m² IV 1X/wk (day 1) for 4 wk, followed by 2-wk rest		
		5-FU	Escalating doses, 250, 300, 350, ... mg/m²/d IV x 4 d (days 2-5) q 4 wk		0
		Leucovorn	20 mg/m²/d IV x 4 d (days 2-5) q 4 wk		
		CPT-11	100 mg/m² IV 1X/wk (on day 1) q 2 wk (wk 1, 3 & 5)		

a Enrolled as of 03/31/95 (data cut-off date for NDA submission).
b Conducted under IND [redacted] held by the

continued

Table 6.F-1. Ongoing US Phase I Studies of CPT-11 with Pharmacokinetic Assessment

Protocol No. Investigator(s)	Study Design	Drug	Regimen	No. of Pts[a]
M6475/0013 Rothenberg	Open-label, non-comparative, dose-escalating study to determine the MTD, DLT & pharmacokinetics of CPT-11 when administered every 2 wk to patients with refractory colorectal cancer.	CPT-11	125-350 mg/m^2 IV every other wk	4
M6475/0024 Saltz	Open-label, non-comparative, dose-escalating study to determine the MTD, DLT & pharmacokinetics of combination therapy with CPT-11 & cisplatin in patients with various malignancies.	Cisplatin	30 mg/m^2 IV	7
		CPT-11	85, 85, 110, 125, or 145 mg/m^2 IV 1X/wk for 4 wk, followed by a 2-wk rest	
M6475/0032 Drengler	Open-label, non-comparative, dose-escalating study to determine the MTD, DLT & pharmacokinetics of oral CPT-11 in patients with various malignancies.	CPT-11	20, 40, 66, 100, or 140 mg/m^2 orally 1X/d for 5 days, repeated q 3 wk.	3

[a] Enrolled as of 03/31/95 (data cut-off date for NDA submission).

Table 6.F-2. Ongoing US Phase II Studies of CPT-11 with Pharmacokinetic Assessment

Protocol No. Investigator(s)	Study Design	Drug	Regimen	No. of Pts[a]
LUNG CANCER				
M6475/0015 Multicenter	Open-label, non-comparative study in patients with stage IIIB or IV non-small-cell lung cancer & no prior chemotherapy.	CPT-11	60 mg/m^2 IV 1X/wk for 4 wk, followed by a 1-wk rest.	29
		Cisplatin	80 mg/m^2 IV 1X/wk for 1 wk (administered 2 h after CPT-11 dose), followed by a 3-wk rest.	
M6475/0018 Multicenter	Open-label, non-comparative study in patients with stage IIIB or IV non-small-cell lung cancer & no prior chemotherapy.	CPT-11	100 mg/m^2 1X/wk for 4 wk, followed by a 2-wk rest.	36
M6475/0029 Multicenter	Open-label, non-comparative study in patients with small-cell lung cancer refractory to one prior chemotherapeutic regimen.	CPT-11	125 mg/m^2 IV 1X/wk for 4 wk, followed by a 2-wk rest.	1

[a] Enrolled in the study as of 03/31/95 (data cut-off date for NDA submission).

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REVIEW FOR HFD-150
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

Microbiologist's Review of NDA 20-571
Response to Post-approval Request
June 7, 1996

A. 1. **APPLICATION NUMBER:** NDA 20-571

APPLICANT: The Upjohn Company
7000 Portage Road
Kalamazoo, MI 49001

2. **PRODUCT NAMES:** CAMPTOSAR Injection (Irinotecan Hydrochloride)

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** sterile nonaqueous solution (20 mg/ml) in a single dose 5 ml vial. CAMPTOSAR is intended for dilution with 5% Dextrose Injection or 0.9% NaCl Injection, just prior to intravenous infusion

4. **METHODS OF STERILIZATION:** Aseptic filling

5. **PHARMACOLOGICAL CATEGORY:** Anti-neoplastic, for treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy.

6. **DRUG PRIORITY CLASSIFICATION:** 1P

B. 1. **DATE OF INITIAL SUBMISSION:** December 28, 1995

2. **AMENDMENT:** none

3. **RELATED DOCUMENTS:** INDs:
DMF

4. **RECEIVED FOR REVIEW:** January 24, 1996
Date of Consult Request: January 3,1996

C. **REMARKS:**

CAMPTOSAR (Irinotecan Hydrochloride) Injection, a single-dose parenteral formulation, is supplied as a sterile solution and contains no preservatives. The drug product contains sorbitol and lactic acid as excipient, and a pH of 3.5. It is a derivative of

camptothecin a cytotoxic chemotherapeutic agent and a specific inhibitor of mammalian topoisomerase I. The drug product is to be manufactured by the Upjohn Company in Kalamazoo, MI

Upjohn submitted a response to the post-approval request on June 6, 1996. They have addressed all the comments made by microbiologist. Upjohn has agreed to provide post-approval information with regard to the validation for depyrogenation (experimental details on endotoxin controls sterility and release criteria (selections of vials representative of an entire production run), and a microbiological environmental monitoring program. Upjohn disagreed with the Review Microbiologist's recommendation on the basis of monitoring anaerobic microorganisms, but the response from Upjohn is acceptable

D. CONCLUSIONS:

The applicant has provided post-approval commitments to address the microbiology issues. The submission is recommended for approval on the basis of sterility assurance.

Brenda Uratani 6/7/96

Brenda Uratani, Ph.D.
Review Microbiologist

cc:

PK 6/7/96

NDA 20-571
HFD-150 / Div. File
HFD-805 /Uratani
HFD-150 /CSO/Vaccari
drafted by: Breuda Uratani, 6/7/96
R/D initialed by: P.Cooney, 6/7/96

REVIEW FOR HFD-150
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

Microbiologist's Review # 1 of NDA 20-571
February 27, 1996

A. 1. **APPLICATION NUMBER:** NDA 20-571

APPLICANT: The Upjohn Company
7000 Portage Road
Kalamazoo, MI 49001

2. **PRODUCT NAMES:** CAMPTOSAR Injection (Irinotecan Hydrochloride)

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** sterile nonaqueous solution (20 mg/ml) in a single dose 5 ml vial. CAMPTOSAR is intended for dilution with 5% Dextrose Injection or 0.9% NaCl Injection, just prior to intravenous infusion.

4. **METHOD(S) OF STERILIZATION:** Aseptic filling

5. **PHARMACOLOGICAL CATEGORY:** Anti-neoplastic, for treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy.

6. **DRUG PRIORITY CLASSIFICATION:** 1P

B. 1. **DATE OF INITIAL SUBMISSION:** December 28, 1995

2. **AMENDMENT:** none

3. **RELATED DOCUMENTS:** INDs:
DMFs:

4. **RECEIVED FOR REVIEW:** January 24, 1996
Date of Consult Request: January 3,1996

C. **REMARKS:**

CAMPTOSAR (Irinotecan Hydrochloride) Injection, a single-dose parenteral formulation, is supplied as a sterile solution and contains no preservatives. The drug product contains sorbitol and lactic acid as excipient, and a pH of 3.5. It is a derivative of camptothecin, a cytotoxic chemotherapeutic agent and a specific inhibitor of mammalian topoisomerase I. The drug product is to be manufactured by the Upjohn Company in Kalamazoo, MI.

D. CONCLUSIONS:

The application is recommended for approval on the basis of sterility assurance. However, the applicant should make a commitment to provide the information listed in "Microbiologist's Letter to the Applicant" postapproval.

Brenda Uratani 2/27/96

Brenda Uratani, Ph.D.
Review Microbiologist

3/6/96

cc:

NDA
HFD-150 / Div. File
HFD-805 /Uratani
HFD-150 /CSO/Vaccari
drafted by: Brenda Uratani, 2/27/96
R/D initialed by P.Cooney, 2/27/96

L. Faccagi
JUN 14 1996

DIVISION OF ONCOLOGIC DRUG PRODUCTS/HFD-150
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-571 **DATE REVIEWED:** 13-JUN-1996
REVIEW #: 2 **REVIEWER:** Robert P. Barron

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT BC 012	10-JUN-1996	11-JUN-1996	11-JUN-1996

NAME & ADDRESS OF APPLICANT: The UPJOHN COMPANY
7000 Portage Road
Kalamazoo, MI 49002-0199

DRUG PRODUCT NAME

Proprietary:	CAMPTOSAR™ INJECTION
Established:	Irinotecan Hydrochloride Trihydrate
Code Name and Number:	U-101440E (Upjohn); CPT-11 (Yakult)
Chem.Type/Ther.Class:	1-P

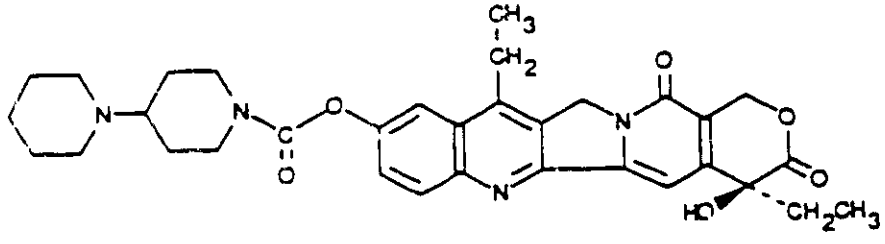
PHARMACOL. CATEGORY/INDICATION: Antineoplastic agent (topoisomerase I inhibitor) indicated for the treatment of patients with following carcinoma of the colon or rectum whose disease has recurred or progressed following 5-fluorouracil-based therapy.

DOSAGE FORM:	Injection
STRENGTHS:	20 mg/mL as HCl salt, Trihydrate
ROUTE OF ADMINISTRATION:	IV infusion
Rx/OTC:	xx **Rx** ___ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: (4*S*)-4,11-diethyl -4-hydroxy-9-[4-piperidinic piperidino)carbonyloxy]-1*H*-pyrano[3',4',6,7]indolizino[1,2-*b*]quinoline-3,14(14*H*,12*H*)dione hydrochloride, trihydrate

Empirical Formula: $C_{33}H_{38}N_4O_6.HCl.3H_2O$ M.W. = 677.19



• HCl

• $3H_2O$

SUPPORTING DOCUMENTS: None

RELATED DOCUMENTS (if applicable): None

CONSULTS: None

REMARKS:

While the amber vial and label limits the effectiveness of point-of-use visual inspection for gross particulate contamination, the inclusion of a test and limits at release for particulate matter which is one-half that of the current USP <788> limits for small volume injections is considered acceptable. However, no data on the extent of particle load have been provided in the applicant's response of 10-JUN-1996 by method GP 485 and it appears that the particulate levels have not been monitored under the stability protocol. Both sets of data should be submitted to NDA.

However, it should be noted that this product will be admixed with D5W and 0.9% Bacteriostatic Sodium Chloride Injection (normal saline) which also must meet the USP limits for particulate matter under Small volume injections and therefore the added particle load of the 5 mL product is not considered significant.

CONCLUSIONS & RECOMMENDATIONS:

Based on the consideration of the specification for the product and those of the admixing solvents, the response is considered acceptable and the application is approvable. Method GP-450 will be subject to the normal validation requirements.

Considered

Robert P. Barron
Review Chemist

RHWood 6-14-96
Rebecca H. Wood, Ph.D.
~~Oncology~~ Chemistry Team Leader

Concur only if Addendum of 6-14-96 (RHW) is added to AP letter.

cc: Orig. NDA 20-571
HFD-150/Division File
HFD-150/RPBarron/date
HFD-150/LVaccari
HFD-150/RHWood

L Vaccari

JUN 14 1996

NDA 20-571
CAMPTOSAR INJECTION (irinotecan hydrochloride)

CHEMISTRY TEAM LEADER REVIEW: 6-14-96

ADDENDUM TO CHEMISTRY REVIEW (R. Barron, 6-13-96):

THE FOLLOWING PARAGRAPHS SHOULD BE ADDED TO THE NDA APPROVAL LETTER:

The approval of the application is conditional upon revision of the protocol for drug product stability studies to include specificatons and test methods for the monitoring of visible and subvisible particulate matter, as well as colloidal, suspended, or precipitated drug substance or other materials. The stability study protocol shall include the testing of each production batch of Camptosar Injection (irinotecan hydrochloride) at monthly intervals up to the two year expiration time. Test results shall be reported to the FDA at 3 month intervals, or sooner if failures occur.

The reasons for the above condition are as follows:

(1) The drug product has not been monitored for particulate matter at the time of release or in any stability studies covering the two year expiry time, as recommended by the USP 23 and the FDA guidelines for injectable solutions. In addition, the drug substance has a relatively low solubility and stability.

(2) The drug product container is a dark amber color with a label covering most of the surface, making it impossible for the end user to examine the contents. USP 23 (p.1651) states that the container for injectable drug products is to be made of material that permits inspection of the contents.

Rebecca H Wood 6-14-96
Rebecca H. Wood, Ph.D.
Chemistry Team Leader

Distribution: HFD-150 / NDA 20-571 orig.
/ Div. File
/RHWood
/RBarron/CPHolberg/RDeLap
/LVaccari/DPease

Chem

DIVISION OF ONCOLOGIC DRUG PRODUCTS/HFD-150
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-571

DATE REVIEWED: 15 May 1996

REVIEW #: 1 (Original)

REVIEWER: Robert P. Barron

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	28-DEC-95	28-DEC-95	02-JAN-96
Amendment BC	13-FEB-96	15-FEB-96	20-FEB-96

NAME & ADDRESS OF APPLICANT:

The UPJOHN COMPANY
7000 Portage Road
Kalamazoo, MI 49002-0199

DRUG PRODUCT NAME

Proprietary: CAMPTOSAR™ INJECTION
Established: Irinotecan Hydrochloride Trihydrate
Code Name and Number: U-101440E (Upjohn); CPT-11 (Yakult)
Chem.Type/Ther.Class: 1-P

PHARMACOL. CATEGORY/INDICATION: Antineoplastic agent (topoisomerase I inhibitor) indicated for the treatment of patients with following carcinoma of the colon or rectum whose disease has recurred or progressed following 5-fluorouracil-based therapy.

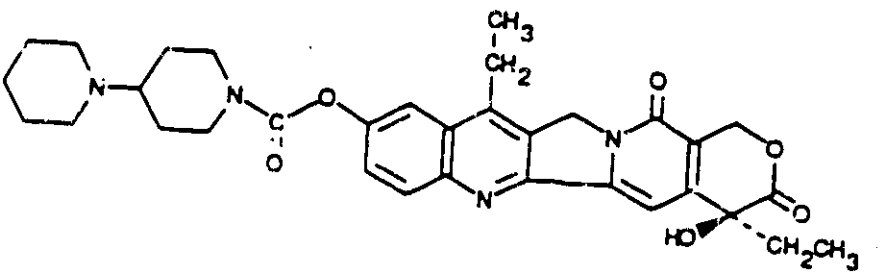
DOSAGE FORM: Injection
STRENGTHS: 20 mg/mL as HCl salt, Trihydrate
PROPOSED DOSING SCHEDULE: 125 or 150 mg/m² 1x/wk for 4 wk/2 wk rest
ROUTE OF ADMINISTRATION: IV infusion over 90 minutes
Rx/OTC: xx Rx ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: (4*S*)-4,11-diethyl-4-hydroxy-9-[4-piperidiniopiperidino)carbonyloxy]-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-3,14(14*H*,12*H*)dione hydrochloride, trihydrate

Empirical Formula: $C_{33}\ H_{38}\ N_4\ O_6.HCl.3H_2O$ M.W = 677.19

Stereochemistry: Only the S enantiomer of the molecule at the chiral center of the "E" ring (4 position) is active and will be used in the product..



• HCl

• $3H_2O$

SUPPORTING DOCUMENTS:

Document	DMF holder	Function	Status
DMF			Acceptable
DMF			Acceptable
DMF			Acceptable

RELATED DOCUMENTS (if applicable):

1. Memorandum and Minutes of meeting dated September 6, 1995 with applicant on pre-NDA Chemistry issues.
2. Chemistry Review by Liang Zhou, Ph.D. of IND dated May 18, 1995
3. Memorandum dated May 8, 1995 from Peter Cooney, Supervisory Microbiologist to IND on acceptability of aseptic fill manufacturing procedures.
4. Fax dated January 26, 1996 from Upjohn provided address of manufacturing facilities for EER.

CONSULTS:

1. Microbiological consult dated for review of manufacturing procedures completed on 27-FEB-1996 with deficiencies summarized in section B.8. of this review.
2. Environmental Assessment consult was dated . In HDF-102 reply dated January 29, 1996 the preliminary review found the EA was fileable & appeared to qualify as Tier 0 approach. The applicant was subsequently asked to provide information on the species of tree, etc., which is the source of the starting for the product.
3. EER for CGMP compliance of three manufacturing sites involved in isolation and synthesis of bulk drug was issued on January 24, 1996. Mr. Ralph Erickson of KAN-DO has been assigned to do the inspection of three locations in on, or about. April 15, 1996. EER were acceptable per communication from Mr. Erickson to L. Vaccari reported in team meeting of 25-APR-1996
4. A request for trademark review dated March 7, 1996 found the proposed trademark, Camptosar™ Injection acceptable by a narrow margin on
5. Consult to Dr. Koutsoukos for statistical analysis of stabiltiy data to establish expiration date for product. Review is pending.

REMARKS:

1. Foreign Marketing Experience. Irinotecan hydrochloride is currently approved and marketed in Japan under the tradenames of CAMPTO Injection and TOPOTECIN Injection In September 1995 the product was approved for sale in France under the tradename CAMPTO for the treatment of inoperable advanced colorectal cancer in patients who had been previously treated with adjuvant or palliative 5-fluorouracil (5-FU) chemotherapy.

2. US Experience. contracted the product development of a CPT-11 parenteral formulation to In 1990, IND was filed and

clinical trials were begun in the US under the auspices of G.H. Besselaar Associates of Princeton, NJ. In April 1994, signed an agreement with The Upjohn Company to finish development of and to secure registration of CPT-11 for sale in the US. The Upjohn Company will manufacture the product for the US market at their Kalamazoo facility using advanced aseptic processing based on rationale described in IND This procedure found acceptable by CDER Microbiologists. It should be noted that the product for trials was manufactured using heat sterilization.

3. **Exclusivity.** Exclusivity under patent # 4,604,463 is to 5-July-2004. Upjohn requests five years of exclusivity for drug product not previously marketed in the US.

4. **Pivotal Trials.** The NDA includes information on eleven variations of the formulation of the product manufactured by three firms, Upjohn (1), and which were used in eighty four trials. Each product was manufactured using sterilization except the Upjohn product, which was processed. The marketed product will be manufactured using Formulation of Upjohn by processing. The reviewing medical officers have identified three pivotal trials to support the efficacy of the product and involved eleven different lots of the product as summarized in Section B.5.B of this review.

5. **Clinical/Stability Lots.** Three lots of product at 27 L yielding approximately 5,000 finished vials have been manufactured by Upjohn and were studied as demonstration batches in the NDA. Actual production levels upon approval will be 40 L or approximately 7,475 vials.

3. **Pharmacological/Metabolism.** Irinotecan hydrochloride (CPT-11) is classified as a pro-drug due to the metabolic generation of the 5-hydroxy analog, identified as SN-38, as the active moiety (see proposed metabolic pathway below). . Both CPT-11 and SN-38 exhibit pH-dependent equilibrium between the lactone (active) and hydroxy acid (inactive) forms. ~~So~~ s result the CPT-11 product is formulated, and usually administered in mildly acidic solution (i.e., 5% dextrose in water (preferred) or 0.9% normal saline) by IV over 90 minutes. The efficacy and absence of toxicity associated with the administration of the product has been described as "schedule dependent" rather than "dose dependent" due to bioavailability (pharmacokinetic) considerations and the requirement of metabolism of CPT-11 to yield the active moiety.

Figure 2.F-3. Proposed Metabolic Pathway for CPT-11

CONCLUSIONS & RECOMMENDATIONS:

The NDA is not approval from a chemistry standpoint. The applicant should adequately address the concerns in the noted in he draft letter in Part H of the review.

Robert P. Barron 5/15/96
Robert P. Barron
Review Chemist, HFD-150

Rebecca H. Wood, Ph.D.
Chemistry Team Leader, HFD-150

cc: Orig. NDA 20-571
HFD-150/Division File
HFD-150/RPBarron/5/15/96
HFD-150/LVaccari
HFD-150/RHWood
R/D Init by:
filename: N20571.RD4

stat

Statistical Review and Evaluation

NDA#: 20-571 MAY 28 1996

Title: CAMPTOSAR™ Injection (Irinotecan Hydrochloride Injection)

Applicant: The Upjohn Company

Name of Drug: CPT-11 (Irinotecan)

Indication: Treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy

Documents Reviewed: Volumes 1, 43, 44, 45 of submission dated December 28, 1995. Volume 1 of submission dated April 1, 1996, and Volumes 1-4 of submission dated April 15, 1996.

Medical Officers: Isagani Chico, M.D. and Anthony Murgo, M.D.

RELEVANT STATISTICAL ISSUES:

1) The analyses based on the pooled data of the three pivotal studies should be cautiously interpreted. There were some minor differences in the eligibility criteria among the pivotal studies. There were at least two different dose levels used within each study, and at least three different dose levels in all studies. No formal tests of homogeneity were performed.

2) The components of the **Clinical benefit** endpoint such as **weight, performance status, cancer-related symptoms** were not prospectively defined in the protocols. What constituted improvement in patients signs/symptoms was not defined in the submission.

In Section 1 we give a brief background of CPT-11. Section 2 contains a description of the pivotal studies submitted in this NDA. Section 3 gives the efficacy results and analyses for the pivotal studies. Section 4 gives the overall summary of these studies and Section 5 contains the conclusions and recommendations regarding this application. A summary of up-dated data will be briefly described in an Appendix for both the efficacy (Appendix A) and the safety (Appendix B) results of the pivotal studies. Electronic data files were provided for all the pivotal studies by the sponsor. A copy of the "Statistical Review and Evaluation" of IND protocol submission dated 3/27/1996, is enclosed. IND contains the design of the post marketing study required under the accelerated approval mechanism for NDA # 20-571.

1) BACKGROUND: In this NDA the sponsor seeks approval of CPT-11 for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy based on the results of three uncontrolled Phase II pivotal studies under the accelerated approval mechanism. Tumor response and clinical benefit are the main endpoints of this submission.

The sponsor used a data cutoff date for the pivotal studies of March 31, 1995 for the original submission of this NDA dated December 28, 1995. The sponsor submitted on April 15, 1996 up-dated data with a data cutoff date of December 31, 1995. This review will focus on the pivotal studies' data of the original submission. A summary of the up-dated data will be briefly described in the Appendix.

2) DESCRIPTION OF STUDIES:

Pivotal studies in patients with previously treated colorectal cancer: There are three studies, considered the pivotal studies for CPT-11, conducted in patients with metastatic colorectal cancer that recurred or progressed following prior 5-FU therapy, in this submission. These include the following protocols: protocols 0001, 0003R, and 0006. All three studies were multicenter, open-label, phase II studies. The objectives of the studies were to evaluate the antitumor activity of CPT-11 in patients with metastatic colorectal cancer that had recurred or progressed following a 5-FU-based chemotherapeutic regimen and to assess the toxicity of CPT-11 in these patients.

Protocol 0001 (San Antonio Regional) enrolled 48 patients with metastatic colorectal cancer who had progressive disease after at least one 5-FU-based chemotherapeutic regimen given for metastatic disease or recurrent disease within 6 months after adjuvant therapy with a 5-FU-based regimen in 4 institutions. The first 9 patients were treated at a starting dose of 150 mg/m^2 and the subsequent 39 patients were treated at a starting dose of 125 mg/m^2. Patients who achieved a complete response to therapy were to receive an additional four courses of therapy. Patients who achieved a partial response or whose disease remained stable could continue to receive therapy until disease progression or intolerable toxicity occurred. Tumor measurements were to be obtained at baseline, after the first and second courses of therapy in all patients, and then after every other subsequent course of therapy. If a > 50% reduction in tumor dimension relative to baseline was observed, an additional tumor measurement was to be obtained after the next course of therapy to confirm the response. After that, measurements were to be obtained after every other course of therapy.

Protocol 0003R (Mayo North Central Cancer Treatment Group [NCCTG]) enrolled 90 patients with histological or cytological confirmation of recurrent or progressive metastatic colorectal cancer after at least one previous 5-FU-based chemotherapeutic regimen was received, in 25 institutions within the NCCTG. The starting dose was 125 mg/m^2, with subsequent escalation of the dose to 150 mg/m^2 in patients who completed an entire course of therapy without experiencing any toxicities of greater than grade 1. Patients who attained a

complete response to therapy were to receive an additional four courses of therapy. Patients who attained a partial response to therapy or whose disease remained stable could continue to receive therapy until disease progression or intolerable toxicity occurred. Tumor measurements were to be obtained at baseline, prior to the second and third courses of therapy, and prior to every other subsequent course of therapy.

