

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20571/S9

CORRESPONDENCE



Pharmacia & Upjohn

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA
Telephone: (616) 833-4000

Office of:
Christiane H. Vanderlinden, R.Ph., M.S.
Regulatory Affairs Manager

Telephone No. (616) 833-4355
Facsimile No. (616) 833-8237

November 17, 1999

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)

Pediatric Use: Waiver Request

Dear Sir or Madam:

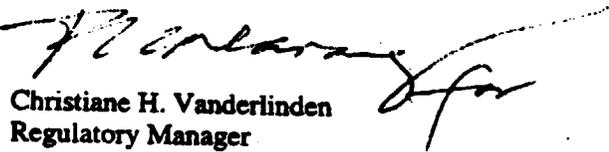
In accordance with 21 CFR § 314.55 (c)(2) Pharmacia and Upjohn wishes to request a 'full waiver' authorization from the FDA from providing 'Pediatric Use' information for the above referenced NDA (# 20-571) for the treatment of colorectal cancer. Men and women over the age of 40 years constitute the largest population at risk. Additional basis for this waiver request is noted below.

Federal Register notice of the Final Rule for 'Regulations Requiring Manufacturers to Assess Safety and Effectiveness of new drugs and Biological Products in Pediatric Patients' (vol. 63, no. 231, pg. 66648), notes colorectal cancer in the FDA list identifying it as a disease with insufficient significance in the pediatric population.

If you have questions related to this submission, please contact me at (616) 833-4355 or address correspondence to mailstop 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY


Christiane H. Vanderlinden
Regulatory Manager
Regulatory Affairs

CHV:mlw
cc: Loretta Arscott (FAX: 301 594 0499)



Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

February 23, 2000

DESK COPY

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)

Amended Package Insert for Supplement 009

Dear Sir or Madam:

As discussed and agreed upon in a telephone conversation with Ms. Brenda Atkins on January 28, 2000, we are submitting an amended package insert updated for the new survival data submitted on January 31. This amendment includes the revisions originally submitted in sNDA 009 on October 19, 1999, and the additional revisions resulting from the survival update. Several editorial and other changes have been made to shorten, simplify and make the package insert user-friendly.

Attachment 1: Annotated manuscript version of the amended proposed insert showing deletion and addition of text, and the rationale for each revision. This document contains the sections of the package insert that have been totally revised and should be reviewed in conjunction with the mock-up of the Camptosar package insert provided in Attachment 3. Electronic versions of the manuscript version are provided in MS Word and pdf formats (*annotated manuscript version.doc and annotated manuscript version.pdf*).

Attachment 2: Clean manuscript version of the amended proposed insert. Electronic versions in MS Word and pdf formats (*manuscript version.doc and manuscript version.pdf*) are also provided.

Attachment 3: Amended package insert mock-up. This document shows the revisions made to the current package insert with reference to the manuscript version of Attachment 1 for the totally revised text. It also includes revisions to tables and figures that were part of the previously approved package insert. An electronic version in "pdf" format is provided (*amended package insert mock-up.pdf*); no MS Word version is available for this mock-up since our current system only retains the approved package inserts in "pdf" format.

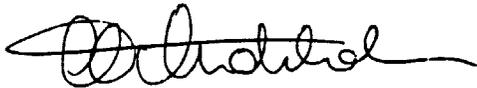
We are providing 11 additional desk copies of the attachments as requested.

The electronic files are provided on one CD-ROM. They are contained in the directory N20571, subdirectory *Labeling*. McAfee VirusScan Software for Windows, v.4.0.3a, was used to verify that the CD-ROM is free of viruses.

If you have any questions regarding this submission, please contact me at (616) 833-4355 or by fax at (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY



Christiane H. Vanderlinden
Regulatory Manager
Regulatory Affairs

CHV:lmf

Attachments

cc: Brenda Atkins – cover letter

DUPLICATE



Pharmacia & Upjohn

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Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

BC

Office of:
Christiane H. Vanderlinden
Regulatory Affairs Manager



Mailstop: 0636-298-113
Telephone: 616/833-4355
Fax: 616/833-8237

October 29, 1999

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
Attachment to NDA Supplement

Dear Sir or Madam:

Reference is made to the efficacy NDA supplement submitted on October 19, 1999 for first-line therapy of metastatic colorectal cancer for Camptosar Injection NDA 20-571.