Protocol 0006 (CPT-11 Colorectal Study Group) enrolled 166 patients with metastatic colorectal cancer whose disease had progressed within 6 months of treatment with one 5-FU-based regimen for metastatic colorectal carcinoma or recurred within 6 months of adjuvant therapy with a 5-FU-based regimen in a multicenter study that was conducted at 30 institutions. The first 64 patients who were enrolled were treated with a starting dose of 125 mg/m^2. The starting dose was reduced to 100 mg/m^2 for the subsequent 102 patients because the toxicity at the 125 mg/m^2 dose was perceived to be greater than that observed in other studies. Increases in dose in increments of 25 mg/m^2, up to a maximum dose of 150 mg/m^2, were allowed at the start of a new course of therapy in patients who experienced no toxicity during an entire course on the same dose. Patients who attained a complete response to therapy were to receive an additional two courses of therapy; those who attained a partial response to therapy or whose disease remained stable could continue to receive treatment until disease progression or intolerable toxicity occurred. Tumor measurements were to be obtained at baseline and then after every two courses of therapy. If a patient responded to therapy, a tumor measurement was to be obtained 4 to 6 weeks later to confirm the response.

Endpoints: The primary efficacy variable was **tumor response** to treatment, defined as the total percentage of patients who experienced either a complete response or a partial response to CPT-11 therapy. The secondary efficacy variables were:
1) time to response, defined as the period from first dose of CPT-11 to the first objective documentation of response;
2) duration of response, defined as the period from date of first objective documentation of response to the date of first objective documentation of disease progression or to the off-study date or data cutoff date, whichever came first;
3) time to disease progression (TTP), defined as the period from the date of initial treatment to the date of first objective documentation of disease progression or to the off-study date or data cutoff date, whichever came first;
4) survival time, defined as the period from the date of administration of the first dose of CPT-11 to the last date the patient was known to be alive;
5) Clinical benefit, defined as stabilization or increase in body **weight**, maintenance or improvement in **performance status**, improvement in **cancer-related symptoms**, or a longer time to disease progression with second-line CPT-11 treatment than that observed during therapy with first-line 5-FU-based chemotherapy. The components of the clinical benefit endpoint were not prospectively defined.

Documentation of disease progression at the time of entry into the studies (i.e. following 5-FU therapy) was assessed for the patients who responded to CPT-11 by an independent review

panel. The time to tumor progression on 5-FU was not examined by the independent panel for the patients whose best response to CPT-11 was stable disease or progressive disease. For these patients, the dates of disease progression that were specified by the investigators on the prestudy worksheets were used in the analysis.

3) EFFICACY RESULTS:

Statistical methodology: The following statistical methodology was used by the sponsor for the data analysis: For response rate, 95% confidence intervals (CI) were calculated based on the normal approximation to the binomial distribution. Duration of response, time to response, time to disease progression, and survival time were analyzed using Kaplan-Meier methods, with the SAS procedure LIFETEST. If the exact date for an event was not available for the time-to-event analysis, the observation was censored according to the sponsor in the following way: 1) If the date of disease progression was not known, both the time to progression and duration of response were censored. The date used was the off-study date or the data cutoff date of March 31, 1995. 2) If the date of death was not available, survival time was censored. The date used was last available date the patient was known to be alive. Response data were analyzed for each pivotal study. Data from the pivotal studies were also pooled and displayed by starting dose and across all starting doses by the sponsor. This review will not consider any data analyses across all starting dose levels. The analyses based on the pooled data of the three pivotal studies will be included only for display purposes.

Results: The estimates of duration of response include censored data for eight patients without documented evidence of disease progression as of the March 31, 1995 data cutoff date. These eight patients include two patients in protocol 0003R and six patients in protocol 0006. The off-study date or the data cutoff date was used to calculate the duration of response for these patients.

The estimates of time to disease progression include censored data for 64 patients without documented evidence of disease progression as of the March 31, 1995 data cutoff date. These 64 patients include 9 of the 48 patients in protocol 0001, 9 of the 90 patients in protocol 0003R, and 46 of the 166 patients in protocol 0006. The estimates of time to disease progression for the 38 patients who responded to CPT-11 include censored data for eight patients. These eight patients include two patients in protocol 0003R and six patients in protocol 0006.

As of the time of last follow-up, 10 of the 48 patients in protocol 0001, 23 of the 90 patients in protocol 0003R, and 74 of the 166 patients in protocol 0006 were still alive. The 74 patients who were still alive in protocol 0006 included 26 of the 64 patients who were treated with the 125 mg/m^2 starting dose and 48 of the 102 patients who were treated with the 100 mg/m^2 starting dose. The estimates of survival time include censored data for patients who were still alive as of the data cutoff date. The date used in the analysis for these patients was the last date the patient was known to be alive.

Table A1 of the Appendix summarizes the patient pretreatment demographic characteristics by study as presented by the sponsor. There were not any analyses done by this reviewer that incorporated the demographic characteristics of the patients due to the small size of the studies and the non-existence of a comparative arm.

The following three tables summarize the results of the pivotal studies for the intent to treat patient population.

Reviewer's Table 1: Summary of results for the Intent to treat population

Protocol	0001	0003R	0006		total
Number of patients	48	90	166		304
			100 mg/m2 N=102	125 mg/m2 N=64	
PR + CR	20.8%(10/48)	13.3%(12/90)	7.8%(8/102)	12.5%(8/64)	12.5%
95% CI (percent)	[9.3, 32.3]	[6.3, 20.4]	[2.6, 13.1]	[4.4, 20.6]	[8.8, 16.2]
SD	62.5%	55.6%	39.2%	45.3%	49%
Median Time to Response (months)	2.6	1.5	2.7	2.7	2.6
Range					
Median Duration of Response (months)	6.4	5.9	5.2	5.6	5.8
Range					
Median TTP (months)	3.9	3.5	2.8	3.2	3.2
Range					
Median Survival (months)	10.4	8.1	7.8	10	8.3
Range					

1) CR, PR, SD stand for complete response, partial response, and stable disease respectively.
2) There are still 21 and 19 patients on study from protocols 0003R and 0006 respectively.
3) Cutoff date: March 31, 1995
4) Timing of measuring response was different for the various dose levels

Reviewer's Table 2: Summary of Results for the Responders

Protocol	0001	0003R	0006		total
Number of responders (%)	10/48 21%	12/90 13.3%	16/166 N=8/102 (7.8)	N=8/64 (12.5)	38/304 12.5%
Dose (mg/m^2)	125/150	125	100	125	
Median Time to Response (months)	2.6	1.5	2.7	2.7	2.6
Range					
Median Duration of Response (months)	6.4	5.9	5.2	5.6	5.8
Range					
Median TTP (months)	8.3	7.4	8.4	9.3	7.9
Range					
Median Survival (months)	20.9	12.5	8.7	10.9	11.3
Range					

1) There are still 21 and 19 patients on study from protocols 0003R and 0006 respectively.
2) Cutoff date: March 31, 1995
3) Timing of measuring response was different for the various dose levels

Reviewer's Table 3: Summary of Results for the Evaluable Patient Population

Protocol	0001	0003R	0006		total
Number of patients	43	66	162		261
			100 mg/m2 N=93	125 mg/m2 N=59	
PR + CR	23.3%(10/43)	18.2%(12/66)	8.6%(8/93)	13.6%(8/59)	14.6%(38)
95% CI (percent)	[10.6, 35.9]	[8.9, 27.5]	[2.9, 14.3]	[4.8, 22.3]	[10.3, 18.8]
SD	69.8%	71.2%	43%	49.2%	55.9%

1) There are still 21 and 19 patients on study from protocols 0003R and 0006 respectively.
2) Cutoff date: March 31, 1995
3) Timing of measuring response was different for the various dose levels

Clinical Benefit: The clinical benefit analysis was based on prospectively collected weight and performance status (evaluated by the ECOG Performance Status Scale in protocols 0001 and 0003R and by the SWOG Performance Status Scale in protocol 0006) information and retrospectively collected tumor-related signs and symptom data. According to the protocols, assessments were to be made prior to study entry (baseline), at the time of each CPT-11 treatment (physical examinations and performance status were only to be recorded at the start of each course in protocol 0006) and at the end of the study, and information was to be recorded on the study case report forms on the following: physical examination, weight, performance status, vital signs, and laboratory assays.

Clinical benefit was evaluated for patients who had an objective response to CPT-11, for patients whose best response to CPT-11 was stable disease, and for all patients who were treated with CPT-11 in the pivotal studies.

The sponsor provided the following retrospectively defined comparisons for the clinical benefit variables: Each patient's baseline weight, defined as the weight obtained prior to the administration of the first dose of CPT-11 in course 1, was compared with three measures of on-study weight for that patient. The three weights selected for comparison with the baseline weight were the best weight on study, the average weight on study, and the weight at the beginning of the last course of CPT-11. The frequency of patients whose weight increased by > 3% from baseline, remained stable, or decreased by > 3% from baseline was summarized. Stable weight was defined as a weight that remained within 3% of the baseline value.

The sponsor presented a frequency table of the distribution of patients who maintained, improved, or had a decline in their performance status by comparing the best performance status, most frequent (modal) performance status, and the performance status at the beginning of the last course with the baseline performance status. These were all retrospectively defined analyses.

There were not any comparative analyses performed of prestudy weight trends with those of study weights due to the lack of pretreatment data. The following three tables were presented by the sponsor:

Sponsor's Table 4: Summary of On-Study Weight Changes for 38 Responders to CPT-11 in the Pivotal Studies in Previously Treated Colorectal Cancer

Change from Baseline	On-Study Weight		
	Best	Average	Beginning of Last Course
Increased or Remained Stable	35 (92.1)	29 (76.4)	29 (76.4)
—Increased by > 3%	13 (34.2)	5 (13.2)	8 (21.1)
—Stable (± 3%)	22 (57.9)	24 (63.2)	21 (55.3)
Decreased by > 3%	3 (7.9)	9 (23.7)	9 (23.7)

Pooled data from protocols 0601, 0003R and 0006

Sponsor's Table 5: Summary of On-Study Performance Status for 38 Responders to CPT-11 in the Pivotal Studies in Previously Treated Colorectal Cancer[a]

Change from Baseline	On-Study Performance Status		
	Best	Modal[b]	Last
Improved or Maintained Performance Status	36 (94.8)	35 (92.1)	32 (84.1)
—Improved 1 to 0	4 (10.5)	4 (10.5)	4 (10.5)
2 to 0	2 (5.3)	2 (5.3)	1 (2.6)
2 to 1	--	--	1 (2.6)
—Maintained 0	24 (63.2)	23 (60.5)	20 (52.6)
1	6 (15.8)	6 (15.8)	6 (15.8)
Decline in Performance Status from 0 to 1	2 (5.3)	3 (7.9)	6 (15.8)

[a] Pooled data from protocols 0601, 0003R & 0006

[b] Most frequent occurrence

Sponsor's Table 6: Summary of Clinical Benefit Information: Pivotal Studies in Patients with Previously Treated Colorectal Cancer[a]

Clinical Benefit Parameter	% of Responders (Complete & Partial)	% of Patients with Stable Disease	% of All Patients
Weight (Average versus Baseline)			
Increased (> 3%)	13.2%	8.2%	9.3%
Stable	63.2%	48.6%	50.6%
Decreased (< 3%)	23.7%	43.2%	40.1%
Performance Status (Modal)			
Improved	15.8%	11.0%	12.6%
Maintained	76.3%	74.5%	72.8%
Declined	7.9%	14.4%	14.7%
Median Time to Decline in Performance Status	6.4	4.0	2.8
(Range in Months)	(1.4 -16.3)	(1.0-12.4)	(0.1-16.3)
Decrease in Tumor Signs/Symptoms	81.8%	31.1%	39.2%
Decrease in Pain	85.7%	21.0%	31.0%
Time to Tumor Progression			
CPT-11 > First-Line 5-FU Regimen	48.5% (16/33)	28.9% (24/83)	23.5% (43/183)

[a] Pooled data from protocols 0001, 0003R & 0006.

Tumor-Related Signs & Symptoms:. According to the sponsor, eleven (28.9%) of the 38 patients who responded to CPT-11 were retrospectively reported by the investigators or other study personnel to have tumor-related signs and symptoms at study entry. The most frequent prestudy tumor-related sign/symptom was pain, which was reported for 7 (63.6%) of the 11 patients. What constitutes improvement in patients signs/symptoms was not defined. The following table was presented by the sponsor:

Sponsor's Table 7: Prestudy Tumor-Related Signs and Symptoms in Patients Who Responded to CPT-11 in the Pivotal Studies in Previously Treated Colorectal Cancer[a]

Protocol	Patient No.	Signs and Symptoms Present at Baseline	Improved on CPT-11
M/6475/0001		Back pain Hot flashes	Yes Yes
		Constipation	Yes
M/6475/0003R		Swelling in abdomen (Ascites)	Yes
		Decreased appetite	Yes
		Pain	Unknown[b]
M/6475/0006		Sacral pain	Yes
		Fatigue	No[c]
		Left flank pain due to urinary obstruction by tumor[d] Left subcostal pain due to urinary obstruction by tumor[d] Urinary frequency Dysuria	Yes Yes Yes Yes
		Right upper quadrant abdominal pain Left lower quadrant abdominal pain	Yes Yes
		Right upper quadrant abdominal pain Right shoulder pain Swelling in abdomen (ascites)	Yes Yes Yes
		Lower abdominal pain	Yes

[a] 11/38 responders had tumor-related signs or symptoms at baseline.

[b] Patient had pleural and bony metastases. The investigator summary did not comment on a change in the degree of pain for this patient. However, the Expert Panel found definite documentation of a decrease in pain.

[c] Patient had fatigue which was not felt by the research staff to have improved.

[d] Patient had a mass in the prostate which resulted in left hydroureter, left hydronephrosis and likely caused flank pain. His symptoms of urinary frequency and dysuria were due to bladder invasion by tumor.

4) SUMMARY:

Based on the intent-to-treat population, the objective response to therapy was 20.8% (10/48) in protocol 0001 and 13.3% (12/90) in protocol 0003R . In protocol 0006, the response rate was 12.5% (8/64) for the patients who received the 125 mg/m^2 starting dose and 7.8% (8/102) for the patients who received the 100 mg/m^2 starting dose. Objective response rates based on the evaluable population were: 23.3% (10/43) in protocol 0001, 18.2% (12/66) in protocol 0003R, and 13.6% (8/59) for the 125 mg/m^2 starting dose and 8.6% (8/93) for the 100 mg/m^2 starting dose in protocol 0006.

The median duration of response was 6.4 months (range: 2.7 to 13.7 months) in protocol 0001. Based on available data, the median duration of response was 5.9 months (range: 2.6 to 15.1 months) in protocol 0003R and 5.6 months (range: 2.8 to 8.8 months) for the 125 mg/m^2 starting dose and 5.2 months for the 100 mg/m^2 starting dose in protocol 0006.

The median duration of response for the 38 responders pooled from the three pivotal studies was 5.8 months (range: 2.6 to 15.1 months). Median duration of response was 5.2 months (range: 3.0 to 6.1 months) for the 8 responders who received the 100 mg/m^2 dose, 5.2 months (range: 2.6 to 15.1 months) for the 28 responders who received the 125 mg/m^2 starting dose, and 11.6 months (range: 9.5 to 13.7 months) for the 2 responders who received the 150 mg/m^2 starting dose.

The clinical benefit measurement included stabilization or improvement (≥ 3%) in weight, maintenance or improvement in performance status, and improvement or resolution of tumor-related signs or symptoms. There are not any data on clinical benefit for prior therapy (5-FU) for those who responded to the CPT-11 treatment. It is difficult for this reviewer to assess that the CPT-11 treatment had some "clinical benefit", since this is not a randomized controlled study. On the other hand the toxicities associated with treatment are quite numerous and in some cases severe. Thus, any clinical benefit could be offset by these toxicities.

The median time to disease progression was 8.3 months (range: 3.9 to 16.4 months) for the 10 responders in protocol 0001. The median time to disease progression was 7.4 months (range: 3.5 to 19.9 months) for the 12 responders in protocol 0003R; in protocol 0006, the median time to disease progression was 9.3 months (range: 5.6 to 11.6 months) for the 8 responders who received the 125 mg/m^2 starting dose and 8.4 months (range: 5.5 to 9.5 months) for the 8 responders who received the 100 mg/m^2 dose.

The median time to disease progression for the 38 responders pooled from the pivotal studies was 7.9 months (range: 3.5 to 19.9 months). Median time to disease progression was 7.4 months (range: 3.5 to 19.9 months) for the 28 responders who received the 125 mg/m^2 starting dose, 8.4 months (range: 5.5 to 9.5 months) for the 8 responders who received the 100 mg/m^2 starting dose, and 14.4 months for the 2 responders who received the 150 mg/m^2 starting dose.

The median survival time for responders was 20.9 months (range, 6.8 to 25.9 months) in protocol 0001 and 12.5 months (range: 4.5 to 22.1 months) in protocol 0003R. In protocol 0006, median survival time was 10.9 months (range: 10.0 to 12.4 months) for the responders who were treated with the 125 mg/m^2 starting dose and 8.7 months (range: 7.4 to 9.8 months) for the responders who were treated with the 100 mg/m^2 starting dose.

The median survival time for the 38 responders was 11.3 months (range: 4.5 to 25.9 months). Median survival time was 8.7 months (range: 7.4 to 9.8 months) for the 8 responders who received the 100 mg/m^2 starting dose, 12.3 months (range: 4.5 to 24.1 months) for the 28 responders who received the 125 mg/m^2 starting dose, and 24.1 months (range: 22.4 to 25.9 months) for the 2 responders who received the 150 mg/m^2 starting dose.

5) CONCLUSIONS AND RECOMMENDATIONS:

More data are needed from randomized controlled studies to assess the efficacy of CPT-11 for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy. Objective tumor response rate estimates from the pivotal studies are variable because of the small sample sizes and the differences in the eligibility criteria. Moreover, clinical benefit is very difficult to assess in Phase II studies which are not randomized and lack a control treatment. A randomized, blinded (double-blind is preferable), controlled study of the CPT-11 treatment that will collect data on clinical benefit for patients with previous 5-FU chemotherapy will be of great importance to substantiate any clinical benefit of the CPT-11 treatment for this patient population. A study that would include a crossover arm for patients first treated with 5-FU (then crossover to the CPT-11 arm) among other arms will help in determining if there is any indication that the CPT-11 treatment results in some clinical benefit. A copy of this reviewer's "Statistical Review and Evaluation" of IND protocol, that describes the design for the post marketing study under the accelerated approval mechanism for this NDA, is attached at the end of this review.

The safety issues related to CPT-11 treatment are of concern. Treated patients experienced an increased number of adverse events in the pivotal trials that would need to be addressed in the labeling after further discussions by the members of the Oncologic Drugs Advisory Committee.

From the data presented, this reviewer concludes that there is evidence to support the efficacy of CPT-11 for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy, under the agency's accelerated approval mechanism. Further discussions are needed to elucidate the safety profile of CPT-11.

Antonis Koutsoukos, Ph.D.
Mathematical Statistician

concur: Dr. Gnecco

Dr. Chi 5/28/96

cc:

Archival NDA 20,571
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Koutsoukos/ 5-24-1996/ WP6.1/ c:\nda20751\cpt11.rvw
This review consists of 14 pages (1-14) of text and an Appendix of 15 pages (15-29) of text.

APPENDIX A:

Sponsor's Table A1: Pretreatment Demographic Characteristics by Study: Pivotal Studies in Patients with Previously Treated Colorectal Cancer

Protocol No.:	0001		0003R		0006			
Starting Dose (mg/m^2):	150[a]/125		125		125		100	
Patient Population:	ITT[b] N=48	Evaluable N=43	ITT N=90	Evaluable N=66	ITT N=64	Evaluable N=59	ITT N=102	Evaluable N=93
Age (y)								
Mean	59	58	62	61	61	61	59	59
Median	63	60	63	63	61	60	64	64
Range								
Distribution (No. & %)								
< 35	2 (4.2)	2 (4.7)	3 (3.3)	3 (4.5)	0 (0.0)	0 (0.0)	8 (7.8)	8 (8.6)
35-49	11 (22.9)	10 (23.3)	12 (13.3)	8 (12.1)	6 (9.4)	6 (10.2)	14 (13.7)	13 (14.0)
50-64	13 (27.1)	12 (27.9)	34 (37.8)	27 (40.9)	35 (54.7)	32 (54.2)	33 (32.4)	29 (31.2)
≥ 65	22 (45.8)	19 (44.2)	41 (45.6)	28 (42.4)	23 (35.9)	21 (35.6)	47 (46.1)	43 (46.2)
Sex (No. & %)								
Male	26 (54.2)	23 (53.5)	58 (64.4)	40 (60.6)	32 (50.0)	30 (50.8)	50 (49.0)	44 (47.3)
Female	22 (45.8)	20 (46.5)	32 (35.6)	26 (39.4)	32 (50.0)	29 (49.2)	52 (51.0)	49 (52.7)
Ethnic Origin (No. & %)								
White	38 (79.2)	33 (76.7)	86 (95.6)	63 (95.5)	52 (81.3)	47 (79.7)	93 (91.2)	84 (90.3)
African American	6 (12.5)	6 (14.0)	4 (4.4)	3 (4.5)	7 (10.9)	7 (11.9)	5 (4.9)	5 (5.4)
Hispanic	4 (8.3)	4 (9.3)	0 (0.0)	0 (0.0)	5 (7.8)	5 (8.5)	2 (2.0)	2 (2.2)
Oriental Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	2 (2.2)
Performance Status (No. & %)								
0	29 (60.4)	27 (62.8)	34 (37.8)	29 (43.9)	38 (59.4)	35 (59.3)	45 (44.1)	44 (47.3)
1	18 (37.5)	15 (34.9)	43 (47.8)	32 (48.5)	21 (32.8)	20 (33.9)	52 (51.0)	44 (47.3)
2	1 (2.1)	1 (2.3)	13 (14.4)	5 (7.6)	5 (7.8)	4 (6.8)	5 (4.9)	5 (5.4)

[a] 9 48 patients received the 150-mg m^2 starting dose.

[b] Intent to treat

sponsor submitted on April 15, 1996, up-dated data with a Cutoff date of December 31, 1995. re was one more responder in protocol 0006, for the dose of 125 mg/m^2. There are fewer censored time to event observations in this up-dated data set than the original with a cutoff date of March 31, 1995. The following three tables summarize the results of the pivotal studies:

Reviewer's Table A2: Summary of results for the Intent to treat population

Protocol	0001	0003R	0006		Total
Number of patients	48	90	166		304
			100 mg/m^2 N=102	125 mg/m^2 N=64	
PR + CR	21%(10/48) 1 CR	13.3%(12/90) 0 CR	7.8%(8/102)	14.1%(9/64) 1 CR	12.8%
95% CI (percent)	[9.3, 32.3]	[6.3, 20.4]	[2.6, 13.1]	[5.5, 22.6]	[9.1, 16.6]
SD	62.5%	55.6%	39.2%	43.8%	43%
Time to Response (mos)	2.6	2.1	2.8	2.8	2.7
Range					
Duration of Response (mos)	6.4	5.9	6.2	5.6	6
Range					
TTP (months)	4.8	4.0	3.3	5.0	4.0
Range					
Survival (months)	10.4	8.1	9.3	10.7	9.0
Range					

1) CR, PR, SD stand for complete response, partial response, and stable disease respectively
2) Cutoff date December 31, 1995
3) Timing of measuring response was different for the various dose levels

Reviewer's Table A3: Summary of results for the Responders

Protocol	0001	0003R	0006		Total
Number of responders	10/48 21%	12/90 13.3%	16/166 N=8/102	N=8/64	38/304 12.5%
Dose (mg/m^2)	125/150	125	100	125	
Time to Response(mos)	2.6	2.1	2.8	2.8	2.7
Range					
Duration of Response(mos)	6.4	5.9	6.2	5.6	6
Range					
TTP (months)	8.3	7.4	10.6	9.5	9.2
Range					
Survival (months)	22.3	14.8	16.3	20.8	20.5
Range					

1) All the time to event endpoints represent the median time to an event and they are measured in months
2) Cutoff date: December 31, 1995
3) Timing of measuring response was different for the various dose levels

Reviewer's Table A4: Summary of results for the Evaluable Patients

Protocol	0001	0003R	0006		Total
Evaluable patients	43	66	162		261
			100 mg/m^2 N=93	125 mg/m^2 N=59	
PR + CR	23.3%(10/43) 1 CR	18.2%(12/66)	8.6%(8/93)	15.3%(9/59) 1 CR	14.9%(39)
95% CI (percent)	[10.6, 35.9]	[8.9, 27.5]	[2.9, 14.3]	[6.1, 24.4]	[10.6, 19.3]
SD	69.8%	71.2%	43%	47.5%	55.6%

1) Cutoff date: December 31, 1995
2) Timing of measuring response was different for the various dose levels

The sponsor presented the time to progression for the patients who responded to the CPT-11 treatment and the time to progression of these patients on the 5-FU treatment in the following table:

Sponsor's Table A5: Time to Tumor Progression (TTP) on 5-FU Compared with CPT-11 for 38 Patients Who Responded to CPT-11 in Pivotal Studies in Previously Treated Colorectal Cancer

Patient No.	TTP (months)		Difference In TTP (CPT-11 > 5-FU)
	5-FU	CPT-11	
Protocol M/6475/0001			
	2.1	16.4	Yes
	6.1	12.4	Yes
	8.7	12.4	Yes
	10.9	7.0	No
	2.4	6.7	Yes
	8.8	5.1	b
	8.1	5.5	No

Sponsor's Table A5: Time to Tumor Progression (TTP) on 5-FU Compared with CPT-11 for 38 Patients Who Responded to CPT-11 in Pivotal Studies in Previously Treated Colorectal Cancer

Patient No.	TTP (months)		Difference In TTP (CPT-11 > 5-FU)
	5-FU	CPT-11	
	10.5	3.9	No
	--	12.9	c
	15.1	9.7	No
Protocol M/6475/0003R			
	4.2	19.9	Yes
	7.9	7.0	No
	3.1	3.5	Yes
	7.2	7.0	No
	42.4	11.1	b
	2.8	7.6[d]	Yes
	20.0	8.2	No
	11.1	7.4	No
	34.3	10.9[d]	d
	6.1	7.2	Yes
	6.7	7.4	Yes
	3.8	5.3	Yes
Protocol M/6475/0006			
	3.1	9.5	Yes
	12.0	7.2	b
	5.5	8.2[d]	Yes
	15.2	9.6	No
	5.4	5.8	Yes
	11.5	8.7[d]	d

Sponsor's Table A5: Time to Tumor Progression (TTP) on 5-FU Compared with CPT-11 for 38 Patients Who Responded to CPT-11 in Pivotal Studies in Previously Treated Colorectal Cancer

Patient No.	TTP (months)		Difference in TTP (CPT-11 > 5-FU)
	5-FU	CPT-11	
Protocol M/6475/0006 (continued)			
	2/0	5/5	Yes
	10.1	9.5[d]	d
	11.2	6.9	No
	19.4	10.1	No
	12.1	9.2	b
	16.5	8.6[d]	d
	8.6	11.6[d]	Yes
	12.3	5.6	No
	2.9	6.9	Yes
	11.8	8.9[d]	d

[a] Date of progression on 5-FU not confirmed by independent review committee [116]; the date reported by the investigator was used in the analysis.