Further to a telephone conversation with Ms. Loretta Arscott on October 28, 1999, we are submitting a claim of categorical exclusion from the environmental assessment requirement for this NDA supplement.

If you have questions related to this submission, please contact me at (616) 833-4355 or address correspondence to mailstop 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Christiane H. Vanderlinden
Regulatory Manager
Regulatory Affairs

CHV:lmf
Attachments

DUPLICATE

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE <i>(Title 21, Code of Federal Regulations, 314 & 601)</i>	Form Approved: OMB No. 0910-0338 Expiration Date: April 30, 2000 See OMB Statement on page 2.
	FOR FDA USE ONLY
	APPLICATION NUMBER 20-571

APPLICANT INFORMATION	
NAME OF APPLICANT Pharmacia & Upjohn Company	DATE OF SUBMISSION October 29, 1999
TELEPHONE NO. (Include Area Code) (616) 833-4355	FACSIMILE (FAX) Number (Include Area Code) (616) 833-8237
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 7000 Portage Road Kalamazoo, Michigan 49001	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION	
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)	
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) Irinotecan Hydrochloride Injection	PROPRIETARY NAME (trade name) IF ANY CAMPTOSAR® Injection
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) (4S)-4,11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino)carbonyloxy]-1H-pyrano[3',4':6,7] indolizino[1,2-b]quinolone-3,14(4H,12H)dione hydrochloride	CODE NAME (if any) CPT-11, PNU-101440E
DOSAGE FORM: Injection	STRENGTHS: 20 mg/mL
	ROUTE OF ADMINISTRATION: Intravenous
(PROPOSED) INDICATION(S) FOR USE: Treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy.	

APPLICATION INFORMATION	
APPLICATION TYPE (check one)	
<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)	

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE	<input type="checkbox"/> 505 (b) (1)	<input type="checkbox"/> 505 (b) (2)	<input type="checkbox"/> 507
IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION			
Name of Drug	Holder of Approved Application		

TYPE OF SUBMISSION (check one)			
<input type="checkbox"/> ORIGINAL APPLICATION	<input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION	<input type="checkbox"/> RESUBMISSION	
<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT	<input type="checkbox"/> SUPAC SUPPLEMENT
<input type="checkbox"/> EFFICACY SUPPLEMENT	<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT	<input checked="" type="checkbox"/> OTHER

REASON FOR SUBMISSION General Correspondence- Attachment to NDA Supplement
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PROPOSED MARKETING STATUS (check one)	<input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx)	<input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
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NUMBER OF VOLUMES SUBMITTED _____ 1	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC
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ESTABLISHMENT INFORMATION
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)			
IND	IND	DMF	DMF); DMF
			DMF

EF



Pharmacia & Upjohn

Office of:
John S. Walker
Regulatory Affairs Manager

Mailstop: 0636-298-113
Telephone: 616/833-8263
Fax: 616/833-8237

December 7, 1998

Robert Justice, M.D., Acting Director,
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
Status of Phase 4 Commitments

Dear Dr. Justice:

Please refer to your letter of October 22, 1998 approving Supplement 008 to the above referenced NDA. Your Approval Letter contained information on Phase 4 commitments and a reminder of which commitments have not yet been fulfilled. The purpose of this letter is to provide an update on the status of our Phase 4 commitments. The commitments referenced in your October 22, 1998 letter are repeated below in italicized text along with our comments.

1. Study M/6475/0017 was to provide a determination of the biliary index in patients with hepatic compromise. The study report was to have been submitted within approximately 2 year of the approval date.