[b] Patient received prior 5-FU regimen for adjuvant therapy; therefore, difference in time to tumor progression cannot be assessed.

[c] Patient had stable disease on prior to 5-FU regimen.

[d] Patient still on study as of data cutoff date (03/31/95), so the observation is censored.

The sponsor collected data on Tumor-related signs and symptoms retrospectively on 153 (50.3%) of the 304 patients who had data at baseline. The most frequently reported symptom was pain (67.3%; 103/153). Table A6 summarizes the tumor-related signs and symptoms that were retrospectively reported for the 153 patients. What constitutes improvement in patients signs/symptoms was not defined.

Sponsor's Table A6: Tumor-Related Signs & Symptoms for Patients in Pivotal Studies in Previously Treated Colorectal Cancer[a,b]

Symptom	No. Pts with Symptoms at Baseline	No. (%) Improved on CPT-11
Pain at primary or metastatic site	103	32 (31.0%)
Fatigue/Weakness	32	9 (28.1%)
Anorexia/Decreased appetite	25	7 (28.0%)
Back Pain	24	8 (33.3%)
Nausea/Vomiting	23	4 (17.3%)
Cough/Dyspnea	15	8 (53.3%)
Swelling in abdomen	12	7 (58.3%)
Diarrhea	11	3 (27.2%)
Other pain	11	2 (18.1%)
Tumor-associated fever	8	3 (37.5%)
Swelling in feet	5	1 (20.0%)
Constipation	3	2 (66.6%)

[a] Pooled data from protocols 0001, 0003R & 0006.
[b] 153/304 patients had tumor-related signs or symptoms at baseline.

PPENDIX B

SAFETY:

This section describes the safety summary results for some of the drug-related medical events through December 31, 1995 for the 304 patients who were treated with CPT-11 in the US pivotal studies in previously treated colorectal cancer. The corresponding section from the Integrated Summary of Safety Information of the original NDA submission (safety results through March 31, 1995), has been replicated by the sponsor in the April 1, 1996 submission. The following convention was adopted by the sponsor to show numerical changes in data in the in-text tables between the NDA and the Safety Update Report. Data through the December 31, 1995 data cutoff date are designated in bold [eg, **1 (0.3)**], with the corresponding number from the NDA included in brackets (eg, [1 (0.3)]). If there were no numerical changes between the NDA and Safety Update Report, then the numbers appear as in the NDA, eg, no bold or brackets: 3 (0.3). All tables in this section have been taken from the April 1, 1996 submission of the Safety Update Report.

The Medical Officer's review will include a more detailed discussion about the safety data.

(1) Late Diarrhea:

The following table, provided by the sponsor, summarizes the frequency of late diarrhea by patient, course, and maximum grade for all patients and by starting dose. Grade 3 and 4 late diarrhea was reported for 30.6% (93/304) of the patients and in 11.5% (125/1091) of the courses. The frequency of de 3 and 4 late diarrhea increased somewhat with increasing dose. The occurrence of grade 3 and 4 diarrhea was not significantly different by dose.

Sponsor's Table 24. Frequency of Late Diarrhea[a]
Pivotal Studies in Patients with Previously Treated Colorectal Cancer[b]

	No.	No. (%) with Diarrhea	Maximum NCI Grade				No. (%) Grade 3 + 4
			1	2	3	4	
ALL PATIENTS							
Patients	304	267 (87.8)	**97** [98]	**77** [76]	50	43	93 (30.6)
Courses	**1091** [1060]	**699 (64.1)** [685 (64.1)]	**410** [401]	**164** [159]	75	50	**125 (11.5)** [125 (11.8)]
STARTING DOSE = 100 mg/m^2							
Patients	102	89 (87.3)	**38** [39]	**27** [27]	18	6	24 (23.5)
Courses	**357** [334]	**254 (71.1)** [242 (72.5)]	**167** [160]	**58** [53]	23	6	**29 (8.1)** [29 (8.7)]
STARTING DOSE = 125 mg/m^2							
Patients	193	171 (88.6)	58	48	32	33	65 (33.7)

Courses	679 [671]	417 (61.4) [415 (61.8)]	231 [229]	160	49	37	86 (12.7) [86 (12.7)]
STARTING DOSE = 150 mg/m²							
Patients	9	7 (77.8)	1	2	0	4	4 (44.4)
Courses	55	28 (50.9)	12	6	3	7	10 (18.2)

[a] Occurred > 24 h after administration of CPT-11

According to the sponsor, among all patients enrolled, 37.5% (114/304) had a dose modification associated with late diarrhea: 23.5% (24/102) of those who received the 100 mg/m^2 starting dose, 43.5% (84/193) of those who received the 125 mg/m^2 starting dose, and 66.7% (6/9) of those who received the 150 mg/m^2 starting dose. Of the 267 patients who experienced late diarrhea, fewer than half (42.7%; 114/267) required an adjustment in their dose during treatment. Only 4 (1.3%) of the 304 patients discontinued treatment because of late diarrhea.

(2) Nausea/Vomiting:

The following table, provided by the sponsor, summarizes the frequency of nausea and vomiting by patient, course, and maximum grade for all patients and by starting dose. Grade 3 or 4 nausea was reported for 16.8% (51/304) of the patients and in 5.4% (59/1091) of the courses, and grade 3 or 4 vomiting was reported for 12.5% (38/304) of the patients and in 3.8% (42/1091) of the courses. There no significant difference in the occurrence of grade 3 or 4 nausea by dose. However, the occurrence of grade 3 or 4 vomiting was significantly different ($p < 0.0001$) by dose.

Sponsor's Table 29. Frequency of Nausea & Vomiting
Pivotal Studies in Patients with Previously Treated Colorectal Cancer[a]

	No.	No. (%) with Event	Maximum NCI Grade 1	2	3	4	No. (%) Grade 3 + 4
ALL PATIENTS							
Nausea							
Patients	304	262 (86.2)	125 [126]	86 [85]	50	1	51 (16.8)
Courses	1091 [1060]	619 (56.7) [609 (57.5)]	409 [402]	151 [148]	58	1	59 (5.4) [59 (5.6)]
Vomiting							
Patients	304	203 (66.8) [201 (66.1)]	86 [84]	79	30	8	38 (12.5)
Courses	1091 [1060]	379 (34.7) [373 (35.2)]	218 [213]	119 [118]	34	8	42 (3.8) [42 (4.0)]

STARTING DOSE = 100 mg/m²								
Nausea								
	Patients	102	86 (84.3)	**47** [48]	**28** [27]	11	0	11 (10.8)
	Courses	**357**	**183 (51.3)** [175 (52.4)]	**126** [121]	**44** [41]	13	0	**13 (3.6)** [13 (3.9)]
Vomiting								
	Patients	102	55 (53.9) [53 (52.0)]	33 [31]	20	2	0	2 (2.0)
	Courses	**357**	**81 (22.7)** [76 (22.8)]	**50** [46]	**28** [27]	3	0	**3 (0.8)** [3 (0.9)]
STARTING DOSE = 125 mg/m²								
Nausea								
	Patients	193	167 (86.5)	75	54	37	1	38 (19.7)
	Courses	**679** [671]	**415 (61.9)** [413 (61.5)]	**268** [266]	103	43	1	**44 (6.5)** [44 (66.6)]
Vomiting								
	Patients	193	139 (72.0)	51	55	27	6	33 (17.1)
	Courses	**679** [671]	**277 (40.8)** [276 (41.1)]	158	82	30	6	**36 (5.3)** [36 (5.4)]
STARTING DOSE = 150 mg/m²								
Nausea								
	Patients	9	9 (100.0)	3	4	2	0	2 (22.2)
	Courses	55	21 (38.2)	15	4	2	0	2 (3.6)
Vomiting								
	Patients	9	9 (100.0)	2	4	1	2	3 (33.3)
	Courses	55	21 (38.2)	9	9	1	2	3 (5.5)

* Protocols 0001, 0003R & 0005

According to the sponsor, among all patients enrolled, 13.5% (41/304) of the patients who experienced nausea and 13.5% (41/304) of the patients who experienced vomiting required an adjustment in their dose during treatment.

(3) Dehydration:

According to the sponsor, at the time of the Safety Update Report, grade 3 or 4 dehydration was reported for 4.3% (13/304) of the patients and in 1.2% (13/1091) of the courses. Grade 3 or 4 dehydration was reported for 5.9% (6/102) of patients starting with the 100 mg/m² dose and for 3.6% (7/193) of patients starting with the 125 mg/m² dose; none of the patients starting with the 150 mg/m² dose experienced grade 3 or 4 dehydration. Dehydration was listed among the reasons for discontinuation for 2 (0.7%) of the 304 patients.

Dyspnea:

ording to the sponsor, at the time of the Safety Update Report, dyspnea was reported for 22.0% (67/304) of the patients and in 9.0% (98/1091) of the courses. Grade 3 or 4 dyspnea was reported for 3.6% (11/304) of the patients and in 1.1% (12/1091) of the courses. Grade 3 or 4 dyspnea was reported for 2.0% (2/102) of patients starting with the 100 mg/m^2 dose and 4.7% (9/193) of patients starting with the 125 mg/m^2 dose; none of the patients starting with the 150 mg/m^2 dose reported grade 3 or 4 dyspnea. Dyspnea was judged to be related to administration of CPT-11 for 7.2% (22/304) of the patients. Of the 67 patients with dyspnea, 37 had lung tumors; this includes 12 of the 22 patients whose dyspnea was judged to be related to administration of CPT-11. Of the 11 patients with grade 3 or 4 dyspnea, 6 had lung tumors. Only one (0.3%) of the 304 patients discontinued treatment because of dyspnea, and there were no reports of pulmonary fibrosis.

(5) Neutropenia:

(a) Frequency of Neutropenia

The following table, provided by the sponsor, summarizes the frequency of neutropenia by patient, course, and maximum grade for all patients and by starting dose. Grade 3 or 4 neutropenia was reported for 26.3% (80/304) of the patients and in 12.0% (131/1091) of the courses. The frequency of grade 3 and 4 neutropenia was similar at initial doses of 100 and 125 mg/m^2, but increased in patients initially receiving the 150 mg/m^2 dose. The occurrence of grade 3 and 4 neutropenia was not significantly different by dose.

Sponsor's Table 32. Frequency of Neutropenia
Pivotal Studies in Patients with Previously Treated Colorectal Cancer[a]

	No.	No. (%) with Neutropenia	Maximum NCI Grade				No. (%) Grade 3 + 4
			1	2	3	4	
ALL PATIENTS							
Patients	304	**164 (53.9)** [162 (53.3)]	**32** [31]	**52** [51]	45	35	80 (26.3)
Courses	**1091** [1060]	**440 (40.3)** [425 (40.3)]	**167** [160]	**142** [136]	**89** [87]	42	**131 (12.0)** [129 (12.2)]
STARTING DOSE = 100 mg/m^2							
Patients	102	**46 (45.1)** [45 (44.1)]	10	**14** [13]	12	10	22 (21.6)
Courses	**357** [334]	**127 (35.6)** [116 (34.7)]	**36** [33]	**53** [47]	**26** [24]	12	**38 (10.6)** [36 (10.8)]
STARTING DOSE = 125 mg/m^2							
Patients	193	**112 (58.0)** [111 (57.5)]	**22** [21]	36	32	22	54 (28.0)
Courses	**679** [671]	**271 (39.9)** [267 (39.8)]	**114** [110]	78	56	23	**79 (11.6)** [(11.8)]
STARTING DOSE = 150 mg/m^2							

Patients	9	6 (66.7)	0	2	1	3	4 (44.4)
Courses	55	42 (76.4)	17	11	7	7	14 (25.5)

[a] Protocols 0001, 0003R & 0006.

According to the sponsor, among all patients enrolled, 23.0% (70/304) had a dose modification associated with neutropenia: 10.8% (11/102) of those who received a starting dose of 100 mg/m^2, 28.5% (55/193) of those who received a starting dose of 125 mg/m^2, and 44.4% (4/9) of those who received a starting dose of 150 mg/m^2. The CPT-11 dose was modified for 43.8% (71/162) of the patients who experienced neutropenia. Only 5.6% (17/304) of the patients received G-CSF at any time for neutropenia. Neutropenia was listed as a reason for discontinuing treatment for 5 (1.6%) of the 304 patients.

(b) Simultaneous Neutropenia and Fever

According to the sponsor, neutropenic fever, defined as grade 4 neutropenia and > grade 2 fever in the pivotal studies, occurred in only 3.0% (9/304) of the patients (Table 35) and in just 0.9% (10/1091) of the courses (Table 36). Neutropenic fever occurred in 2.0% (2/102) of the patients receiving the 100 mg/m^2 starting dose, 2.6% (5/193) of the patients receiving the 125 mg/m^2 starting dose, and 22.2% (2/9) of the patients receiving the 150 mg/m^2 starting dose. All nine patients were hospitalized and recovered after receiving antibiotic therapy. There were no fatal outcomes in these nine patients who experienced neutropenic fever. According to the sponsor, there was one patient protocol 1) who died of potentially drug-related neutropenic sepsis, but was afebrile at the time of this event, therefore, was not included in Tables 35 and 36. There were no new cases of neutropenic fever during the safety update period. Narrative summaries for the patients who experienced neutropenia fever were included in the NDA

Sponsor's Table 35. Number (%) of Patients (N=304) with Simultaneous Neutropenia & Fever Pivotal Studies in Patients with Previously Treated Colorectal Cancer[a]

Grade of Neutropenia	Grade of Fever				
	0	1	2	3	4
0	256 (84.2)				
1		9 (3.0)	1 (0.3)		
2		4 (1.3)	9 (3.0)		
3		6 (2.0) [5 (1.6)]	7 (2.3) [8 (2.6)]		
4		3 (1.0)	8 (2.6)	1 (0.3)	

[a] Protocols 0001, 0003R & 0006.

The following table gives the simultaneous Grade 2,3,4 Fever and 3,4 Neutropenia for the pivotal studies.

Reviewer's Table: Events of simultaneous Grade 2,3,4 Fever and 3,4 Neutropenia

Protocol	Patients (%)	Courses	Events
0001 (n=48)	6 (12.5)	1 2 1,2	8 1 1
0003R (n=90)	4 (4.4)	1	4
0006 (n=166)	7 (4.2)	1 2 3 5	5 1 1 1

Cutoff date: March 31, 1995

Sponsor's Table 36. Number (%) of Courses (N=1091 [1060]) with Simultaneous Neutropenia & Fever Pivotal Studies in Patients with Previously Treated Colorectal Cancer[a]

Grade of Neutropenia	Grade of Fever				
	0	1	2	3	4
0	**1019 (93.4)** [988 (93.2)]	1 (0.1)			
1	1 (0.1)	**17 (1.6)** [16 (1.5)]	**1 (0.1)** [2 (0.2)]		
2		11 (1.0)	11 (1.0)		
3		9 (0.8)	**7 (0.6)** [7 (0.7)]		
4		4 (0.4)	9 (0.8)	1 (0.1)	

[a] Protocols 0001, 0003R & 0006.

(c) Simultaneous Neutropenia and Late Diarrhea

According to the sponsor, Grade 3 or 4 neutropenia occurred simultaneously with grade 3 or 4 late diarrhea in 7.2% (22/304) of the patients (Table 38) and in 2.0% (22/1091) of the courses (Table 39). Simultaneous grade 3 or 4 neutropenia/late diarrhea occurred in 2.0% (2/102) of the patients receiving the 100 mg/m^2 starting dose, 18.8% (7/193) of the patients receiving the 125 mg/m^2 starting dose, and 33.3% (3/9) of the patients receiving the 150 mg/m^2 starting dose. Sixteen of the 22 patients were hospitalized for supportive care. There were no fatal outcomes in the patients who experienced simultaneous grade 3 or 4 neutropenia/late diarrhea.

Sponsor's Table 37. Number (%) of Patients (N=304)
with Simultaneous Neutropenia & Late Diarrhea
Pivotal Studies in Patients with Previously Treated Colorectal Cancer*

Grade of Neutropenia	Grades of Late Diarrhea				
	0	1	2	3	4
0	188 (61.8)				
1		11 (3.6)	9 (3.0)	1 (0.3)	4 (1.3)
2		21 (6.9)	7 (2.3)	5 (1.6)	6 (2.0)
3		16 (5.3)	6 (2.0)	4 (1.3)	8 (2.6)
4		5 (1.6)	3 (1.0)	3 (1.0)	7 (2.3)

* Protocols 0001, 0003R, 0006.

Sponsor's Table 38. Number (%) of Courses (N=1091) [1060])
with Simultaneous Neutropenia & Late Diarrhea
Pivotal Studies in Patients with Previously Treated Colorectal Cancer*

Grade of Neutropenia	Grade of Late Diarrhea				
	0	1	2	3	4
0	**900 (82.5)** [872 (82.3)]				
1	1 (0.1)	30 (2.8)	**19 (1.7)** [18 (1.7)]	1 (0.1)	5 (0.5)
2		**48 (4.4)** [47 (4.4)]	9 (0.8)	**7 (0.6)** [7 (0.7)]	**8 (0.7)** [8 (0.8)]
3		**21 (1.9)** [21 (2.0)]	8 (0.8)	4 (0.4)	**7 (0.6)** [7 (0.7)]
4		**7 (0.6)** [7 (0.7)]	4 (0.4)	4 (0.4)	**7 (0.6)** [7 (0.7)]

* Protocols 0001, 0003R, 0006.

(6) Leukopenia:

According to the sponsor, the occurrence of leukopenia was similar to that of neutropenia; There was no substantial difference in the frequency of grade 3 or 4 leukopenia between the NDA and the Safety Update Report; in the NDA, grade 3 or 4 leukopenia was reported for 27.6% (84/304) patients and in 12.4% (131/1060) of the courses. At the time of the Safety Update Report, grade 3 or 4 leukopenia occurred in 28.0% (85/304) of the patients and in 12.3% (134/1091) of the courses.

According to the sponsor, the frequency of grade 3 or 4 leukopenia increased modestly as the first dose of a course increased. There was no apparent relationship between the frequency of grade 3 and 4 leukopenia and CPT-11 starting dose. Among all patients enrolled, 14.5% (44/304) had a dosage modification associated with grade 3 or 4 leukopenia: 10.8% (11/102) of the patients who received the 100 mg/m^2 starting dose, 15.5% (30/193) of the patients who received the 125 mg/m^2 starting dose, and 33.3% (3/9) of the patients who received the 150 mg/m^2 starting dose. Forty-four (23.0%) of the 191 patients who experienced leukopenia required a modification in their CPT-11 dose. Leukopenia was listed as a reason for discontinuation from treatment for 3 (1.0%) of the 304 patients.

The last table compares the proportion of 304 patients of the pivotal studies experiencing selected medical
its by CPT-11 starting dose of the original NDA submission with that of safety update report
submission.

Sponsor's Table 85. Proportion of 304 Patients with Previously Treated Colorectal Cancer Experiencing Selected Medical Events by CPT-11 Starting Dose[a]: NDA versus Safety Update Report

	Starting Dose (mg/m²)						All Doses N=304	
	100 N=102		125 N=193		150 N=9			
Grade 3 & 4 Medical Events	NDA	Safety Update	NDA	Safety Update	NDA	Safety Update	NDA	Safety Update
Leukopenia	33.3%	34.3%	24.4%	24.4%	33.3%	33.3%	27.6%	28.0%
Late Diarrhea[b]	23.5%	23.5%	33.7%	33.7%	44.4%	44.4%	30.6%	30.6%
Neutropenia	21.6%	21.6%	28.0%	28.0%	44.4%	44.4%	26.3%	26.3%
Abdominal Pain	18.6%	19.6%	15.0%	15.5%	0.0%	0.0%	15.8%	16.4%
Asthenia	16.7%	16.7%	10.4%	10.4%	0.0%	0.0%	12.2%	12.2%
Nausea	10.8%	10.8%	19.7%	19.7%	22.2%	22.2%	16.8%	16.8%
Early diarrhea[c]	5.9%	5.9%	9.3%	9.3%	0.0%	0.0%	7.9%	7.9%
Dehydration	5.9%	5.9%	3.6%	3.6%	0.0%	0.0%	4.3%	4.3%
Dyspnea	2.0%	2.0%	4.7%	4.7%	0.0%	0.0%	3.6%	3.6%
Vomiting	2.0%	2.0%	17.1%	17.1%	33.3%	33.3%	12.5%	12.5%
Other Medical Events								
Drug-Related Hospitalizations	18.6%	18.6%	30.0%	30.0%	44.4%	44.4%	26.6%	26.6%
Discontinuations Due to Medical Events	5.9%	5.9%	3.6%	3.6%	0.0%	0.0%	4.3%	4.3%
Neutropenia & Diarrhea[d]	2.0%	2.0%	8.8%	8.8%	33.3%	33.3%	7.2%	7.2%
Neutropenic Fever[e]	2.0%	2.0%	2.6%	2.6%	22.2%	22.2%	3.0%	3.0%
Drug-Related Deaths	1.0%	1.0%	0.0%	0.0%	0.0%	0.0%	0.3%	0.3%

[a] Pooled data from protocols 0001, 0003R & 0006
[b] Occurring > 24 hr after CPT-11
[c] Occurring ≤ 24 hr after CPT-11
[d] Simultaneous grade 3/4 neutropenia and grade 3/4 diarrhea
[e] Simultaneous grade 4 neutropenia and ≥ grade 2 fever

As of the March 31, 1995 data cutoff for the NDA, 23 patients (15 at the 100 mg/m² dose and 8 at the 125 mg/m² starting dose) remained in these studies. During the safety update period, an additional 32 courses (23 at the 100 mg/m² starting dose and 9 at the 125 mg/m² starting dose) were administered to these patients. The addition of these courses to the original safety database of 1338 courses had no effect on the safety profile of CPT-11 that was reported for this patient population in NDA 20-571.

Statistical Review

APR 25 1996

NDA#: 20-571

Applicant: The Upjohn Company

Name of Drug: CPT-11 (Irinotecan)

Indication: Colorectal Carcinoma

Document Reviewed: Submission dated 3/27/1996

Medical Officer: Tony Murgo, MD and Isagani Chico, MD

This IND submission contains the design of the post marketing study under the accelerated approval mechanism for NDA

Protocol #: M6475-0038
The sponsor proposes a multicenter, randomized, open label, controlled three-arm study of CPT-11 alone, the combination of CPT-11 (Irinotecan) + 5-FU/Leucovorin and 5-FU/ Leucovorin in patients with metastatic colorectal cancer who have not received any prior chemotherapy or radiation therapy for treatment of metastatic disease. The primary endpoint is time to progression (TTP). This is defined as the time between the start of the treatment and the time of the first objective documentation of disease progression. If patients go off study before there is evidence of progressive disease, the off-study date will be used as a "pseudo"-endpoint for the date of progression. Secondary endpoints include response rate, the percentage of patients whose TTP is > 6 months, the one-year survival rates, and quality of life assessments measured by the EORTC QLQ-30 instrument.

It is estimated that 220 patients per arm will be required to see a two-month difference in time to progression (from 5 to 7 months) with $\alpha=0.05$ significance level and 80% power. It is assumed the accrual is 50/patients per month with 12 months of follow up time after the last patient has been enrolled.

The randomization will be centralized with study center not a factor. Patients will be stratified by age (<65 or not), performance status (0, >0) and previous therapy (5-FU or no 5-FU) and time from initial diagnosis (<6 months or >6 months).

Statistical issues:

1) Is the change in the median time to progression for the control group of 5 months to 7 months for the treatment group a clinically meaningful change to be targeted? The estimated dropout rate should be given and the corresponding adjustment to the sample size should be

stated. Patients who go off study before progression are considered to be treatment failures and not to have (pseudo) progression. These patients should be censored for the TTP analysis. Time to treatment failure should be defined and used as a secondary endpoint.

2) The statement that the sample size is large enough to conclude with high confidence that the response rates in the experimental treatments differ by no more than 11% from the active control should be clarified noting assumptions used. Is this a statement about equivalence of the treatments?

3) Definitions for the "time to event endpoints" should use as the starting point the number of days from the date of randomization, not the day of initiation of treatment, to event.

4) The "Intent to Treat", viz., all patients as randomized, analyses of all the efficacy variables should be considered the primary analyses. The sponsor should provide methodology for adjusting the p-values associated with various endpoints because of the multiple comparisons (this study has three arms).

5) The sponsor should state prospectively in the protocol a small set of the most important covariates to be used in all the exploratory analyses that adjust for prognostic factors (e.g. Cox regression, ANCOVA, etc.). In addition, the sponsor should provide alternative ways of analyzing the time to event data if the proportional hazards assumption does not hold (e.g., stratified logrank test, Peto and Peto, etc). Cox regression analyses should be considered exploratory, and any claims about the treatment effect should be considered in conjunction with other tests, such as the stratified logrank test.

6) What kind of randomization algorithm will be used? Statistical comparisons of baseline characteristics should be prospectively defined and included in the data analysis to assess the quality of the randomization procedure.

7) All statistical tests should be two-sided.

8) Survival is commonly used as the primary endpoint for colorectal cancer studies because of the difficulty inherent in measuring TTP in this disease. The primary endpoint used for the approval of the 5-FU/Leucovorin combination for this indication was survival with a median time of about 12 months. The standard time to event analysis of this endpoint should be performed in addition to the simple rate comparison.

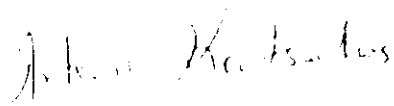
9) The sponsor needs to specify an interim analysis plan for the safety assessments. What are the criteria under which the trial would be terminated based on the safety? An interim analysis plan is also recommended for the primary efficacy endpoint. Such a prospective plan would insure the statistical error rates are well-defined should the need arise to stop the trial early in the event of an unexpected high drop-out rate in any arm for any reason (this is an open label study) or in the case of better results in the treatment arm.

10) **Quality of Life:**

The sponsor should prospectively identify (in the protocol) a small subset of questions with the most relevant components of Quality of Life (particularly those related to disease related-symptoms).

Analyses utilizing "last observation carried forwards" or imputing means for the missing observations (average of remaining observations) are of concern since they have a high potential for bias unless data are missing at random. This is a strong assumption and needs to be verified. Multiplicity problems arise for analyses repeated at various time points (i.e. analyses at each cycle). The question is can one assume that the missing mechanism is ignorable (then all data could be used in the analysis), or non-ignorable (then not all data could be used in the analysis, i.e. one could look at the time trends of the completers and the non-completers between the two treatment arms)? In either case, one has to fit an appropriate statistical model. Formal longitudinal analyses (i.e. GEE or Laird/Ware methods, etc.) may be used for determining time trends in the quality of life data. A full assessment of dropout patterns by treatment arm is an essential first step.

Comparisons of the clinical benefit measurements at various times with the baseline measurements raise the problem of multiple comparisons. What changes from baseline could be considered clinically meaningful for the clinical benefit variables? There are not stated in the protocol and should be prospectively defined.



Antonis Koutsoukos, Ph.D.
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concur: Dr. Gnecco C Gnecco 4/21/96

Dr. Chi Chi 4/25/96

cc:

Archival NDA#: 20-571
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HFD-150/Dr. Murgo
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HFD-710/chron

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This review consists of 4 pages of text.

Statistical Review and Evaluation of Stability Data JUN 1 4 1996

NDA#: 20-571

Title: Stability testing statistical analysis of CAMPTOSAR™ Injection (Irinotecan Hydrochloride Injection)

Applicant: The Upjohn Company

Name of Drug: CPT-11 (Irinotecan)

Indication: Treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy

Medical Officers: Isagani Chico, M.D. and Anthony Murgo, M.D.

Chemist: Robert Barron

1. BACKGROUND: The objective was to determine the stability of CPT-11 based on the time when an appropriate confidence band crosses its associated specification limit for various degradation products. This intersection determines the expiration date. The sponsor has proposed a 24 month expiration dating period.

2. SPONSOR'S RESULTS:
This reviewer presents the sponsor's regression analyses of potency, total impurity and of the known primary degradation products Data reported out to 18 months on three lots of product manufactured by the sponsor using fill procedures and stored inverted under three sets of conditions. The batch size in each case was 27 L, or about 4,500 finished vials. Executed batch records are provided. The sponsor tested the similarity of the degradation curves for each batch by applying appropriate statistical tests. Batches were pooled whenever it was appropriate. 95% one-sided lower confidence bands and the associated specification limits were given for the variables previously mentioned. The sponsor's results and graphs of the linear regression analyses are attached at the end of this document.

3. CONCLUSIONS: The results of the linear regression analyses of the potency, total impurity and of the known primary degradation products support the 24 month expiration dating period proposed by the sponsor.

Antonis Koutsoukos

Antonis Koutsoukos, Ph.D.
Mathematical Statistician

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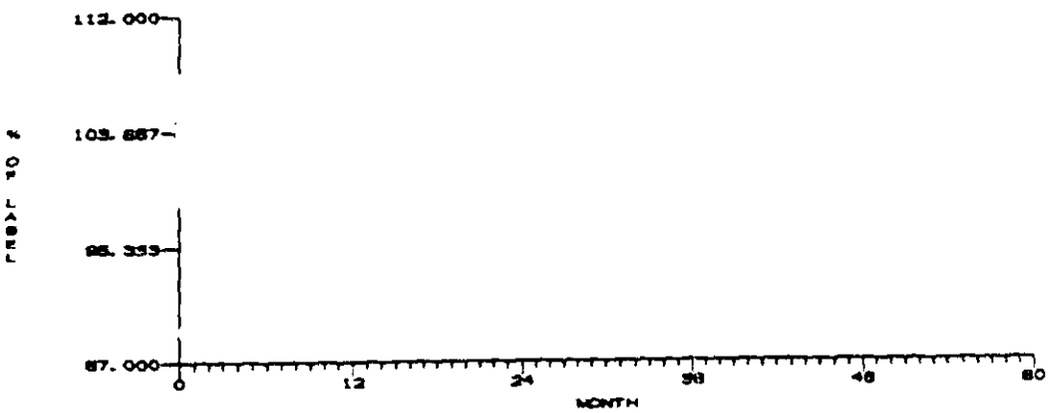
Koutsoukos/ 06-10-1996/ WP6.1/ Directory c:\nda20751\stab.rvw
This review consists of 2 pages (1-2) of text and 7 pages (3-9) of graphs.

Irinotecan Hydrochloride Injection NDA
Item 3. Chemistry, Manufacturing and Controls
Part IIH. Drug Product

FIGURE IIH.1 Regression Analysis - Irinotecan Hydrochloride Injection 20 mg/mL at 25°C/60% RH.

TITLE: IRINOTECAN HCL TRIHYDRATE INJ 20 MG/ML (CPT-11)
ASSAY FOR: IRINOTEC HCL TRIHYDR
ASSAY METHOD: HPLC

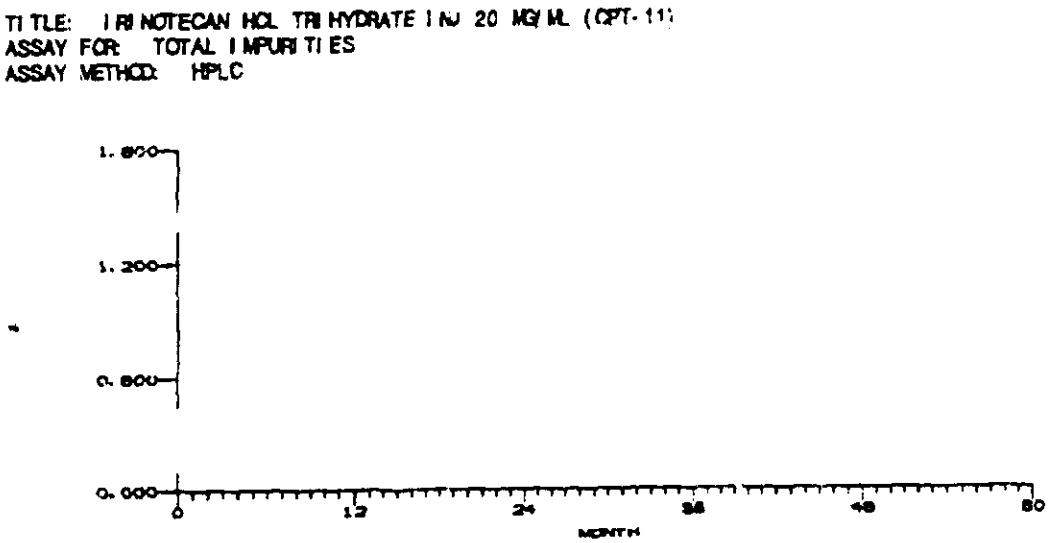


THE ESTIMATED RATE OF CHANGE IS -0.8625% OF LABEL PER MONTH
Y-INTERCEPT OF 102.648 % OF LABEL
LOWER LIMIT IS 90.0000 % OF LABEL
ESTIMATED SHELF LIFE IS GREATER THAN 60 MONTH
MINIMUM ESTIMATED SHELF LIFE IS GREATER THAN 60 MONTH
STORAGE CONDITION: 25 DEG C/ 60%
LOTS TESTED:
37430 37370 37371

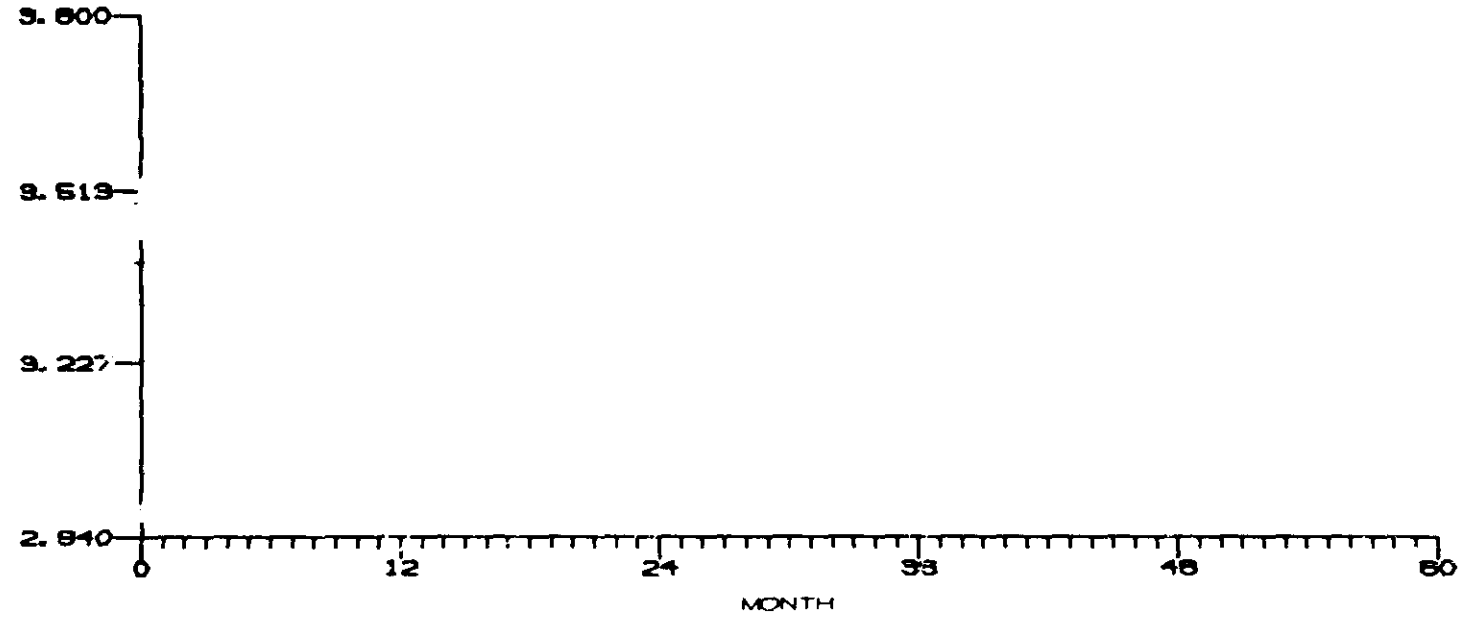
3

Irinotecan Hydrochloride Injection NDA
Item 3. Chemistry, Manufacturing and Controls
Part IIIL Drug Product

FIGURE IIIL2 Regression Analysis - Total Impurities in Irinotecan Hydrochloride Injection 20 mg/mL at 25°C/60% RH

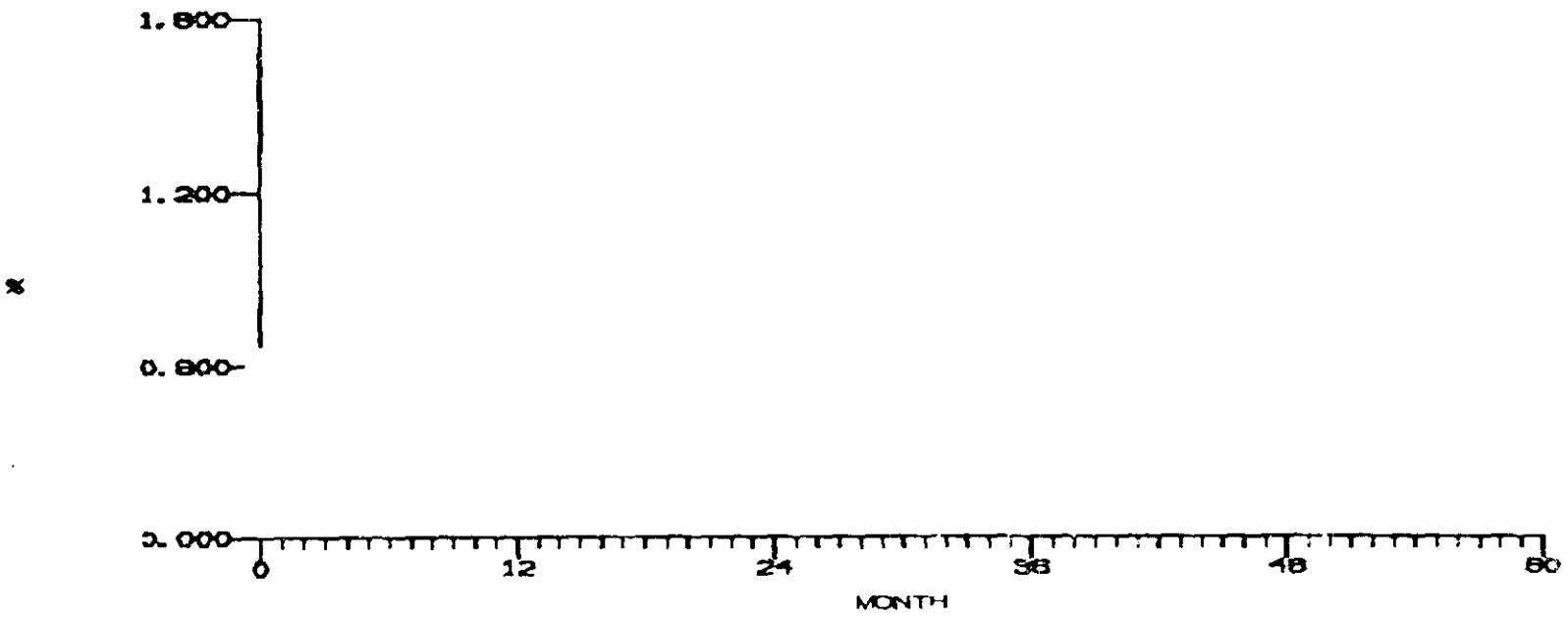


TITLE: IRINOTECAN HCL TRIHYDRATE INJ 20 MG/ML (CPT-11)
ASSAY FOR: PH
ASSAY METHOD:



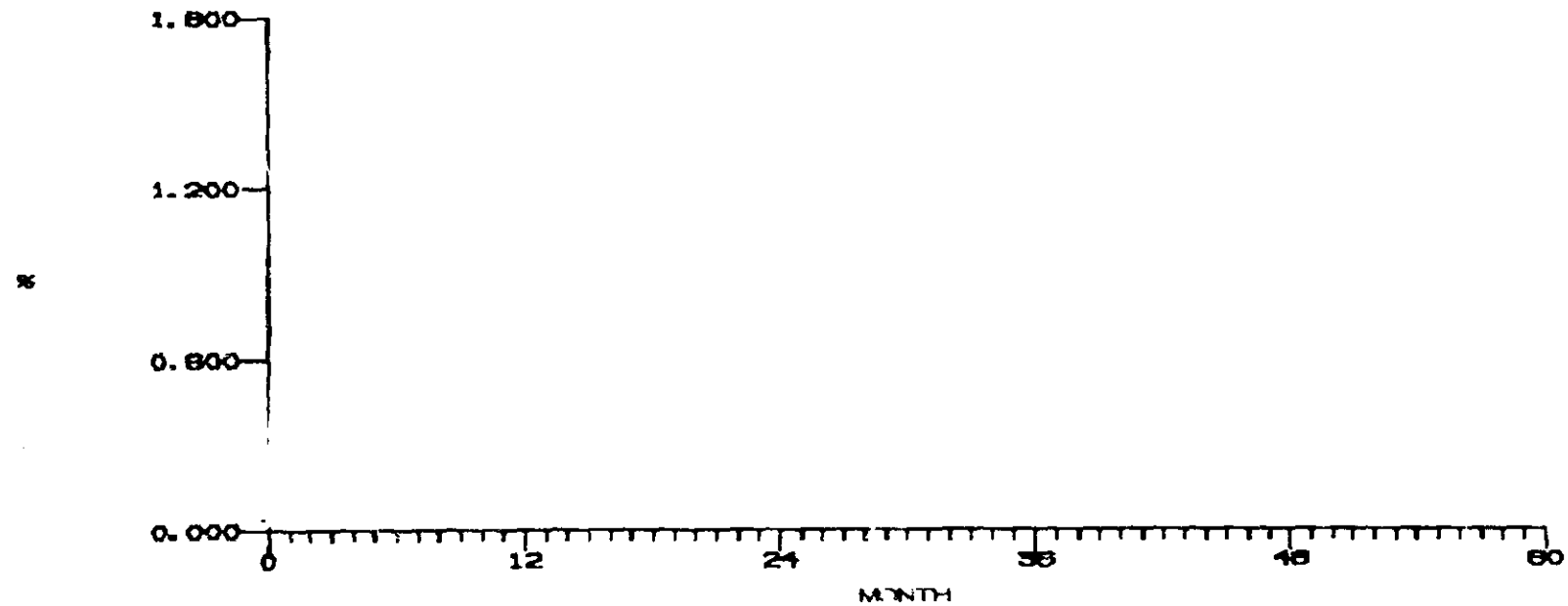
THE ESTIMATED RATE OF CHANGE IS -0.0002 PER MONTH
Y-INTERCEPT OF 3.494
LOWER LIMIT IS 3.0000
ESTIMATED SHELF LIFE IS GREATER THAN 60 MONTH
MINIMUM ESTIMATED SHELF LIFE IS GREATER THAN 60 MONTH
STORAGE CONDITION:25 DEG C-1 60%
LOTS TESTED:
37430 37370 37371

TITLE: IRINOTECAN HCL TRIHYDRATE INJ 20 MG/ML (CPT-11)
ASSAY FOR: U1
ASSAY METHOD: HPLC



THE ESTIMATED RATE OF CHANGE IS 0.0014% PER MONTH
Y-INTERCEPT OF 0.057 %
UPPER LIMIT IS 0.3000 %
ESTIMATED SHELF LIFE IS GREATER THAN 60 MONTH
MINIMUM ESTIMATED SHELF LIFE IS GREATER THAN 60 MONTH
STORAGE CONDITION:25 DEG C-I 60%
LOTS TESTED:
37430 37370 37371

TITLE: IRINOTECAN HCL TRIHYDRATE INJ 20 MG/ML (CPT-11)
ASSAY FOR: Y1
ASSAY METHOD: HPLC



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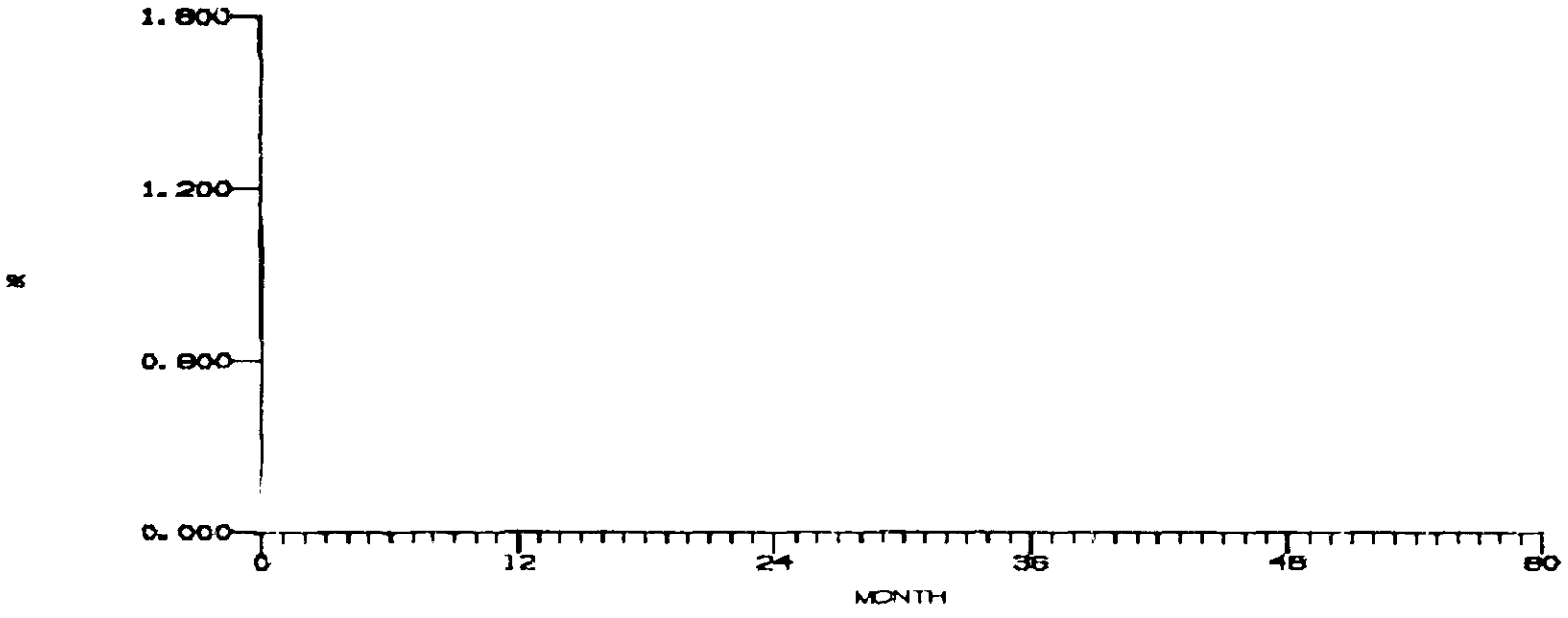
Y-INTERCEPT OF 0.059 %
UPPER LIMIT IS 0.3000 %
ESTIMATED SHELF LIFE IS GREATER THAN 60 MONTH
MINIMUM ESTIMATED SHELF LIFE IS GREATER THAN 60 MONTH
STORAGE CONDITION: 25 DEG C-I 60%
LOTS TESTED:
37430 37370 37371

(2)

TITLE: IRINOTECAN HCL TRIHYDRATE INJ 20 MG/ML (CPT-11)
ASSAY FOR: SN38
ASSAY METHOD: HPLC



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UPPER LIMIT IS 0.3000 %
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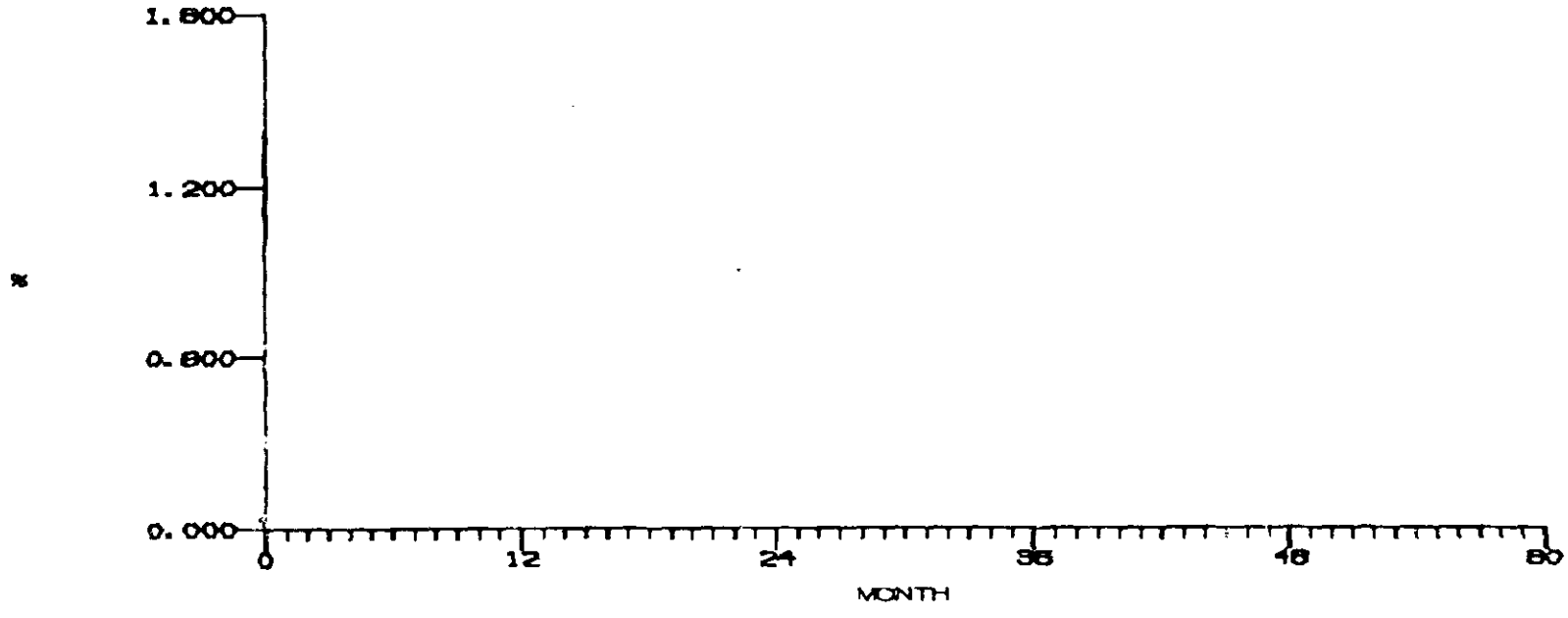
MINIMUM ESTIMATED SHELF LIFE IS GREATER THAN 60 MONTH
STORAGE CONDITION: 25 DEG C-I 60%
LOTS TESTED:
37430 37370 37371

(A)

007

TITLE: IRINOTECAN HCL TRIHYDRATE INJ 20 MG/ML (CPT-11)
ASSAY FOR: D1
ASSAY METHOD: HPLC



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Y-INTERCEPT OF 0.049 %
UPPER LIMIT IS 0.3000 %
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MINIMUM ESTIMATED SHELF LIFE IS GREATER THAN 60 MONTH
STORAGE CONDITION:25 DEG C-1 60%
LOTS TESTED:
37430 37370 37371

(9)

Consult #569 (HFD-150)

CAMPTOSAR irinotecan hydrochloride for intravenous use

The Committee found the proposed trademark to be acceptable by a narrow margin. The Committee has serious concerns with potential look alike/sound alike conflicts with the following trademarks: ONCOSPAR, CYTOSAR-U, HYCAMPTIN and NEOSAR, and USAN name: camptoterin. The Committeehas the highest sensitivity for names in drug classes where mix-ups have the direst consequences, such as oncolytic agents.