We have currently enrolled 14 patients out a planned total enrollment of 60 patients for this study. We have experienced difficulty in enrollment to study 0017 because patients with hepatic dysfunction often do not meet the performance status entry requirements. However, we are currently taking steps to expand the study and have recently added three additional study sites to increase the accrual rate. The projected date for completion of the study report is fourth quarter 2000.

2. An in vitro metabolism study had been conducted to study the effect of irinotecan (10 and 100 TM) on the metabolism of substrates of the major human cytochromes P450 (CYP1A2, 2C9, 2C19, 2D6 2E1 and 3A4). This report was to have been submitted to the Agency by September 1996. In addition, an evaluation of the ability of therapeutically-relevant concentrations of APC and SN-38 to inhibit major CYP450 enzymes was to have been completed by January 1997.

Pharmacia & Upjohn
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USA

Telephone (616) 833-4000

CAL 877 8488

CAMPTOSAR® Injection
Status of Phase 4 Commitments

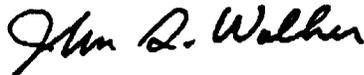
3. Protein binding of the human irinotecan metabolite APC was to have been determined. An evaluation was to have been made of the effect of SN-38 on the protein binding of commonly used co-medications that meet the following criteria: (1) highly protein bound to albumin, (2) drug clearance that is not restricted (i.e., blood flow rate limited clearance) and (3) narrow therapeutic index. The effects of commonly administered co-medication that are highly bound to albumin on the protein binding of total SN-38 (lactone plus hydroxyacid forms) was to have been evaluated. These were to have been completed by approximately December 1996.

Please be advised that we consider commitments # 2 and #3 to have already been fulfilled. Please refer to our submissions of August 12, 1996 and March 4, 1997 for details of the documentation that was submitted to address these commitments. We would appreciate receiving your comments if you feel any aspect of these commitments still needs to be addressed by Pharmacia & Upjohn.

If you have questions related to this submission, please contact me at (616) 833-8263 or address correspondence to mailstop 0636-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



John S. Walker
Regulatory Affairs Manager

JSW:kmv

Attachments



Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

March 28, 2000

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)**

Labeling: PI

Dear Sir/Madam:

Attached please find the P&U's version (dated March 27) of the PI labeling for use of Camptosar Injection in first line treatment of metastatic colorectal cancer. The modifications are based on the FDA versions (Label Review #1) received by P&U on March 22, 2000.

As advised, three versions of the PI are attached:

- 1. camp1stXX.doc = strikeout/double underline manuscript version in WORD with rationales**
- 2. camp1st.pdf = a PDF file containing a mock-up of the current PI with a clean manuscript version incorporated.**
- 3. cpt1stCC.doc = clean manuscript version in WORD for possible FDA revisions**

An electronic copy of the attachments of this submission was also sent via e:mail to Ms. Brenda Atkins (Project Manager) this morning. Also enclosed is a CD-ROM with the above mentioned files. The absence of viruses on this media has been confirmed using VirusScan NT v. 4.0.3.

NDA 20-571
Page 2

If you have questions related to this submission, please contact me at (616) 833-4355 or address correspondence to mailstop 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Christiane H. Vanderlinden PH ID FCP
for
Christiane H. Vanderlinden
Regulatory Manager
Global Regulatory Affairs

CHV:kmv

cc: Complete Desk Copy for Ms. Brenda Atkins



Pharmacia & Upjohn

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA
Telephone: (616) 833-4000

January 21, 2000

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)**

120-day Safety Update: Waiver Request

Dear Sir/Madam:

In accordance with 21 CFR §314.90, Pharmacia & Upjohn wishes to request a waiver authorization from providing a 120-day safety update for NDA 20-571/sNDA 009 for Camptosar® Injection in first-line therapy of metastatic colorectal cancer.

This waiver is requested based on the following:

1. A survival update for the two studies, 0038 and V303, supporting the sNDA will be submitted at the FDA's request by February 1, 2000.
2. Based on verbal communication with Ms. Brenda Atkins, Consumer Safety Officer, it is our understanding that the medical reviewer considers that a waiver is permissible as long as new safety information continues to be submitted as the company has been doing.

If you have any questions regarding this submission, please contact me at (616) 833-4355 or by fax at (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Christiane H. Vanderlinden
Regulatory Manager
Regulatory Affairs

CHV:kmv
Attachments

DUPLICATE



Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

April 5, 2000

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)

SUPPL NEW CORRESP
SNC

General Correspondence
Response to FDA Request

Dear Sir or Madam:

Please refer to your facsimile dated March 31, 2000 regarding the increased mortality rate observed in the "Mayo Clinic" CPT-11/5-FU/LV arm of the "6C" North Central Cancer Treatment Group (NCCTG) study.

Pharmacia & Upjohn (P&U) has carefully reviewed the situation with regard to the current toxicity information from the "Mayo Clinic" CPT-11/5-FU/LV arm of the "6C" NCCTG first-line colorectal trial. We have spoken at length to Dr. Richard Goldberg, the principal investigator of that trial, regarding the information available from the 65 patients treated on that study.

We agree that use of this regimen should not be advocated, and, given the toxicity concerns, we certainly have no wish to do so. However, we do not feel that we wish to discuss this regimen in the package insert at this time. Like the AIO regimen, it will not be the subject of promotion because there is insufficient evidence to support its efficacy or safety. P&U prefers to deliver an unambiguous message to clinicians about the efficacy and safety of those combination CPT-11/5-FU/LV regimens (Saltz and de Gramont) which have adequate documentation.

An immediate and strong signal is being sent to the oncology community by the abandonment of the regimen on the part of the NCCTG and the NCI. Furthermore, Dr. Goldberg concurs with P&U that information regarding the toxicity concerns raised by the

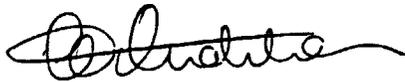
Mayo Clinic CPT-11/5-FU/LV regimen must be included in a publication regarding the phase I data and that the publication must include an enjoinder against use of the regimen in clinical practice.

In summary, P&U believes that the measures already being taken will adequately discourage use of this regimen.

If you have questions related to this submission, please contact me at (616) 833-4355 or address correspondence to mailstop 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



Christiane H. Vanderlinden
Regulatory Manager
Global Regulatory Affairs

CHV:lmf

DUPLICATE



Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

February 9, 2000

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

SUPL NEW CORRESP

SNC to 5009

CAMPTOSAR® Injection
(Irinotecan Hydrochloride Injection)

SE, - 009 (BS)

General correspondence
Response to FDA request

Per CSO

Dear Sir/Madam:

With reference to your facsimile dated February 7, 2000, we are providing a response to the question of the statistical reviewer. The FDA question is stated in bold italics below, and our response follows.

FDA Question

In the updated survival data for V303 and 0038, has P&U performed any tests with respect to the proportionality assumption of survival?

Response

Yes, the assumption of proportionality of hazards was tested for both PNU 0038 and RPR V303 data, following the same methods used for study 0038 in sNDA 009 submitted on October 19, 1999. These methods were described in "Appendix 12a - Documentation of Statistical Methods" of the study report (Vol. 1.14, Pg. 254-283), under section "Hypothesis Testing and Primary Endpoint Analysis" on Pg. 259. For the reviewer's convenience, we are providing a copy of the previously submitted Appendix 12a in attachment.

The output of the SAS procedure used for the Cox models regarding the tests on proportional hazard for each of the covariates can be provided should the reviewer find this useful.