The Committee also feels that the proper established name for this product should be irinotecan hydrochloride injection to be in conformance with the USP parenteral product categories.

Overall, the Committee finds the trademark acceptable with concerns.

T W Boung 4/26/96
Chair,CDER Labeling and Nomenclature Committee

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Mr. Dan Boring, Chair, (HFD-530) ONDC/DNDC II

From: Division of Oncology Drug Products, HFD-150

Attention: Robert Barron, Chemist
Phone: (301) 594-1548

Date: March 7, 1996

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Camptosar ™ Injection **NDA:** 20-571

Established name, including form: irinotecan hydrochloride
injection for intravenous use

Other trademarks by the same firm for companion products: - -

Indications for Use (may be a summary if proposed statement is lengthy):

Camptosar is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy.

Initial comments from the submitter: (concerns, observations, etc.)

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: original NDA 20-571
HFD-150/division file
HFD-150/RBarron
HFD-150/LVaccari

SUMMARY OF APPLICATION:

Indication: Camptosar is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU based therapy.

Accepted for Accelerated Review: At the preNDA meeting, October 4, 1995, it was agreed that the NDA would be submitted for consideration under 21 CFR 314 Subpart H - Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses.

The sponsors proposed basis for approval consists of three pivotal US studies:

Trial M/6475/0001 Completed with 48 patients
Trial M/6475/0003R (interim study report)
Trial M/6475/0006 (interim study report)

All three studies were/are multisite, open-label, phase II studies and used/use the same dosage schedule of once weekly treatment with irinotecan for 4 consecutive weeks, followed by a 2 week rest (one course). Objectives in all studies were/are to evaluate the antitumor activity of irinotecan in patients with metastatic colorectal cancer that had recurred or progressed following a 5-FU based chemotherapeutic regimen.

E. A. + Fonsi

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

CAMPTOSAR™

(Irinotecan Hydrochloride Injection)

(CPT-11)

NDA 20-571

THE UPJOHN COMPANY

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ONCOLOGY DRUG PRODUCTS
(HFD-150)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-571

Camptosar

(Irinotecan Hydrochloride Injection)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application tosar™, The UpJohn Company has prepared an environmental ssment (attached) in accordance with *21 CFR 25.31a(a)* which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Irinotecan hydrochloride, trihydrate (Irinotecan) is a semi-synthetic derivative of comptothecin, a naturally occurring alkaloid extracted from the plant *Nothapodytes foetida*. Irinotecan injection is indicated for treatment of carcinoma of the colon or rectum in patients failing to respond or relapsing after treatment with 5-fluorouracil (5-FU) based therapy. The drug substance is manufactured by The drug product is manufactured by The Upjohn Company, Kalamazoo, Michigan. The finished drug product will be used mainly at hospitals and clinics.

The manufacture of semi-synthetic Irinotecan starts with purified Camptothecan, which is obtained from the wood of the *Nothapodytes foetida* tree. This species is not found in Appendix I-III of the "Convention on International Trade in Endangered Species of Wild Fauna and Flora" (CITES) or 50 CFR Chapter I of the US Fish and Wildlife Service. The Environmental Assessment provides sufficient reports and information to support the proposition that harvesting will not have a detrimental impact on the environment.

Drug substance may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at licensed incineration facilities. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the site of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-571

CAMPTOSAR™

(Irinotecan Hydrochloride Injection)

DIVISION of ONCOLOGY DRUG PRODUCTS
(HFD-150)

CENTER FOR DRUG EVALUATION AND RESEARCH

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ENVIRONMENTAL ASSESSMENT REPORT (EA)

1. DATE

November 17, 1995
February 6, 1996 (revised)
April 26, 1996 (revised)
June 3, 1996 (revised)

2. NAME OF APPLICANT

The Upjohn Company

3. ADDRESS

The mailing address and telephone number of The Upjohn Company's headquarters are:

7000 Portage Road
Kalamazoo, Michigan 49001
Corporate telephone number: (616) 323-4000

4. DESCRIPTION OF THE PROPOSED ACTION

4.a. Requested Approval

The Upjohn Company has filed an NDA pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for CAMPTOSAR® (irinotecan hydrochloride) Injection 20 mg/mL, packaged in amber glass vials with butyl rubber serum stoppers coated with Fluoro-Resin D film on the top flange surface and on the bottom plug surface and secured in place with aluminum (or equivalent alloy) overseals with plastic flip-off caps. This Environmental Assessment (EA) is submitted pursuant to 21CFR Part 25.31a(a).

4.b. Need for Action

This environmental assessment is required to accompany the New Drug Application (NDA) #20-571 for Irinotecan Hydrochloride Injection (CPT-11; U-101440E; CAMPTOSAR® Injection). Irinotecan Hydrochloride Injection is indicated for treatment of carcinoma of the colon or rectum in patients failing to respond or relapsing after treatment with 5-fluorouracil (5-FU)-based therapy.

The first-year patient population is estimated to be 3,214.

4.c. Production Locations

- Drug Substance

The drug substance will be purchased by The Upjohn Company (Upjohn) from:

The active ingredient of the drug substance will be provided to by:

- Drug Product

Irinotecan Hydrochloride Injection will be formulated and packaged at the Upjohn facility, located in the northern portion of the City of Portage in Kalamazoo County, Michigan. Kalamazoo County is in the southwest corner of the State Approximately 140 miles equidistant from Chicago and Detroit. The facility is approximately 1.7 miles northeast of the center of the City of Portage, approximately 5.4 miles south of the center of the City of Kalamazoo, and directly to the south of the Kalamazoo/Battle Creek International Airport.

The area in the immediate vicinity of the Upjohn facility is a mix of zoning including heavy and light industry, general business, and single- and multiple-family residences. The Upjohn facility is on land zoned for heavy industry. The site is directly bordered by airport property, residences, and undeveloped land. The climate is temperate. In terms of the Universal Transverse Mercator Coordinate System (UTM), the plant is

located in Zone 16 at 619.1 Km east and 4674.1 Km north, which corresponds to latitude 42°12'42" north and longitude 85°33'25" west.

This complex consists of approximately 80 buildings including chemical and pharmaceutical manufacturing operations, offices, laboratories, utility operations, and various other support buildings (see non-confidential Appendix 1). The plant site occupies a portion of approximately 810 hectares lying south of Bishop Road, east of Portage Road, north of Centre Street, and west of Sprinkle Road in Portage, Michigan.

4.d. Locations of Use

The ultimate use and disposal of the finished product will be mainly at hospitals, and clinics. Finished products will be stored in distribution centers throughout the U.S. prior to transportation for sale.

4.e. Disposal Sites

Disposal of drug substance or drug product may result from processing or distribution activities in the form of off-specification lots, returned goods, or from end user disposal of individual units of empty or partly empty finished product containers. The present infrastructure at the proposed manufacturing sites provides for the following recovery and/or ultimate disposal mechanisms:

- Off-Specification Lots of Drug Substance and Active Ingredient

See environmental assessment as non-confidential Appendix 6 and environmental assessment as non-confidential Appendix 7 for a discussion of off-specification lots of drug substance and active ingredient.

- Off-Specification Lots of Drug Product and Returned Goods

Off-specification formulated lots or returned goods of the drug product to Upjohn's Kalamazoo, Michigan facility will be incinerated in an on-site incinerator (interim status treatment storage and disposal facility).

Please refer to format item 6. for specific disposal operations covering air, water, and solid waste streams.

- Discarded Product in Hospital or Clinic Setting

Any discarded product or product containers generated in a hospital or clinic setting would typically be disposed in accordance with applicable Federal, State and local regulations.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

- Formulating

The material safety data sheet (MSDS) for irinotecan hydrochloride trihydrate is enclosed as non-confidential Appendix 2.

The list of ingredients used in formulating the drug product, Irinotecan Hydrochloride Injection, is included as non-confidential Appendix 5.

Full information dealing with impurities in the drug substance is contained in DMF version dated December 15, 1995. Specifically, potential impurities are reported in Vol. 3, pp. 1085-1101; usual impurities are reported in Vol. 3, pp. 1102-1107; and structural determination of impurities are reported in Vol. 3, pp. 1116-1130. The Chemical Abstracts Service (CAS) No. of the drug substance is reported in Vol. 3, p. 960.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

The drug substance and drug product are not expected to be introduced into the environment through transportation and storage. Product will be shipped in Department of Transportation (DOT) specification packaging. Irinotecan hydrochloride trihydrate is not regulated as a hazardous material under current DOT regulations. Product ready for shipment will be stored in either the manufacturing facility or distribution centers. Both maintain security through limited access.

6.a. Substances Expected to be Emitted

Portions of the ingredients, as listed in non-confidential Appendix 5, may be released to the environment as a result of the proposed action.

Please refer to format item 6.b. for specific disposal operations covering air, water, and solid waste streams.

Permits and other actions covering specific environmental regulations in force at Upjohn's chemical processing complex, including permit numbers and expiration dates where applicable, are summarized in the Permits Chart established as non-confidential Appendix 3 to include:

- Permit Description
- Regulatory Agency
- Permit No.
- Issue Date
- Expiration Date

6.b. Control Exercised

- Chemical Process

See environmental assessment as non-confidential Appendix 6 and environmental assessment as non-confidential Appendix 7 for a discussion of waste streams disposal of drug substance and active ingredient.

- Pharmaceutical Formulation

- Air Emissions

The Upjohn Company is operating under an air consent judgment with the Michigan Department of Environmental Quality (MDEQ, formerly MDNR) dated March 15, 1991, which requires that an inventory be taken of all equipment with the ability to emit or to control by December 15, 1991 and that complete permit applications be submitted to the MDEQ by July 1, 1993.

The Sterile Injectables area where Irinotecan Hydrochloride Injection is manufactured is currently operating under air use permit #923-92. The equipment and materials used in this formaulation are included in this air use permit. In the processing of Irinotecan Hydrochloride Injection containment isolator(s) (glove boxes) are used to handle the dry materials. It is assumed that .2% of the dry materials handled would be lost to the exhaust system which is controlled via HEPA filtration with an efficiency of 99.99%. A Nalgene blower exhaust fan is also used for maintaining exhaust flow and ensuring proper air balance.

The air consent judgment also requires that LAER (lowest achievable emission rate) controls be installed on all consent judgment volatile organic compounds (VOC)

emitting processes by July 1, 1995. The emission of this compound along with the processing equipment has been reviewed by the MDEQ. Upjohn believes that the emissions resulting from the process do not represent any meaningful quantity of emissions from our Portage Road manufacturing site.

- Liquid Waste Streams

Liquid waste streams will result as equipment is rinsed, cleaned, and sanitized. In addition, the external surface of the filled vials will be rinsed prior to inspection. The rinse water and waste streams will be disposed through Upjohn's sanitary sewer collection system. This wastewater stream will subsequently be discharged to the City of Kalamazoo's Wastewater Treatment Plant in compliance with the City of Kalamazoo's Industrial Pretreatment Program (IPP).

- *Industrial Pretreatment Program.* In response to Federal and State requirements governing the City of Kalamazoo's IPP, Upjohn was issued a discharge permit in the form of an Industrial Control Document (ICD) dated March 25, 1994 through March 31, 1999. In addition, incorporated by reference are The City of Kalamazoo Sewer Use Ordinance and Sewer Use Regulations Nos.

  - 1-89 (dated December 5, 1989), providing details on violations and penalties for noncompliance;

  - 91-1 (dated April 29, 1991), providing pollutant discharge limits for metals;

  - and 94-1 (dated February 9, 1994) providing pollutant discharge limits for petroleum hydrocarbons.

These documents detail additional specific discharge requirements and regulations. Projecting to the fifth year of production, all discharges from the production of Irinotecan Hydrochloride Injection are permitted and will not impact the limits imposed under the ICD and accompanying Sewer Use Regulations.

- Solid Waste

All unused, discarded, or returned product will be incinerated in an approved on-site incinerator.

- *Incinerator.* An on-site approved incinerator is being operated as a Resource Conservation and Recovery Act (RCRA) interim status treatment storage and disposal facility under #MID000820381 in compliance with 40 CFR 264, Subpart O requirements.

Additionally, 40 CFR 265.1(b) and Section 3005(e) of RCRA provide for the continued operation of an existing facility that meets certain conditions, until final administrative disposition of the owner's and operator's permit application is made.

A hazardous waste RCRA Part B/Act 451, Part 111 permit application has been submitted to the Waste Management Division of the Michigan Department of Natural Resources (now the Michigan Department of Environmental Quality , MDEQ) in Lansing, Michigan. The Upjohn facility is operating under interim status provisions until action is taken on the permit application. MDEQ action on the permit application is expected in 1996.

The MDEQ Air Quality Division air permit issued on July 15, 1980 (#242-80), revised to incorporate the Act 451, Part 111 requirements, was approved on May 26, 1993.

The incinerator is a two-stage system: the primary chamber rotary kiln operates at a minimum of 700°F; the secondary chamber, where final destruction of the product and off-gasses occurs, operates at a minimum of 1,904°F. The incinerator is equipped with a pollution control equipment train designed to remove gaseous and particulate pollutants. The pollution control equipment consists of: a quench section, an acid-gas pre scrubber, a Venturi scrubber, an entrainment separator, an induced draft fan, and an exhaust stack.

All necessary permits are in place for the manufacture of this product to begin, as an existing interim status facility in accordance with Section 3005(e) of RCRA and Michigan Act 64 licensing requirements.

Ash generated as a result of the incineration process will be sent to a permitted hazardous waste landfill. At the present time, Upjohn uses the following facilities:

- Chemical Waste Management, Trade Waste Incinerator Division, 7 Mobile Avenue, Sauget, IL, operating under EPA ID No. ILD 098 642 424 and Illinois Environmental Protection Agency No. IEPA 1631210009;
- Systech Environmental Corporation in Alpena, MI, operating under EPA ID No. MID981200835 and State Air Permit No. 587-93; or in Paulding, OH, operating under EPA ID No. OHD005048947 and State Air Permit Nos. 0363000002P016 and 0363000002P017;
- Continental Cement in Hannibal, MO, operating under EPA ID No. MOD054018288 and Air Permit No. 1086-004A;
- Upjohn may use other facilities for such disposal which are suitable for that purpose and properly permitted.

We have identified hazardous waste as well as air permits as given to us by these facilities, but there may be other permits and licenses applicable which are currently held by the facilities. While Upjohn has contracts with each of these facilities that require compliance with all applicable laws and regulations, Upjohn does not own, operate, or control these facilities. The waste stream profiles established with the hazardous waste landfill sites contain an affirmation by the facility of its compliance status. All facilities are audited and approved for use by Upjohn environmental auditors prior to the first shipment of waste from Upjohn to the site.

Solid waste will also result as particulate is captured in the recirculating HEPA filtration system. HEPA filters which become loaded are sealed in plastic bags and sent off-site to a permitted non-hazardous landfill. At the present time, Upjohn uses the following landfills:

- Westside Landfill in Three Rivers, MI (Waste Management of Michigan, Inc.) operating under State of Michigan Solid Waste Disposal License No. 8147 for bulk, uncrushed material;
- Orchard Hills Landfill in Watervliet, MI, operating under State of Michigan Solid Waste Disposal License No. 8113 for any finished drug product;
- or a comparable facility.

6.c. Citation of and Statement of Compliance with Applicable Emission Requirements

See environmental assessment as non-confidential Appendix 6 and environmental assessment as non-confidential Appendix 7 for a listing of Japanese and local regulations or standards cited as applicable to the proposed action as well as their statements of compliance.

- The Upjohn Company

The following regulations or standards are cited as applicable to the proposed action:

1. Federal Food, Drug and Cosmetic Act, PL 75-717, as amended, including subsections 306(a) and (b) [debarment].
2. Clean Air Act PL 91-604, as amended.
3. Clean Water Act PL 95-217, as amended.
4. Safe Drinking Water Act PL 93-523.
5. Resources Conservation and Recovery Act of 1976 PL 94-580, as amended.

6. Occupational Safety and Health Act of 1970, as amended.
7. Hazardous Materials Transportation Act of 1975, as amended.
8. Standards from the American National Standards Institute.
9. National Fire Protection Agency Standards.

    a. National Electrical Code Standards
    b. Life Safety Requirements

10. Act # 451 of 1994, Michigan Natural Resources and Environmental Protection Act, as amended including:
    - Part 31, Water Resources Protection
    - Part 55, Air Pollution Control
    - Part 111, Hazardous Waste Management
    - Part 115, Solid Waste Management
    - Part 121, Liquid Industrial Waste
    - Part 625, Mineral Wells
11. Act #399 of 1976, Michigan Safe Drinking Water Act, as amended.
12. Act #368 of 1978, Public Health Code.
13. Chapter 28 of the Kalamazoo City Code (Services and Wastewater) as amended by ordinance No. 1190.
14. Michigan Occupational Safety and Health Act of 1970, as amended. (Local regulation applicable to the State of Michigan.)

- *Emission Requirements.* Upjohn states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees or administrative orders applicable to the manufacture of Irinotecan Hydrochloride Injection at its facilities in Kalamazoo, Michigan, as well as emission requirements set forth in applicable Federal, State, and local statutes and regulations applicable to the manufacture of Irinotecan Hydrochloride Injection at its facilities in Kalamazoo, Michigan.

- *OSHA Requirements.* Upjohn certifies that it has comprehensive programs and practices in place addressing all applicable OSHA requirements.

6.d. Discussion of the Effect of Approval on Compliance with Current Emissions

A new filling line was purchased and placed in the existing sterile manufacturing facility. Formulation of the solution will take place in an existing potent drug room using a new dedicated manufacturing tank. In summary, capital equipment has been, or will be, purchased for formulation, filling, vial washing and labeling. Existing facilities with no new environmental control equipment are used for the entire formulation, filling, and packaging process.

Projecting to the fifth year of production, all discharges from the production of Irinotecan Hydrochloride Injection are permitted and will not affect compliance with current emission requirements. Waste water emission for this drug product will be < 1% of the permit limit.

6.e. Expected Introduction Concentrations

A theoretical expected introduction concentration for the aquatic environment can be calculated for irinotecan hydrochloride trihydrate utilizing the following equation:

EIC-aquatic (ppm) = A x B x C x D

where:

A = kg/year production
B = L/liters per day entering POTWs*
C = year/365 days
D = $10E^6$ mg/kg (conversion factor)

*1.115×10^{11} liters per day entering publicly owned treatment works (POTWs). (see 1992 Needs Survey in References)

The foregoing calculation assumes no depletion by hydrolysis, photolysis, or biodegradation.

CDER has routinely found that drugs at concentrations less than 1 ppb have no significant effect on relevant standard test organisms and therefore are unlikely to have a significant effect on the environment. CDER has also determined that information for environmental assessment format items 7, 8, 9, 10, and 11 will normally not be needed whose expected introduction concentration is less than 1 ppb. Since the calculated EIC for irinotecan hydrochloride trihydrate is less than 1 ppb, the format items mentioned above have not been included for Sections 7 and 8. However, the FDA has requested in its April 16, 1996 communication to The Upjohn Company that, even though this action qualifies for Tier 0, because flora is used in the production of this NME, Upjohn should provide detailed information in an appendix regarding the plant and provide summary information in format items 9-11 which focus on the use of the plant.

Based on worst-case analysis, irinotecan hydrochloride trihydrate may reasonably be anticipated to be nontoxic according to the definition found at 21 CFR 25.15(b)(6).

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

Based on information in CDER's revised guidance document (see Guidance for Industry in References), information for this format item is not included for this document.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

Based on information in CDER's revised guidance document (see Guidance for Industry in References), information for this format item is not included for this document.

9. USE OF RESOURCES AND ENERGY - FLORA USED IN PRODUCTION

Irinotecan hydrochloride, trihydrate (irinotecan) is a semi-synthetic derivative of camptothecin, a naturally occurring alkaloid extracted from the plant *Nothapodytes foetida*.

- *Geographic Region.* The starting material for the drug substance manufacturing process is a plant alkaloid, camptothecin (CPT). CPT is extracted from a subtropical plant named *Nothapodytes foetida (NPF)* (old name: *Mappia foetida).* The description and identification of the plant are contained in the article excerpted from Volume Three of *Flora of Taiwan* (non-confidential Appendix 8, pp. A 35 and A 36).

The tree material is harvested from plantations in Taiwan and in small islands in the southern part of Japan and from wild private forests in India. There are two areas of sourcing the *NPF* plant from plantations in Taiwan: 1) Taitung and 2) Chaii, as indicated in the map representation of the geographic region (non-confidential Appendix 9, p. A 37). The two islands in Japan where *NPF* is cultivated are: 1) Ishigaki and 2) Iriomote, as indicated in the map representation of the geographical region (non-confidential Appendix 9, p. A 38). In India, there are seven different harvesting locations: 1) Sagar, 2) Kumta, 3) Ajra, 4) Satara, 5) Mahabaleshwar, 6) Bhor, and 7) Pune, as indicated in the map representation of the geographical region (non-confidential Appendix 9, p. A 39).

- *Plant Description/Identification.* Non-Confidential Appendix 8, pp. A 35 and A 36, includes photocopies of an article excerpted from the *FLORA OF TAIWAN, Vol. Three.*

- *Use of Wild or Cultivated Plants.* In India, plants are currently harvested from the private natural forest. Preparations are underway for conversion to a plantation setting which should be completed in the next few years. In Taiwan and the southern regions of Japan, 100% sourcing of the plant is from plantations.

- *Method of Harvest.* Only branches of the *NPF* are used and cut into chips.

The regrowth rate from branch cuttings is 2 to 3 years for the branches to mature. *NPF* plants are cultivated from seeds collected from the natural forest. The growth rate from seed is after 5 to 6 years of cultivation.

Harvesting of *NPF* branches should have no anticipated, potential adverse effect on the environment or to any endangered or threatened wildlife species because:

- there are no known uses of the plant (humans, food source/habitat for fauna) other than the production of the drug substance;

- the resource used is renewable; the tree grows back and therefore is a sustainable harvest;

- in Taiwan and the southern regions of Japan, 100% sourcing of the cultivated plant is from plantations;

- in India the private natural forest is not a habitat for any endangered species;

- at the Indian supply farms, there is a governmental oversight of the harvesting process;

- the plant is not subject to Convention on International Trade and Endangered Species (CITES) or cited in the classification as an endangered or threatened species.

- *Additional Uses of the Plant.* There are no known uses of the plant other than the production of the drug substance.

- *Growth Rate and Percent Sustainable Harvest.* The plant is cultivated in plantations and private natural forests, and the regrowth rate is considered relatively rapid for this type of species. The regrowth rate from branch cuttings, the primary source of material, is 2 to 3 years for the branches to mature. The growth rate from initial seeding of the plantations and farms is after 5 to 6 years of cultivation.

The percent of sustainable harvest from the wild private forests in India is estimated to be 10%. The wild harvest as a percent of the annual total harvest of *NPF* from all locations is estimated to be 25%.

- *Bulk Weight.* The starting bulk weight of the material is contained in DMF Vol. 1, p. 17, with drug substance final yield found in Vol. 2, p. 315. Harvesting data are confidential and will be submitted directly to the DMF and FDA.

- *Government Oversight.* At the Indian supply location, a government official inspects the harvesting process and gives authorization for permission to transport the material. will be submitting photocopies of confidential certification documentation directly to the DMF and FDA. At the Japanese and Taiwanese supply locations, there are no regulations for oversight by the governmental agencies.

- *Plant Endangerment.* The plant is not subjected to CITES or cited in the classifications as an endangered or threatened species.

- *Cultivated Source/Synthetic Route.* See *Use of Wild or Cultivated Plants,* above. There are no plans, at this time, to convert to a synthetic route of manufacture for the drug substance.

10. MITIGATION MEASURES

- Manufacturing Source

Measures taken to avoid potential adverse environmental impacts associated with the proposed action include:

- use of equipment systems to prevent emission levels from exceeding limits established by Federal, State and local regulations;

- disposal of final washing aqueous streams to the municipal sewer system for biological treatment at the City of Kalamazoo Water Reclamation Plant;

- as required by the U.S. OSHA's Hazard Communication Standard of November 25, 1983, hazards concerning chemicals are transmitted to affected employees in the manufacturing sector which include labeling and other forms of warning.

- an extensive spill control plan to protect employees and environmental compartments is in place at The Upjohn Company Portage Road facility to mitigate any adverse effects of inadvertent releases to the environment.

Material safety data sheets (MSDSs) are available on site. Employees associated with the manufacture of Irinotecan Hydrochloride Injection have appropriate training. Employee protective clothing (eg, gloves, uniforms, and safety shoes) and protective equipment (eg, safety glasses and approved respirators) are used during manufacture to assure compliance with applicable occupational safety requirements.

The Upjohn Company has a comprehensive occupational health and safety program. This includes conduct of preplacement physical examinations of employees and periodic health surveillance examinations of all employees in manufacturing areas. Additionally, the company operates a health clinic to address any employee illness and/or injury occurring during the course of employment. The above procedures will serve to monitor employees for the development of conditions attributable to exposure.

In addition, all employees in Pharmaceutical Manufacturing are required to take basic safety training on an annual basis, which includes:

- Hazard communication and hazardous materials,
- Personal protective equipment and production equipment, and
- Standard operating procedures and personal safety practices.

- Plant Source

No potential adverse impacts are foreseen with the use of the *NPF* plant in the production of CPT; however, measures taken to further mitigate against negative environmental consequences associated with the proposed action include:

- Responsible harvesting techniques are instituted by maintaining an available supply of plants through the use of plantations, governmental oversight of forest sourcing, and only using the branches of the *NPF* plants. This provides for the use of a renewable resource of material which grows again after harvesting within 2 to 3 years after maturation of the branches.

- In Taiwan and the two Japanese islands, the plant is sourced from plantations.

- In India, the plants are currently harvested under controlled governmental oversight conditions from private natural forests. Preparations are currently underway

for conversion to a plantation setting which should be completed within the next few years.

- At the Indian supply location, application to the appropriate government authority in the Agriculture & Forest Department is made for permit to harvest and again, for permit to transport the material to the shipping location. A government official examines the harvested goods and, after satisfaction, the Regional Deputy Director, Wild Life Regional Office, Goernment of India, gives authorization for permission to transport the material in accordance with Federal regulations.

11. ALTERNATIVES TO THE PROPOSED ACTION

Resources and facilities are being used effectively to produce a quality product with minimal environmental impact. The alternative of no action resulting in the deprivation to mankind of potentially beneficial therapy is not anticipated.

12. LIST OF PREPARERS

Following is a listing of those persons, and corresponding qualifications, who participated in the preparation of this assessment. No government agency was consulted for this specific evaluation other than for routine implementation of ongoing environmental programs conducted at existing facilities.

Jeffrey S. Mehring	Environmental Quality and Safety Division Manager, Environmental Health Sciences Ph.D., Agriculture Professional experience: 24 years
Susan I. Shedore	Environmental Quality and Safety Division Environmental Technician A.A., Liberal Arts Corporate experience: 24 years
R. F. Tolbert	Environmental Compliance Engineering Environmental Compliance Engineer B.S., Mechanical Engineering Professional experience: 6 years

R. L. Gerteisen	Pharmaceutical Manufacturing Consultant Sterile Production B.S., Pharmacy/Ph.D., Physical and Industrial Pharmacy Professional experience: 16 years
Babette L. Burleigh	Babette L. Burleigh Manufacturing Project & Reg'y Management Project Manager B.A., Chemistry Professional experience: 12 years
W. H. Senour	Pharm. Manufacturing Engineering Engineer B.S., M.E. Professional experience: 20 years
Ian W.D. Clements	Worldwide Marketing Manager Worldwide Strategic Marketing B.Sc, Genetics, M.S., Immunology Professional experience: 10 years
K. B. Eckert	Acting State Historic Preservation Officer Bureau of History Michigan Department of State Lansing, Michigan

13. CERTIFICATION

The undersigned officials certify that the information presented is true, accurate, and complete to the best of their knowledge.

The undersigned officials certify that the EA summary document (pages 1-18) and Appendices 1-9 contain non-confidential information and acknowledge that this information will be made available to the public in accordance with 40 CFR § 1506.6. **Appendix 10 contains confidential information that is not to be made available to the public.**

Randal S. Senger

June 3, 1996

Randal S. Senger, Manager
Corporate Environmental Affairs
(telephone 616/323-5341)

Date

Jeffrey Mehring

3 JUNE 96

Jeffrey S. Mehring, Manager
Environmental Health Sciences
(telephone 616/323-4746)

Date

14. REFERENCES

1992 Needs Survey, Report to Congress, September 1993, EPA 832-R-93-002.

Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements. Center for Drug Evaluation and Research, CMC 6, November 1995.

15. APPENDICES

Non-Confidential

1 Map of Upjohn's Kalamazoo Pharmaceutical Manufacturing site complex
2 MSDS for the active ingredient, irinotecan hydrochloride trihydrate
3 Permits Chart
4 Chemical Summary
5 Irinotecan Hydrochloride Injection: Ingredients Used in Formulation
6 Yakult Honsha Co, Ltd's Environmental Assessment Report
7 Shiratori Pharmaceutical Co, Ltd's Environmental Assessment Report
8 *FLORA OF TAIWAN, Vol. Three.* Epoch Publishing Co, Ltd, Taipei, Taiwan, Republic of China, pp. 648-649, 1977.
9 Harvesting Location Site Maps: Taiwan, Japan, and India

Confidential

10 Five-Year Market Forecast

Based on information in CDER's revised guidance document (see Guidance for Industry in References), Sections 7 and 8 test results to support this format item are not included for this document.

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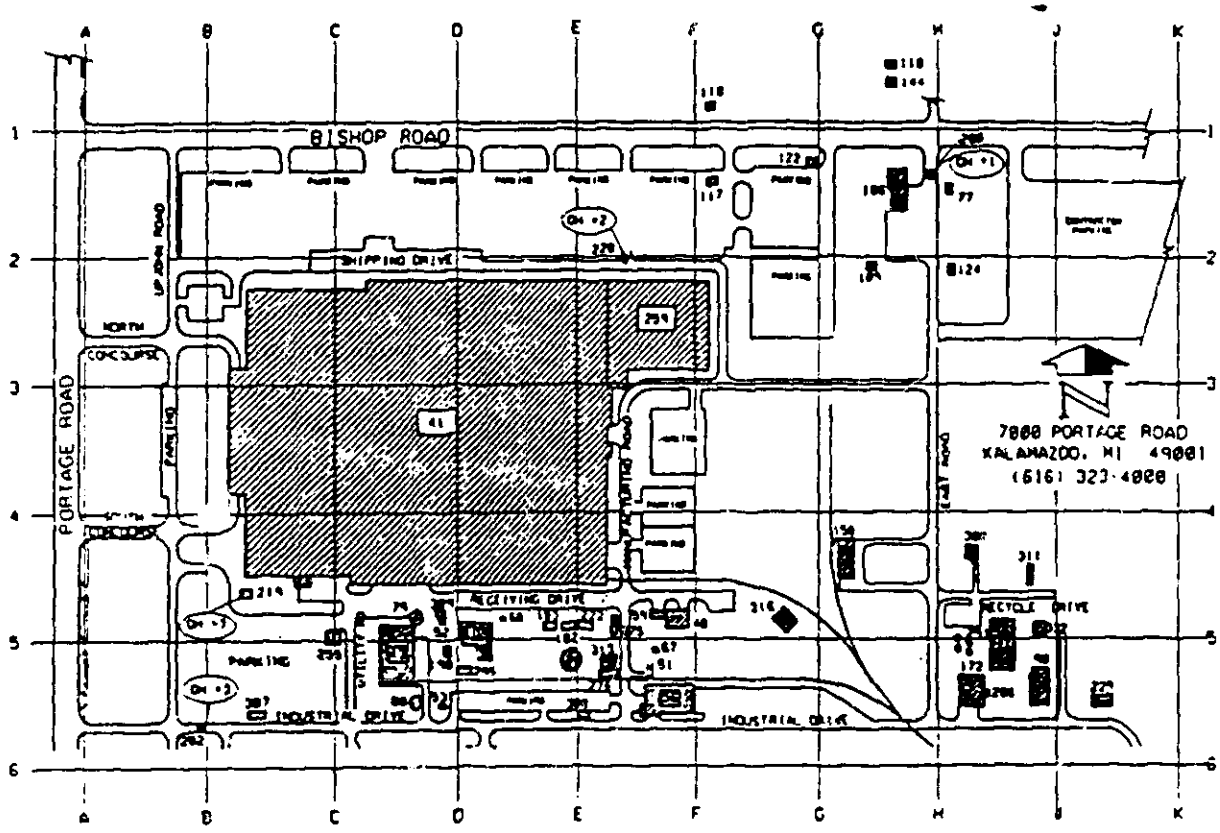
APPENDIX 1

Map of Upjohn's Kalamazoo Pharmaceutical Manufacturing Site Complex

PORTAGE ROAD BUILDINGS
EAST SIDE
North of Industrial Drive



BLDG.	•	NAME	LOCATION
40		GROUND SERV. & WATER UTILITIES	F5
41		PHARMACEUTICAL MANUFACTURING	C4
43		POWER HOUSE	C5
51		SWITCHGEAR HOUSE	F5
52		PUMPHOUSE #1	D5
53		PUMPHOUSE #2	D6
56		GARAGE	F6
59		YARD CREW & WATER DEPT. OFF. E	F5
60		PUMPHOUSE #4	D5
67		METER HOUSE	F5
77		PUMPHOUSE #17	H1
79		WATERSPHERE	D5
80		WATERSPHERE	D6
90		CONSTRUCTION CONTRACTORS SHOP	J5
109		WELLHOUSE	G2
110		PUMP HOUSE WELL #25	H1
117		CHLORINATED WELL #7	F1
118		CHLORINATED WELL #8	F1
122		CHLORINATED WELL #19	G1
124		FIRE TRAINING BUILDING	H2
144		PUMPHOUSE WELL #27	H1
158		PRE-MIX PRODUCTS	G4
172		INCINERATOR BUILDING	H5
182		CENTER RELOCATABLE CLASSROOM	E5
183		WEST RELOCATABLE CLASSROOM	E5

BLDG.	•	NAME	LOCATION
186		FIRE STATION	H1
188		CENTRAL UTILITIES FACILITY	D5
190		COOLING TOWER FIRE PROT. BLDG.	D5
202		GUARDHOUSE #3	B6
219		GUARDHOUSE #7	B5
220		GUARDHOUSE #2	E2
222		EAST RELOCATABLE CLASSROOM	E5
229		ENGINEERING STORAGE BUILDING	J5
255		OIL PUMPHOUSE FOR BOILERS	C5
259		LAB & TECHNICAL SERV. FACILITY	F3
268		GUARDHOUSE #1	H1
275		OFFICE TRAILER	E5
276		OFFICE TRAILER	E5
286		POLE BARN	H3
291		WASTE CONTROL BUILDING	H5
295		METAL BUILDING	D5
307		BACKFLOW PREVENTER BLDG #1	B6
308		BACKFLOW PREVENTER BLDG #2	E6
309		BACKFLOW PREVENTER BLDG #3	D5
311		INSTRUMENTATION BUILDING	J4
313		WATER BOOSTER PUMP STATION	E5
316		STORAGE GARAGE	G5
332		UTILITY STORAGE	J5
388		HAZARDOUS SOLVENT WASTE STORAGE	H4

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APPENDIX 2

Material Safety Data Sheet
Irinotecan Hydrochloride, Trihydrate

NON-CONFIDENTIAL
APPENDIX 2
MATERIAL SAFETY DATA SHEET

Revision date: November 21, 1995
Agent ID#: 51695

1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

COMMON NAME: CPT-11
SYNONYMS: Irinotecan hydrochloride trihydrate
100286-90-6 - CAS NUMBER
(S)-{1,4'-Bipiperidine}-1'-carboxylic acid, 4,11-Diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano {3',4':6,7}indolizino {1,2-b} quinolin-9-yl ester, monohydrochloride, trihydrate
102238 - EDP NUMBER
U-101,440E - UPJOHN U#
MOLECULAR FORMULA: C33-H38-N4-O6.HCl.3H2O
MANUFACTURER/SUPPLIER: PHARMACIA & UPJOHN INC
7171 PORTAGE RD
KALAMAZOO, MI 49001-0199
TELEPHONE NUMBERS: (616) 323-5122 - (24 HOURS)
(616) 323-7555 - (8:00 a.m. - 4:30 p.m.)

2. COMPOSITION/INFORMATION ON INGREDIENTS

INGREDIENT 1
COMMON NAME: CPT-11
CHEMICAL NAME: (S)-{1,4'-Bipiperidine}-1'-carboxylic acid, 4,11-Diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano {3',4':6,7}indolizino {1,2-b} quinolin-9-yl ester, monohydrochloride, trihydrate
% BY WEIGHT: 100 %
CAS NUMBER: 100286-90-6
EXPOSURE LIMIT(S):
UPJOHN EXPOSURE LIMIT-TWA: 0.4 UG/M3

3. HAZARDS IDENTIFICATION

PRIMARY ROUTE(S) OF EXPOSURE: Skin contact, eye contact, ingestion and inhalation.

EFFECTS OF OVEREXPOSURE: The effects of overexposure to this drug in the workplace are not known. CPT-11 is cytotoxic and will produce severe toxic effects to rapidly dividing tissues upon overexposure. When administered clinically by intravenous injection, nausea, vomiting, diarrhea, anorexia and alopecia (hair loss) are sometimes reported. The main toxic effect is leukopenia (reduction in the number of leukocytes in the blood).
TARGET ORGANS: Blood. Gastrointestinal system.
MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE: Not established.

4. FIRST AID MEASURES

EYES: Flush with water for 15 minutes. Hold eyelids open to assure complete contact with water.
SKIN: Wash with soap and water. Remove contaminated clothing.
INHALATION: Remove from exposure.
INGESTION: Call a physician.

5. FIRE FIGHTING MEASURES

FLASH POINT: Not applicable (solid).
LOWER EXPLOSION LIMIT (LEL): Not applicable.
UPPER EXPLOSION LIMIT (UEL): Not applicable.
EXTINGUISHING MEDIA: Water, carbon dioxide, or dry chemical.
FIRE-FIGHTING PROCEDURES: Wear self-contained breathing apparatus and full body protective equipment.
UNUSUAL FIRE OR EXPLOSION HAZARDS: As with all finely divided organic powders, it is advisable to eliminate explosion hazards by methods such as grounding mechanical equipment in contact with the material to prevent the buildup of static electricity, inerting the atmosphere or controlling dust levels.
HAZARDOUS COMBUSTION PRODUCTS: Carbon monoxide. Carbon dioxide. Nitrogen oxides.

6. ACCIDENTAL RELEASE MEASURES

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED: Spilled CPT-11 should be cleaned-up by experienced personnel wearing appropiate protective gear: to prevent water permeation, a Saranex coated Tyvek suit (or equivalent) should be worn with rubber boots, nitrile gloves, chemical goggles, and an approved respirator. Remove ignition sources;

control the generation of dust; provide ventilation. Keep out of drains; prevent entry to surface water, groundwater and soil. Cover with damp towels to minimize dust levels. Carefully scoop spilled material and place in a container. Clean area with water, detergent or an acidified detergent solution. CPT-11 solutions will fluoresce blue/white under an ultraviolet (UV) light set at a wavelength of 365 nm and is easily removed from most surfaces using the above cleaning agents. Clean the area until fluorescent areas which are water soluble have been eliminated. Monitoring the clean-up process using the UV light should avoid unintentionally spreading the contamination by the use of an inappropriate cleaning technique (such as the use of copious volumes of cleaning solution). Note: many materials, other than CPT-11 fluoresce (e.g., cellulose). However, if the fluorescent material is suspected to be CPT-11 and is spread by wetting it should be treated as drug. All clothing, PPE and towels should be UV inspected and if contaminated with CPT-11 should be cleaned or bagged and incinerated.

7. HANDLING AND STORAGE

PRECAUTIONS FOR HANDLING AND STORING: CPT-11 inhibits DNA replication. Handling solids or solutions should be carried out with extreme care to avoid personal exposure, either by skin contact, ingestion, inhalation or other means.

PRODUCT PREPARATION AND ADMINISTRATION: Hospital personnel preparing or administering CPT-11 should wear nitrile gloves, safety glasses, a closed-front gown with knit cuffs and masks. Preparation of all antineoplastic agents should be done in a class II laminar flow biological safety cabinet with exhaust air discharged external to the room environment. All needles, syringes, vials, ampules and other equipment or disposable clothing which have been in contact with CPT-11 should be segregated and incinerated at a temperature not less than 1000 degrees centigrade.

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

RESPIRATORY PROTECTION: Approved respirator.
VENTILATION: Nonrecirculating local exhaust.
PROTECTIVE GLOVES: Nitrile.
EYE PROTECTION: Chemical goggles.
OTHER PROTECTIVE EQUIPMENT: Saranex coated tyvek suits (to prevent water permeation) and rubber booties. All clothing and PPE should be UV

inspected and if contaminated with CPT-11 should be cleaned or bagged and incinerated. CPT-11 has been shown to absorb to rubber (booties).

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE/PHYSICAL STATE: Pale yellow crystalline or crystalline-like powder which fluoresces blue/white when exposed to ultraviolet (UV) light (365 nm). The most intense fluoresence is obtained when drug is in solution or wetted. Bulk drug fluorescence may appear green/yellow on stainless steel surfaces.
BOILING POINT: Not applicable.
FREEZING POINT: Not applicable.
MELTING POINT: 256.5 C (with decomposition)
MELTING RANGE: 250 - 263 C (with decomposition)
MOLECULAR WEIGHT: 677.2
OPTICAL ROTATION: Alpha at 25 degrees = +67.72 degrees (aqueous solution at pH 4.0).
PARTITION COEFFICIENT (n-OCTANOL/WATER): 0.03 (at pH < 6, 0.05 at pH > 9 and 0.37 at pH 7.5)
PH: 3.5 - 4.5 (concentration = 20 mg/ml)
SOLUBILITY IN SOLVENTS: Solubilities (mg/ml):

Gl. Acetic Acid	551.1
Methanol	128.3
Chloroform	43.2
Ethanol	4.5
Acetic Anhydride	2.2
Acetonitrile	1.8
Acetone	0.2
Ethyl Ether	< 0.0005

SOLUBILITY IN WATER: 11 MG/ML (pH dependent)

10. STABILITY AND REACTIVITY

STABILITY: Stable. Aqueous solution is pH dependent. Degradation under basic conditions (pH > 10). Stable for 18 months at room temperature when protected from light. At least three years estimated half-life at room temperature. Stable at temperature up to 50 degrees C and relative humidity 10-92%. Bulk drug is stable for 24 months at room temperature when protected from light. At least three years estimated shelf-life at room temperature.

PHYSICAL CONDITIONS TO AVOID: pH >10 for solution. Exposure to light for solution and bulk drug.
INCOMPATIBILITY WITH OTHER MATERIALS: None known.
HAZARDOUS POLYMERIZATION: Does not occur.

11. TOXICOLOGICAL INFORMATION

ACUTE STUDIES:
EYE IRRITATION (RABBIT): CPT-11 caused minimal and transient irritation to the eyes of rabbits.
SKIN IRRITATION (RABBIT): CPT-11 was not irritating to the intact skin of rabbits, but slightly irritating to the scratch marks (open wounds) of the abraded skin. Dermal absorption via intact skin was found to be slow and minimal and via the abraded skin it was found to be fast but minimal.
INTRAVENOUS LD50 (DOG): 40 - 80 MG/KG
INTRAVENOUS LD50 (RAT): 84 MG/KG
INTRAVENOUS LD50 (MOUSE): 133 MG/KG
ACUTE TOXICITY: Administration of CPT-11 to female beagle dogs resulted in lethal toxicity attributed to immunosuppression, bone marrow suppression and gastrointestinal toxicity, after 5 consecutive daily intravenous doses of 7.5 mg/kg/day and after 4 consecutive daily oral doses of 18.75 mg/kg/day or greater.
ORAL LD50 (RAT): 867 MG/KG
ORAL LD50 (MOUSE): 1,064 MG/KG (approximately)
INTRAPERITONEAL LD50 (MOUSE): 177 MG/KG
SUBCHRONIC/CHRONIC STUDIES: A rat four week intravenous study had a no effect level of 0.8 mg/kg/day.
CHRONIC STUDIES: A rat six month IV study showed effects on blood at 0.0064 mg/kg/day, the lowest dose tested.
OTHER STUDIES: Antigenic potential in guinea pigs.
GENOTOXICITY:
Positive: In vitro - chromosomal aberration (Chinese Hamster cells) with and without activation.
Positive: In vivo - micronucleus test, i.p., mouse.
Negative: In vitro - Ames assay with and without metabolic activation.
REPRODUCTION/FERTILITY: No effects on fertility from IV doses up to 6.0 mg/kg/day. Maternal toxicity was observed at IV doses of 6.0 mg/kg/day.
TERATOGENICITY: Teratology studies showed that IV doses of 1.2 mg/kg/day

in the rat depressed growth in the fetuses. At 6.0 mg/kg/day, external, visceral and skeletal abnormalities were noted. Teratogenic effects have been reported in rabbits at IV dosages of 0.06 mg/kg/day.
CARCINOGENICITY: CPT-11 was shown not to be carcinogenic to rats receiving CPT-11 for 13 weeks and observed for 91 weeks. The no observed effect level was 2 mg/kg/week.

12. DISPOSAL CONSIDERATIONS

WASTE DISPOSAL METHOD: Dispose of by incineration in accordance with applicable international, national, state, and/or local waste disposal regulations.

13. SHIPPING REGULATIONS

Not regulated for transportation by the United States Department of Transportation (DOT), International Maritime Organization (IMO), or International Air Transport Association (IATA). May be subject to state and/or local transportation requirements.

14. OTHER INFORMATION

REVIEWED BY: Environmental Health Sciences.
DISCLAIMER: The MSDS information is believed to be correct but should only be used as a guide. Pharmacia & Upjohn, Inc. disclaims any express or implied warranty as to the accuracy of the MSDS information and shall not be held liable for any direct, incidental or consequential damages resulting from reliance on the information.

15. LABELING

UPJOHN PRECAUTIONARY LABEL CODE(S): N-3
HAZARD: MUTAGEN.
SIGNAL WORD: DANGER!
STATEMENT OF HAZARD/RISK PHRASE: May cause change or damage to genetic material.
PRECAUTIONARY MEASURES: Avoid exposure. Do not get in eyes, on skin, on clothing. Do not breathe dust, vapor, mist or gas. Keep container closed. Use only with adequate ventilation. Wash thoroughly after handling.

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APPENDIX 3

Permits Chart

NON-CONFIDENTIAL
APPENDIX 3
THE UPJOHN COMPANY: PERMIT INDEX

PERMIT DESCRIPTION	REGULATORY AGENCY	PERMIT NO.	ISSUED	EXPIRES
Air Consent Judgment	Michigan Department of Envronmental Quality, Air Quality Division		03/15/91	08/01/96
Air Use Permit	MDEQ, Air Quality Division	923-92	03/29/94	non-expiring until modified
National Pollutant Discharge Elimination System (NPDES)	Michigan Department of Envronmental Quality Michigan Water Resources Commission	MI0002941	09/20/90	current permit extended through first quarter 1996 pending reissuance
Michigan Natural Resources and Environmental Protection Act 451, Part 111 Hazardous Waste Management (On-site Incinerator)	Michigan Department of Envronmental Quality Waste Management Division	Incinerator operated as a RCRA Interim Status Treatment Storage and Disposal Facility under #MID 000820381 pending action on Part B/Act 64 permit app'n.		

PERMIT DESCRIPTION	REGULATORY AGENCY	PERMIT NO.	ISSUED	EXPIRES
Michigan Natural Resources and Environmental Protection Act 451, Part 55 Air Pollution Control (On-site Incinerator)	Michigan Department of Envronmental Quality Air Quality Division	242-80	07/15/80 (revised to incorporate the Act 64 requirements) approved 05/26/93	non-expiring until modified
Wastewater Discharge Permit	City of Kalamazoo Industrial Pretreatment Program	The City of Kalamazoo Sewer Use Ordinance and Sewer Use Regulations/Industrial Control Document	03/25/94	03/31/99
Chemical Process Water Management (CPWM) Injection System (Class 1 wells) Underground Injection Control Permit	U.S. EPA, Region 5 Safe Drinking Water Act	MI-077-1W-0001 MI-077-1W-0002	07/09/93	10/27/96

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APPENDIX 4

Chemical Summary

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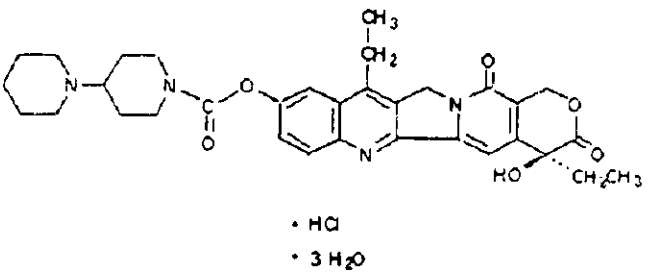
APPENDIX 4

Chemical Summary

Structure



Generic Name	Irinotecan Hydrochloride
Code Name	CPT-11
CAS Registry Number	(S)<1,4'-Bipiperidine>-1'carboxylic acid, 4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1H-pyrano<3,4',:6,7> indolizino<1,2-b>quinolin-9-yl ester, monohydrochloride, trihydrate
CAS Registry Number	100286-90-6 (S-enantiomer, monohydrochloride)
Upjohn Number	U-101440E
Molecular Formula	$C_{33}H_{38}N_4O_6.HCl.3H_2O$
Molecular weight	677.19

Chemical Summary (cont'd)

Melting point	decompose at 256 °C
Appearance	slight yellow to pale yellow powder
Solubility in water (mg/mL) (prepared without heating)	11.0 at 25° C
Solubility in organic solvents	sparingly to slightly

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APPENDIX 5

Irinotecan Hydrochloride Injection: Ingredients Used in the Formulation

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APPENDIX 5

Irinotecan Hydrochloride Injection: Ingredients Used in the Formulation

Name	CAS No.	M.W.	Formula	Appearance
Irinotecan hydrochloride, trihydrate	100286-90-6	677.19	$C_{33}H_{46}ClN_4O_9$	Pale yellow crystalline or crystalline-like powder
D-sorbitol NF Powder	50-70-4	182.17	$C_6H_{14}O_6$	White crystalline solid
Hydrochloric acid, 10% solution or	7647-01-0	36.46	HCl	Clear, colorless liquid
sodium hydroxide, 10% solution (to adjust pH)	1310-73-2	40.0	NaOH	Clear, colorless liquid
Lactic Acid USP racemic	50-21-5	90.08	$C_3H_6O_3$	Yellow to colorless liquid
Nitrogen NF (pumped through water to remove oxygen)	7727-37-9	28.01	N_2	Colorless gas
Water for Injection	7732-18-5	18.0	H_2O	Clear, colorless liquid

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APPENDIX 6

Environmental Assessment Report

May 29, 1995

ENVIRONMENTAL ASSESSMENT CONCERNING MANUFACTURE OF CPT-11

1. Production Site

2. Returned or rejected CPT-11 active ingredient
Returned or rejected CPT-11 active ingredient is converted to SN-38B-11 and then purified with silica gel column chromatography in.
plant with the method described in DMF. In case its purification is difficult, it is forwarded to a contract agent to be burned in incinerators.

The contracted agent:

This agent is authorized for disposal of industrial waste by the local government.

3. Discard of waste
(1) Waste water
High concentration solution of CPT-11 produced from washing of manufacturing equipment is recovered in polyethylene vessels and forwarded to the agent to be burned in incinerators.
Waste water produced during manufacturing is stored in a waste tank. If the concentration of this waste water is higher than 50 mg/L, it is forwarded to the agent to be burned in incinerator. If it is lower than the above value, it is discarded to drain line connected to the activated sludge facility of
to be processed for compliance with the limit parameters mentioned below for discarding into river.

(2) Exhaust gas
Exhaust gas from processes and incinerator is discarded into the air.

(3) Solvents

- Used ethylacetate in processes is stored in polyethylene vessels and forwarded to the agent to be burned in incinerators.

(4) Spill

Spilled CPT-11 or intermediates are forwarded to the agent to be burned in incinerators. The floor is cleaned with water and the water is stored in waste tank and treated with the above mentioned method. Small spills are cleaned with paper towel and packed into polyethylene bags. These are burned in incinerator.

4.

which is in charge of manufacturing CPT-11 complies with the following Japanese regulations and their limit parameters.

(1) Water Pollution Control Law
:The law regulating the quality of the water discharged.

	Limits
pH	5.8 - 8.6
BOD	120mg/L
Suspended Solid	150mg/L

(2) Air Pollution Control Law
:The law regulating the emission of smoke and exhaust gas

	Limits (Boiler)	(Incinerator)
NOx	180ppm	250ppm
SOx	180ppm	13Nm³/H
Soot and Dust	0.3g/Nm³	0.5g/Nm³

(3) Offensive Odor Control Law

	Limits
Hydrogen Chloride	700mg/Nm³
Ammonia	2ppm

This is to certify that manufactures CPT-11 in compliance with the whole Japanese regulations described above.

NON-CONFIDENTIAL
APPENDIX 7

Environmental Assessment Report

DATE May 31, 1995

ENVIRONMENTAL ASSESSMENT CONCERNING MANUFACTURE
OF SN-38B-11

1. Production Site

2. Returned or rejected SN-38B-11
Returned or rejected SN-38B-11 is purified with silica gel chromatography with the method described in DMF. In case its purification is difficult, it is forwarded to a contract agent to be burned in incinerators.

The contracted agent:

These agents are authorized for disposal of industrial waste by the local government.

3. Discard of waste
(1) Waste water
Waste water produced from the process is discarded to drain line connected to the activated sludge facility in to be processed for compliance with the limit parameters mentioned below for discarding into the drainage of

(2) Exhaust gas
Exhaust gas from processes and incinerator is discarded into the air.

(3) Solvents
Used solvents are recycled after purification by distillation. The residues and solvents which are not recycled are forwarded to the agent to be burned in incinerators.

DATE .....

(4) Spill

Spilled SN-38B-11 or intermediates are forwarded to the agent to be burned in incinerators. The floor is cleaned with water and the water is treated with the above mentioned method.

4. which is in charge of manufacturing SN-38B-11 complies with the following Japanese regulations and their limit parameters.

(1) Water Pollution Control Law
:The law regulating the quality of the water discharged.

	Limits
Temperature	below 40 °C
pH	5.7 - 8.7
BOD	300mg/L
Suspended Solid	300mg/L
Normal hexane extractable substances	30mg/L

(2) Air Pollution Control Law
:The law regulating the emission of smoke and exhaust gas

	Limits (Boiler)
NOx	130ppm
Soot and Dust	0.10g/Nm^3

1.This is to certify that manufactures SN-38B-11 in compliance with the whole Japanese regulations described above.

NON-CONFIDENTIAL
APPENDIX 8

Excerpt from *FLOPA OF TAIWAN, Vol. Three*

FLORA
OF
TAIWAN
Volume Three

The research work leading to this publication was jointly sponsored by the National Science Council of the Republic of China and the National Science Foundation of the United States under the U.S.-R.O.C. Cooperative Science Program

Printed in Taiwan, 1977

Price: US$32

2. NOTHAPODYTES Blume 青榨槭屬

Trees and shrubs. Leaves alternate or subopposite, petiolate, simple, 1-nerved. Flowers small, in terminal corymbose or cymose inflorescence; calyx cupular, slightly 5-toothed; petals 5, valvate, usually villose within; stamens 5, hypogynous, usually free, alternate with the petals, the anther-sacs ovate, dorsifixed, dehiscing longitudinally, the filaments filiform; disc hypogynous, cup-shaped; ovary superior, hirsute, 1-celled; style short, the stigma capitate; ovules 2, pendulous. Fruit drupaceous, with a thin rugose endocarp. Seed single; endosperm fleshy.

About five or six species, Indo-Malaya and the Philippines. One species in Taiwan.

1. Nothapodytes foetida (Wight) Sleumer in Notizbl. Bot. Gart. Berlin 15: 2[illegible]. 1940; Howard in Journ. Arnold Arb. 23: 70. 1942; Li, Woody Fl. Taiwan 483. *f. 186.* 1963. 臭青榨槭 Pl. 162

Stemonurus foetidus Wight, Icon. 3: 955. 1843-5.
Mappia ovata Miers in Ann. Mag. Nat. Hist. II. 9: 395. 1852.
Mappia ovata var. *insularis* Matsum. in Bot. Mag. Tokyo 15: 55. 1901, in Matsum. & Hayata in Journ. Coll. Sci. Univ. Tokyo 22: 80. 1906 (Enum. Pl. Form.).

A tree to 15 m tall, the branches angular. Leaves membranaceous to thinly coriaceous, elliptic-ovate to oblong-lanceolate, 10–20 cm long, 5–12 cm broad, long-acuminate at apex, attenuate or rounded at base, oblique, sparsely pubescent above, glabrate beneath or tomentose on the veins, the lateral veins about 7–9 per side, prominent beneath; petioles 1.5–5.0 cm long, strigose. Inflorescence terminal, cymose or corymbose, pubescent; calyx 2.5–3 cm across; petals oblong, 4.2–5 mm long, 1.5–1.8 mm broad, pubescent on both surfaces; stamens 5, the filaments 3–4 mm long, the anthers about 1 mm long; disc slightly lobed, hirsute on the margins and the inner surface; ovary densely pubescent.

S. India, Ceylon, Cambodia to the Ryukyu Islands. Taiwan, Is. Lanyu (Botel Tobago) only.

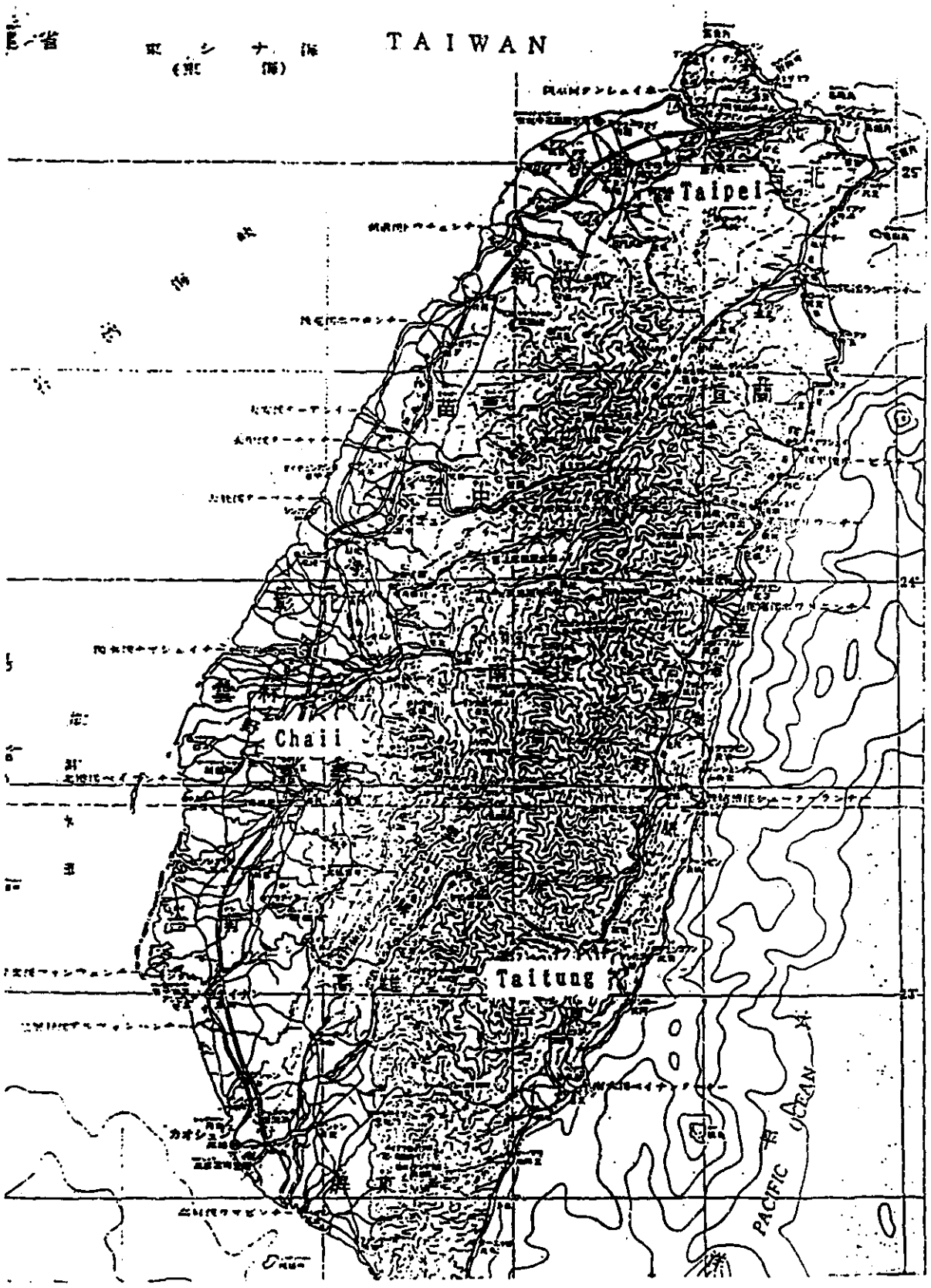
TAITUNG: Is. Lanyu, *Mori s. n.* in 1907*, *Sasaki s. n.* in 1910*.

Pl. 762. Nothapodytes foetida (Wight) Sleumer (ICACINACEAE)

1. fruiting branch; 2. flowering branch; 3. petal; 4. flower; 5. stamen; 6. dissected flower; 7. section of ovary.

NON-CONFIDENTIAL
APPENDIX 9

Harvesting Location Site Maps: Taiwan, Japan, and India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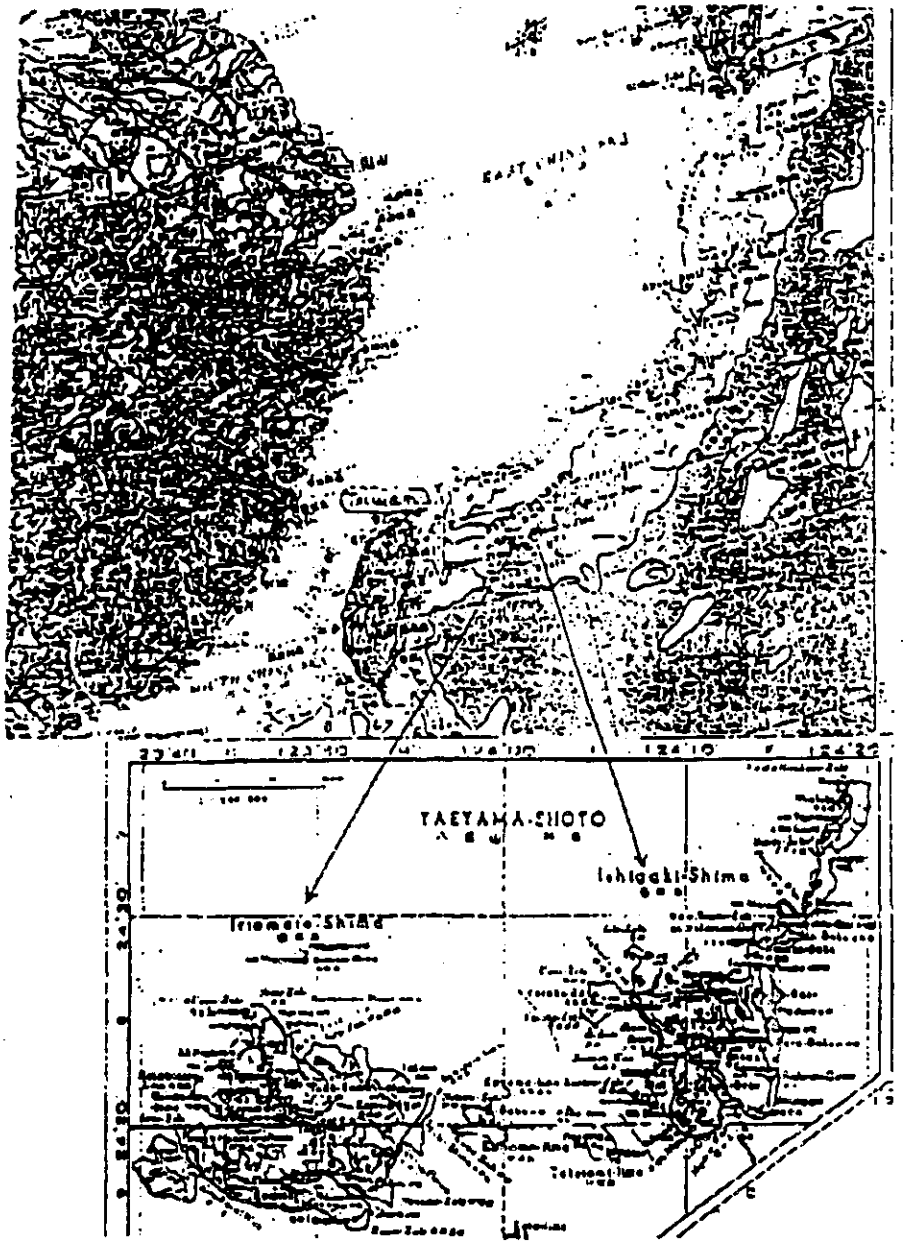
ISHIGAKI AND IRIOMOTE



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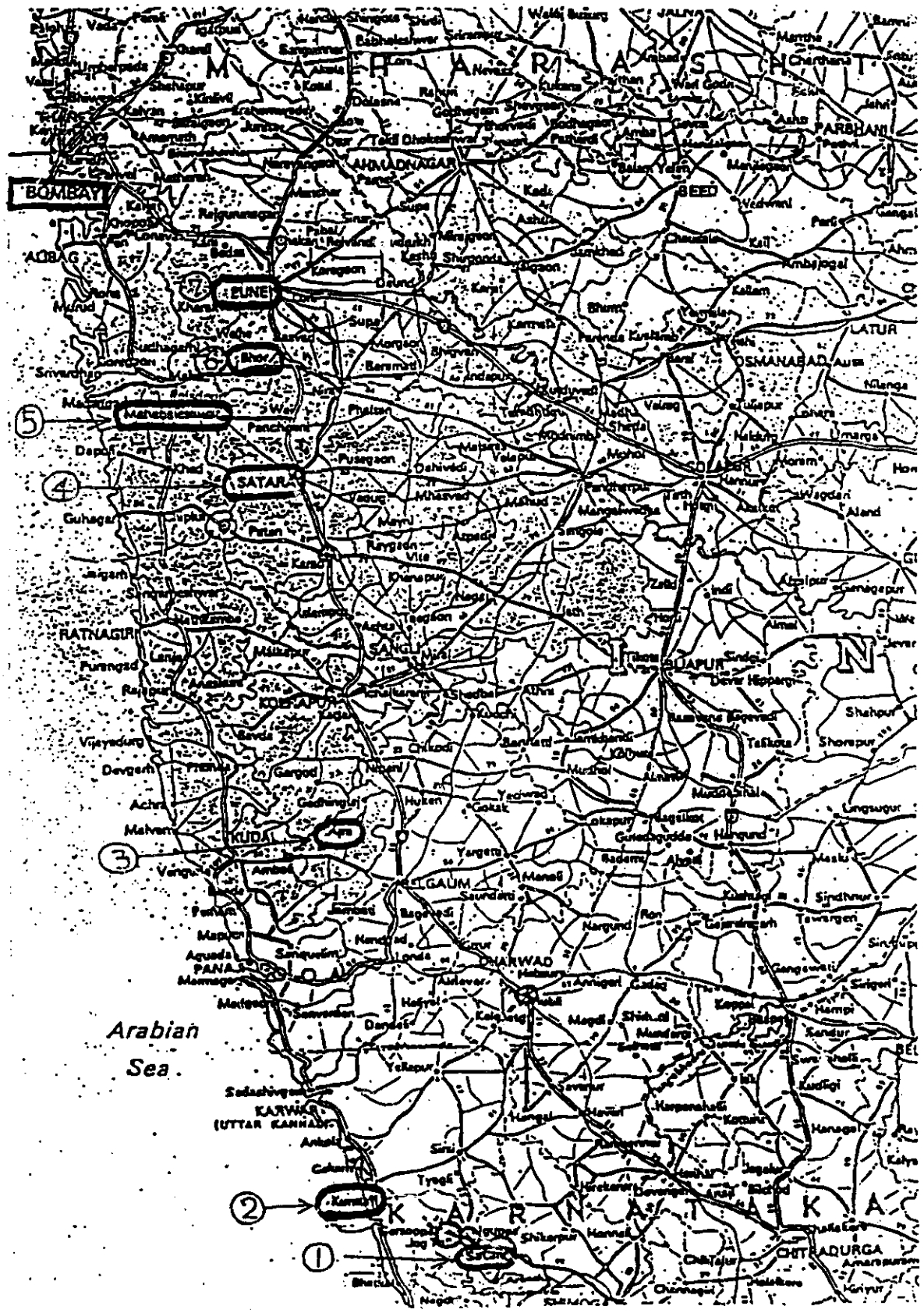
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KUDAL
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BELGAUM
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(UTTAR KANNADA)
Arabian Sea
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L. Vaccari

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-571

JAN 22 1996

The Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001-0199

Attention: Hendrik J. de Koning Gans, MD
Director, Worldwide Regulatory Liason

Dear Dr de Koning Gans:

We have received your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Camptosar (irinotecan HCl) Injection

Therapeutic Classification: Priority

Date of Application: December 28, 1995

Date of Receipt: December 28, 1995

Our Reference Number: 20-571

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 25, 1996 in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations and in accordance with the policy described in the Center for Drug Evaluation and Research Staff Manual Guide CDER 4820.6, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Please request the meeting at least 15 days in advance. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact:

Leslie Vaccari
Project Manager
(301) 594-5778

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

D Pease 1-19-96

Dotti Pease
Chief, Project Management Staff
Oncology Drug Products
Division of Oncology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-571
HFD-150/Div. Files
HFD-80
HFD-150/LVaccari

Drafted: LVaccari/January 5, 1996
R/D init. by: DPease/1-18-96
Final:

ACKNOWLEDGEMENT (AC)

Co. Corres

THE UPJOHN COMPANY

7000 Portage Road
Kalamazoo, Michigan 49001-0199, U.S.A.

Office of:
Hendrik J. de Koning Gans, M.D.
Director, Worldwide Regulatory Liaison

Telephone No. (616) 329-6516
Facsimile No. (616) 329-5409

June 6, 1996

Division of Oncology Drug Products
HFD-150
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 3rd Floor
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852

Re: NDA 20-571
CAMPTOSAR™ Injection
(Irinotecan Hydrochloride Injection)

General Correspondence
Response to FDA Request for Information
Microbiologist's Request for Postmarketing Commitments

Dear Sir or Madam:

In response to your telephone facsimile transmission of May 31, 1996 , we are providing the following information in order to address comments made by the Microbiologist's review of the Sterility Assurance Section of our pending NDA 20-571:

Microbiologist's Comments

Your application NDA 20-571 has been reviewed for sterility assurance and is recommended for approval. However, even though there is supporting evidence to validate the sterilization process in this submission, the following information should be provided post-approval:

1. FDA Request:

Concerning the sterilization and depyrogenation of vials, filling and processing equipments: Please provide experimental details on the amount of endotoxin spiked, number of samples, and the efficiency of endotoxin recovery from the positive controls.

Response:

We agree to provide the requested information. We estimate that our response will be provided by the end of July 1996.

2. FDA Request:

Concerning the microbiological environmental monitoring:

a. It is recommended that a periodic monitoring program for yeasts, molds, and anaerobic microorganisms should be instituted.
b. The number of plates used for each type of monitoring during each filling operation should be indicated.

Response:

a. *We currently have in place a monitoring program for yeasts and molds. We will include details of our monitoring program with our response to item No. 1 above.*

   We do not agree with the reviewer's request for a monitoring program for anaerobic microorganisms. However, we will provide our rationale for why we believe it is not necessary to perform this type of testing when isolator technology is used. We will include our rationale with our response to item No. 1 above. If the Agency is concerned with this approach, we suggest that a teleconference be held to expeditiously resolve any outstanding questions.

b. *We agree to provide the requested information for our program on yeasts and molds. We will include this information with the response to No. 1 above.*

3. FDA Request:

Concerning sterility testing and release criteria:
Information on the selection of vials for sterility testing should be provided. Is the selection of vials representative of an entire production run?

Response:

We agree to provide the requested information. We will include this information with the response to No. 1 above.

Questions regarding this submission should be directed to Mark Baumgartner, Senior Regulatory Manager (616) 329-3102.

Very truly yours,

THE UPJOHN COMPANY

Hendrik J. de Koning Gans, MD
Director, Worldwide Regulatory Liaison

mab 960606.mic

THE UPJOHN COMPANY

7000 Portage Road
Kalamazoo, Michigan 49001-0199, U.S.A.

Office of:
Hendrik J. de Koning Gans, M.D.
Director, Worldwide Regulatory Liaison

Telephone No. (616) 329-8516
Facsimile No. (616) 329-5409

June 6, 1996

Division of Oncology Drug Products
HFD-150
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 3rd Floor
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852

DESK COPY

Re: NDA 20-571
CAMPTOSAR™ Injection
(Irinotecan Hydrochloride Injection)

General Correspondence
Response to FDA Request for Information
Postmarketing Study Commitments

Dear Sir or Madam:

In response to your telephone facsimile transmission of May 31, 1996, requesting a letter of commitment for postmarketing studies, we are providing the following information:

Medical Reviewer Comments/Requests

1. FDA Comment:

Under the Accelerated Approval regulations, the sponsor must conduct a Phase IV study to verify that the surrogate endpoint (in this case objective tumor response, i.e., tumor shrinkage, essentially partial response) is associated with clinically meaningful patient benefit. The sponsor has submitted a Phase III study comparing CPT-11 alone versus 5-FU plus leucovorin versus CPT-11 in combination with 5-FU plus leucovorin in patients with colorectal cancer who have not previously received chemotherapy. The design of that study will be discussed at the June 13, 1996.

Response:

In our submission dated May 30, 1996 (Amendment 009 to NDA 20-571), we have

submitted our Protocol M/6475/0038 entitled, "Irinotecan HCL: A Phase III, Randomized, Controlled Clinical Trial of Irinotecan HCL (CPT-11) Alone, Combined Irinotecan HCl and 5-Fluorouracil Plus Leucovorin, and 5-Fluorouracil Plus Leucovorin Alone in Patients with Untreated Metastatic Colorectal Cancer." The design of this trial reflects considerable discussion between representatives of The Upjohn Company and The Food and Drug Administration; including meetings on March 3, 1994, March 10, 1995, the pre-NDA meeting of October 4, 1995, and most recently, May 1, 1996. This trial is intended to address the post-marketing requirements described under Subpart H and the March 1996 Oncology Initiative, "Reinventing the Regulation of Cancer Drugs." The protocol submitted incorporates changes requested at the May 1 meeting. As previously communicated, this study has recently initiated enrollment.

2. FDA Comment:

In study 0003R, the frequency of grade 3 and 4 late diarrhea was significantly greater in male than in female patients (43.1 versus 15.6%; p=0.01). A difference based on gender was not observed in Study 0001 or Study 0006 nor was it observed in the uncontrolled NCCTG phase II study in patients who did not received prior chemotherapy. Based on the integrated analysis of the data in patients receiving approximately the same regimen of CPT-11, no difference could be found based on gender. Because gender differences in glucuronidation (of acetominophen) have been described, Mark Ratain and Colleagues conducted a prospective study in a cohort of patients receiving CPT-11 on weekly x 4 schedule (Proc. ASCO, Abs #1491, 1996); no significant differences in PK and PD based on gender were found but the number of patients was too small to draw firm conclusions. The sponsor may need to conduct postmarketing studies of PK and PD to exclude gender as a risk factor toxicity including grade 3 or 4 diarrhea.

Response:

Please see response to No. 3 below.

3. FDA Comment:

In Study 0006, the frequency of grade 3 and 4 late diarrhea was significantly greater ($p = 0.0076$) in patients $\geq$ 65 years. Based on the sponsor's integrated analysis of the safety data. Grade 3 and 4 last diarrhea was significantly greater (39.8% vs. 23.4%; $p = 0.0025$) in patients $\geq$ 65 years. Postmarketing studies should be conducted to further evaluate the PK and PD factors contributing to the higher risk for severe late diarrhea in elderly patient population, and to determine whether specific dosing recommendations can be made based on age.

Response:

We believe that the reviewer's request for a post-marketing study to further evaluate an association between age and risk for severe late diarrhea will be met by our ongoing study M/6475/0037 (0037) entitled, "Irinotecan (CPT-11): Phase II, Open-Label, Prospective Evaluation of Age as a Risk Factor for Development of Toxicities in Patients with 5-Fluorouracil Refractory Colorectal Cancer" (Protocol 0037 was submitted in to IND 35,229, Amendment 109, dated August 11, 1995). This is a Phase II study in of approximately 180 patients, utilizing the 125 mg/m^2 weekly, x4 weeks with 2 weeks off dosing regimen. *This study should also allow us to obtain the information requested to evaluate gender as a possible risk factor in developing severe late diarrhea. For the convenience of the reviewer a protocol summary for M/6475/0037 is attached.*

Protocol M/6475/0037 has recently completed enrollment. We estimate that by first quarter 1997 we will have at least two courses of data on all patients and we should be able to provide information on age and gender from these data. Since patients will be followed for at least 1 year from enrollment, we estimate that a final report would be available by fourth quarter 1997.

4. FDA Comment:

Postmarketing studies should be done to determine the optimal dose and schedule of CPT-11 administration. A randomized controlled trial comparing the 125 mg/m^2 to the 100 mg/m^2 starting dose given on the weekly x4 schedule should be considered. Also, consideration should be given to conducting a randomized controlled trial comparing the weekly x 4 every 6 week regimen to the once every 3 week regimen (350 mg/m^2). The latter regimen seems to more popular in Europe.

Response:

Since it appears that the response rate at the 125 mg/m^2 dose level is relatively consistent across several studies, and with appropriate supportive care medical events can be reduced to the level observed in patients treated at the 100 mg/m2 starting dose (based on crude data collected to date in protocol 0037), we propose that sufficient information regarding the therapeutic ratio can be obtained from protocol 0037.

In addition to study 0037, we are also evaluating alternate dose schedules from that which was utilized in the three pivotal trials. We have recently initiated Protocol M/6475/0033 entitled, "Irinotecan Hydrochloride (CPT-11): Phase II Trial Using an Every-Other-Week Dosing Schedule in Patients Previously Treated with 5-FU for Colorectal Cancer" (submitted to IND

We would prefer to focus our resources on the completion of this trial than to initiate an additional evaluation of the once-every-three-weeks regimen (350 mg/m^2). For the convenience of the reviewer a protocol summary for study M/6475/0033 is attached.

Pharmacokinetic Reviewer Comments

1. FDA Comment:

Biliary index should be determined in patients with severe hepatic compromise.

Response:

The Agency has provided comments regarding the potential for hepatic compromise to alter the disposition of CPT-11, SN-38 and SN-38 glucuronide and influence the development of toxicities. The Upjohn Company has initiated Protocol M/6475/0017 Irinotecan (CPT-11) - Phase I Study in Refractory Solid Tumor Patients with Hepatic Dysfunction. The objectives of this study are (1) to determine the initial maximum tolerated dose (MTD) of irinotecan when administered to patients with hepatic dysfunction, (2) to ascertain the pharmacokinetics/ pharmacodynamics of irinotecan and its metabolites (SN-38, and SN-38 glucuronide) in patients with refractory solid tumors and hepatic dysfunction, and (3) to evaluate the qualitative and quantitative toxicities of irinotecan in this patient population. We believe that this study will address the questions raised by the Agency.

Protocol M/6475/0017 is an open label study in refractory solid tumor patients with hepatic dysfunction. Patients will be categorized into four groups based on their biochemical evidence of the degree of liver dysfunction.

Group 1: *Patients with mildly elevated total serum bilirubin concentrations 1.5 - 3.0 x the upper limit of institutional normal (IULN) and serum transaminases ≤ 5 x IULN.*

Group 2: *Patients with moderately elevated total serum bilirubin concentrations 3.1 - 5.0 x IULN and serum transaminases (SGOT and/or SGPT) ≤ 5 x IULN.*

Group 3: *Patients with and serum bilirubin ≤ 1.5 x IULN and elevated serum transaminase (SGOT and/or SGPT) concentrations (5.1 - 20.0 x IULN).*

Group 4: *Patients with both elevated total bilirubin 1.5 - 5.0 x IULN and serum transaminases (SGOT and/or SGPT) 5.1 - 20.0 x IULN.*

Three patients will initially be enrolled into Groups 1 and 3, until the starting dose is determined to be safe. Thereafter, patients can be entered into Groups 2 and 4, as well as additional patients in Groups 1 and 3.

Blood and urine specimens will be collected for 72 hours following CPT-11 dosing to define the pharmacokinetic characteristics of irinotecan, its active metabolite SN-38, and SN-38 glucuronide in patients with hepatic dysfunction. Samples for

pharmacokinetic analyses will be collected on the patients first course of therapy during weeks 1 and 3. This information will be used to establish possible correlations between the pharmacokinetic parameters of irinotecan/SN-38 with toxicity.

Because changes in disposition (biliary index) appear to correlate with toxicity, the Agency has requested that the biliary index should be determined in patients with severe hepatic compromise. Since concentrations of CPT-11, SN-38 and SN-38 glucuronide are being determined, this will permit an assessment of the biliary index in these patients. While Study M/6475/0008 suggested a correlation between increasing biliary index and development of severe late diarrhea, the information from this study should be considered preliminary. Additional studies to further evaluate the relationship between glucuronidation and CPT-11-induced gastrointestinal toxicity are in progress in larger patient populations. Determination of the biliary index in patients with hepatic compromise in Protocol M/6475/0017 will be useful in assessing this relationship as well.

We anticipate the enrollment of patients into this protocol based on their biochemical evidence of the degree of liver dysfunction may be slow to accrual since patients must have adequate performance status. We anticipate that enrollment of the desired number of patients could take 18 months. We currently estimate that a final report for this study will be available in approximately 2 years.

2. FDA Comment:

A mass balance study should be performed in humans, and an attempt to identify the chemical structure of the predominant metabolites of irinotecan present in urine and feces should be made. An attempt to characterize the ability of each predominant irinotecan metabolite to cause tumor regression, late diarrhea or neutropenia should be made.

A clinical protocol (M/6475/0062) to elucidate the fate of camptothecin labeled [^{14}C]CPT-11 is in preparation. Patient recruitment and dosing is planned to begin in November or December 1996. Irinotecan mass balance and metabolism will be studied in four male and four female patients with refractory colorectal cancer dosed with 125 mg/m^2 and 100 μCi [^{14}C]CPT-11. For ethical reasons, a non radiolabeled treatment phase is planned following the single radiochemical dose. It is anticipated that this study will be completed by December 1997 depending on the ability to recruit patients. Interim results for individual patients will be discussed with the Agency to address potential concerns about the existence of putative long-lived and quantitatively significant metabolites.

As information becomes available from the human balance study and structures of any major new metabolites are elucidated, these metabolites will be synthesized where technically possible. Cytotoxic properties will be evaluated in vitro if the metabolites represent a significant proportion of the CPT-11 dose. A review of the current literature

indicates that a novel metabolite of CPT-11 (aminopentanecarb· ·ylate or "APC") has recently been described by Rivory et al. [Rivory LP, Riou JF, Pond, SM, Haaz, MC, Sable S, Vuilhorgne M, Commercon A, Robert J. The identification and properties of a major metabolite of irinotecan (CPT-11) isolated from the plasma of patients. 87th Am Assoc Cancer Res 1996;37, 177]. Preliminary data obtained by the sponsor indicates that APC is a quantitatively significant metabolite of CPT-11 in human urine. Synthesis of this metabolite is in progress.

3. FDA Comment:

The ability of irinotecan, and predominant metabolites, to act as substrate orinhibitor for human cytochromes P450 should be studied in vitro.

Response:

An in vitro metabolism study has been conducted to study the effect of CPT-11 (10 and 100 μM) on the metabolism of substrates of the major human cytochromes P450 (CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4). In this study, CPT-11 was observed to have no inhibitory effects on the activity of these major cytochrome P450 isoforms. Therefore, no significant P450-mediated drug-drug interactions are anticipated for CPT-11. We are targeting submission of the report to the Agency later this summer.

The ability of therapeutically-relevant concentrations of APC and SN-38 to inhibit major human isoforms of CYP P450 will be determined. This work will be completed by January 1997. The effect of other major human metabolites on CYP P450 will be evaluated as data from the definitive human excretion study is accrued and when synthetic standards become available.

4. FDA Comment:

A search for protein binding interactions between SN-38 and medications frequently co-administered with irinotecan should be performed in vitro. A similar in vitro search for protein binding interactions between any highly protein bound metabolites identified in the recommended mass balance study (2. above) and medications frequently co-administered with irinotecan should also be performed.

Response:

The protein binding of the novel human CPT-11 metabolite APC will be determined. The chemical synthesis of APC is in progress.

We will evaluate the effect of SN-38 on the protein binding of commonly used co-medications that meet the following criteria: 1. Highly protein bound to albumin. 2. Drug clearance is not restricted (ie, blood flow rate limited clearance) 3. Narrow therapeutic index.

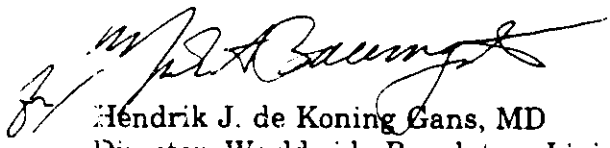
We estimate that this will be completed by December 1996.

The effect of commonly administered co-medications that are highly bound to albumin on the protein binding of total SN-38 (lactone plus hydroxyacid forms) will be evaluated. This will be completed by December 1996.

Questions regarding this submission should be directed to Mark Baumgartner, Senior Regulatory Manager (616) 329-8102.

Very truly yours,

THE UPJOHN COMPANY



Hendrik J. de Koning Gans, MD
Director, Worldwide Regulatory Liaison

Protocol Number: M6475-0037

Protocol Title: Irinotecan (CPT-11): Phase II, Open-Label, Prospective Evaluation of Age as a Risk Factor for Development of Toxicities in Patients with 5-Fluorouracil Refractory Colorectal Cancer

Study Objectives:

- To determine if age is a risk factor for development of irinotecan-induced diarrhea (primary endpoint).
- To determine if age is a risk factor for development of other irinotecan-induced toxicities.
- To determine the pharmacokinetic profile for irinotecan for patients who are ≥ 65 years of age versus those < 65 years of age.
- To collect information on the antitumor activity of irinotecan.
- To collect information on clinical benefit for patients receiving irinotecan.

Study Population:

- Patients with histologic diagnosis of metastatic colorectal carcinoma whose disease has recurred or progressed within six months following one prior 5-FU-based therapy for advanced disease or within six months after adjuvant 5-FU-based therapy

Study Design: Open label

Study Medication: Irinotecan hydrochloride (U-101440E; CPT-11)

Dosage Form: Sterile solution

Route of Administration: Intravenous (in 500 ml 5% dextrose [D5W] as a 90-minute, constant-rate infusion)

Dose and Regimen:

- Irinotecan cycle (six weeks): 125 mg/m^2 weekly for four weeks followed by a two-week rest.
- Dose may be adjusted between 60–150 mg/m^2 based on individual toxicity.

Duration of Subject Participation in Study: Until documented evidence of disease progression, unacceptable toxicity or withdrawn consent

Anticipated Maximum Number of Subjects: 160

Number of Study Centers: 10-13

CLINICAL PROTOCOL
Protocol Summary

Protocol Number: M6475/0033

Protocol Title: Irinotecan Hydrochloride (CPT-11): Phase II Trial Using an Every-Other-Week Dosing Schedule in Patients Previously Treated with 5-FU for Colorectal Cancer

Study Objectives:

1. To determine the antitumor activity of CPT-11 when administered every other week to patients with metastatic colon cancer that has progressed despite prior 5-FU-based chemotherapy.
2. To evaluate the toxicities of CPT-11 on an every-other-week schedule in this patient population.
3. To examine possible relationships between plasma concentrations of CPT-11, SN-38 and SN-38 glucuronide and major toxicities and response.
4. To collect information on clinical benefit for patients receiving CPT-11.
5. To collect information about the incidence and severity of early cholinergic syndrome after CPT-11 administration.

Study Population: Patients with progressive colorectal cancer after failing previous 5-FU-based chemotherapy regimen.

Study Design: Open-label

Study Medication: Irinotecan hydrochloride (U-101440; CPT-11)

Dosage Form: Sterile solution

Route of Administration: Intravenous (in 500 ml 5% dextrose [D5W] as a 90-minute, constant-rate infusion)

Dose and Regimen: 250 mg/m^2 every other week. The initial dose may be adjusted based upon individual toxicity but will not exceed 275 mg/m^2, or be decreased below 125 mg/m^2.

Duration of Treatment and Subject Participation: Patients with histologic diagnosis of metastatic colorectal carcinoma whose disease has recurred or progressed within six months following prior 5-FU-based therapy for advanced disease or within six months after adjuvant 5-FU-based therapy

Number of Subjects Required to Meet Protocol Objectives: 100

Anticipated Maximum Number of Subjects: 120

Number of Study Centers: Multicenter (up to twelve centers)

THE UPJOHN COMPANY

7000 Portage Road
Kalamazoo, Michigan 49001-0199, U.S.A.

Office of:
Hendrik J. de Koning Gans, M.D.
Director, Worldwide Regulatory Liaison

Telephone No. (616) 329-6516
Facsimile No. (616) 329-6409

June 14, 1996

Division of Oncology Drug Products
HFD-150
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 3rd Floor
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852

Re: NDA 20-571
CAMPTOSAR™ Injection
(Irinotecan Hydrochloride Injection)

General Correspondence
Response to FDA Request

Dear Madam or Sir:

We are in receipt of your telephone facsimile transmission of June 14, 1996 which requests revision of the protocol for drug product stability studies. In accordance with your request, we agree to revise the protocol for drug product stability studies to include specifications and test methods for the monitoring of visible and subvisible particulate matter, as well as colloidal, suspended, or precipitated drug substance or other materials. The stability study protocol will include the testing of each production batch of CAMPTOSAR Injection (irinotecan hydrochloride) at monthly intervals up to the two year expiration time. Test results will be reported to the FDA at three month intervals, or sooner if failures occur.

We will provide the revised protocol for stability studies by July 1996.

Sincerely,

THE UPJOHN COMPANY

By /

Hendrik J. de Koning Gans, MD
Director, Worldwide Regulatory Liaison

K:\NDA\20571\gen corr\960614

THE UPJOHN COMPANY

7000 Portage Road
Kalamazoo, Michigan 49001-0199, U.S.A.

Office of:
Hendrik J. de Koning Gans, M.D.
Director, Worldwide Regulatory Liaison

Telephone No. (616) 329-8516
Facsimile No. (616) 329-5409

December 28, 1995

Division of Oncology and Pulmonary
Drug Products (HFD-150)
Center for Drug Evaluation
and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-571
CAMPTOSAR™ Injection
(Irinotecan Hydrochloride Injection)

FIELD COPY STATEMENT

Dear Sir/Madam:

In accord with the final rule published in the FEDERAL REGISTER dated September 8, 1993, (page 47340), this is to certify that the field copy of the Chemistry, Manufacturing and Controls section of NDA 20-571 for CAMPTOSAR™ Injection (Irinotecan Hydrochloride Injection) has been provided to the Detroit District Office.

THE UPJOHN COMPANY

Hendrik J. de Koning Gans, MD
Director, Worldwide Regulatory Liaison

HJD:MAB:cek
Attachments

THE UPJOHN COMPANY

7000 Portage Road
Kalamazoo, Michigan 49001-0199, U.S.A.

Office of:
Hendrik J. de Koning Gans, M.D.
Director, Worldwide Regulatory Liaison

Telephone No. (616) 329-8515
Facsimile No. (616) 329 5400

June 10, 1996

Division of Oncology Drug Products
HFD-150
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 3rd Floor
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852

Amendment 012

Re: NDA 20-571
CAMPTOSAR™ Injection
(Irinotecan Hydrochloride Injection)

Response to FDA Request for Information

Dear Sir or Madam:

Please refer to your telephone facsimile transmission of June 6, 1996, which requested additional information related to chemistry review of the above NDA. Our response to your request is attached.

Please note where we have committed to provide revised specifications and additional test methods, that we anticipate no more than 60 days will be required to provide this additional information.

In addition, we will make the changes to the carton label as outlined in your facsimile of June 7, 1996.

Questions regarding this submission should be directed to Mark Baumgartner, Senior Regulatory Manager (616) 329-8102.

Very truly yours,

THE UPJOHN COMPANY

Hendrik J. de Koning Gans, MD
Director, Worldwide Regulatory Liaison

jmw 960610

THE UPJOHN COMPANY

7000 Portage Road
Kalamazoo, Michigan 49001-0199, U.S.A.

Office of:
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Director, Worldwide Regulatory Liaison

Telephone No. (616) 329-8516
Facsimile No. (616) 329-5409

DUPLICATE

May 30, 1996

Division of Oncology Drug Products
HFD-150
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 3rd Floor
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852

Amendment 009

ORIG AMENDMENT

BH

Re: NDA 20-571
CAMPTOSAR™ Injection
(Irinotecan Hydrochloride Injection)

Phase 4 Study

Dear Sir or Madam:

Please refer to our pending New Drug Application for CAMPTOSAR Injection which was submitted under the provisions of 21 CFR 314 Subpart H - Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses.

Approval under Subpart H is subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to the ultimate outcome. Accordingly, we have recently initiated a controlled multicenter, post-marketing study; protocol M/6475/0038 entitled, "Irinotecan HCL: A Phase III, Randomized, Controlled Clinical Trial of Irinotecan HCL (CPT-11) Alone, Combined Irinotecan HCl and 5-Fluorouracil Plus Leucovorin, and 5-Fluorouracil Plus Leucovorin Alone in Patients with Untreated Metastatic Colorectal Cancer." The design of this trial reflects considerable discussion between representatives of The Upjohn Company and The Food and Drug Administration; including meetings on March 3, 1994, March 10, 1995, the pre-NDA meeting of October 4, 1995, and most recently, May 1, 1996. This trial is intended to address the post-marketing requirements described under Subpart H and the March 1996 Oncology Initiative, "Reinventing the Regulation of Cancer Drugs."

Enclosed with this submission is a copy of protocol M/6475/0038 which has been modified in accordance with discussions from the May 1, 1996 meeting. The protocol has previously been submitted to IND in our IND Amendment, serial number 138, dated March 27, 1996. The revisions to protocol M/6475/0038 were described in our submission to IND dated May 22, 1996 (IND Amendment, serial number 142).

It is projected that protocol M/6475/0038 will be conducted at 45-50 clinical centers. Enrollment in the trial began earlier this month at one center. Once all centers are participating, we anticipate an average enrollment rate of 50 patients/month and we project that it will take one year to enroll. The protocol requires one year follow-up. The final analysis will be performed one year after the last patient has been enrolled. Accordingly, we estimate that our analysis and report will be available in approximately two years.

At the request of the reviewers, we included a copy of protocol M/6475/0038 as Appendix D of the briefing package to the Oncologic Drugs Advisory Committee (copies forwarded to the ODAC Secretary on May 16, 1996). However, in preparing this submission to you, it was discovered that the protocol included in the briefing package to ODAC erroneously included the outdated statistical section (section 24). We have notified the Advisors and Consultants Staff (HFD-21) Office and have made arrangements to provide the correct copies of the protocol.

Questions regarding this submission should be directed to Mark Baumgartner, Senior Regulatory Manager (616) 329-8102.

Very truly yours,

THE UPJOHN COMPANY

Hendrik J. de Koning Gans, MD
Director, Worldwide Regulatory Liaison

mab:\Amend 009

THE UPJOHN COMPANY

7000 Portage Road
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Office of
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DUPLICATE

May 29, 1996

Division of Oncology Drug Products
HFD-150
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 3rd Floor
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852

Amendment 008

ORIG AMENDMENT

Re: NDA 20-571
CAMPTOSAR™ Injection
(Irinotecan Hydrochloride Injection)

(BL)

Chemistry, Manufacturing, andControls
Labeling

Dear Sir or Madam:

Please refer to our pending New Drug Application (NDA) for CAMPTOSAR Injection submitted December 28, 1995. Please also refer to the proposed labeling for vials, cartons, and blister packs provided in NDA 20-571, volume 1.2, pages 3/1/35 and 3/1/36.

Included with this submission are copies of proofs for the labeling for vials, cartons, and blister packs for the drug product. As described during the May 28, 1996 telephone conversation between Mr. Mark Baumgartner of Upjohn and Ms. Leslie Vaccari of your Division, the enclosed labels reflect several minor changes from the label copy included in the NDA. The changes were necessary primarily as the result of space limitations on the vial label. In addition to the revised labels, we are providing copies of pages 3/1/35 and 3/1/36 which have been marked up to indicate the changes made.

Please note that for ease of review, the labels for the vial and blister pack are provided at 200% of actual size.

Questions regarding this submission should be directed to Mark Baumgartner, Senior Regulatory Manager (616) 329-8102.

Very truly yours,

THE UPJOHN COMPANY

Hendrik J. de Koning Gans, MD
Director, Worldwide Regulatory Liaison

mab:\Amend.008