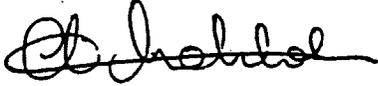
NDA 20-571

Page 2

If you have any questions regarding this submission, please contact me at (616) 833-4355 or by fax at (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY



Christiane H. Vanderlinden
Regulatory Manager
Regulatory Affairs

CHV:lmf
Attachments

DUPLICATE



Pharmacia & Upjohn

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7000 Portage Road
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January 31, 2000

Division of Oncology Drug Products HFD-150
Center for Drug Evaluation and Research
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Rockville, MD 20852



CENTER FOR DRUG EVALUATION
AND RESEARCH

FEB 01 2000

RECEIVED HFD-120

Re: NDA 20-571

NDA SUPP AMEND
SEJ-009
(BM)

CAMPTOSAR® Injection
(Irinotecan Hydrochloride Injection)

Survival Update to Supplement 009

Dear Sir/Madam:

As requested by the FDA in a fax dated December 21, 1999, Pharmacia & Upjohn is amending NDA 20-571 sNDA/009 with the latest available survival follow-up data and analyses for studies 0038 and V303.

The primary survival data are submitted electronically on one CDROM as SAS transport files. As proposed and agreed upon in a telephone conversation on January 19, 2000, two new datasets are submitted for each of the studies. The datasets use the same variable names as those used in the initial submission of sNDA 009 dated October 19, 1999.

Two copies of the CDROM are provided with this submission. They have been scanned with McAfee VirusScan NT v. 4.0.3a. The structure of the file directory and subdirectories contained on the CD, and the data structure for the new datasets are provided in Attachment 1.

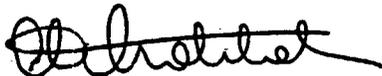
The survival analyses for the 2 studies using the updated survival data are provided in Attachment 2. The analyses are presented as an Addendum to the Clinical Study Reports submitted in the sNDA 009 on October 19, 1999 [Vol. 1.13, pp. 1-159 (M/6475/0038) and Vol. 1.3, pp. 130-339 (RP64174V-303)].

As a result of the updated survival analyses, we plan to submit an amendment for the package insert within the next few weeks.

If you have any questions regarding this submission, please contact me at (616) 833-4355
or by fax at (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY



Christiane H. Vanderlinden
Regulatory Manager
Regulatory Affairs

CHV:mlw

Attachments

DUPLICATE



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December 23, 1999

Division of Oncology Drug Products HFD-150
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Food and Drug Administration
Document Control Room 3rd Floor
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1451 Rockville Pike
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*Gave jacket
to MC - cinco
12-30-99
Dufrenoy*

Re: NDA 20-571

CAMPTOSAR® Injection
(Irinotecan Hydrochloride Injection)

General correspondence
Response to FDA request

SUPL NEW CORRESP
5 NCT 5-009

Dear Sir/Madam:

In this submission, we are providing a response to a request made by the Medical Reviewer in a facsimile dated December 7, 1999.

In our response, which is attached to this letter, we have restated the FDA request in bold italics followed by our response in regular text. The list of references cited in the response, and a copy of the published references are provided in Attachment 1.

If you have any questions regarding this submission, please contact me at (616) 833-4355 or by fax at (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Christiane H. Vanderlinden
Regulatory Manager
Regulatory Affairs

CHV:kmv
Attachments

DUPLICATE

NDA 20-571 sNDA/009 - Camptosar® Injection
Response to FDA Request of December 7, 1999

FDA Request

The contribution of 5-FU/LV to the efficacy of arm B in study 0032 [sic; 0038] needs to be ascertained in comparison to 5-FU/LV in arm C. Please submit a literature review (including copies of the reference articles) discussing your opinion on this issue.

Response

Background on 5-Fluorouracil/Leucovorin Regimens

When Study 0038 was designed in consultation with representatives of the FDA's Center for Drug Evaluation and Research in 1995-1996, it was recognized that differences in treatment administration schedule between the six-week schedule of the irinotecan/5-fluorouracil (5-FU/leucovorin (LV) treatment arm (Arm B) and the 4-week schedule of the 5-FU/LV control arm (Arm C) would need to be addressed. One issue was whether the weekly treatments with 5-FU/LV in Arm B would be intrinsically more effective than the doses and schedules employed in the every-4-week standard 5-FU/LV regimen of Arm C. If Arm B were to prove superior to Arm C, could the benefit be attributed primarily to a better 5-FU/LV dosing regimen rather than to the addition of irinotecan? A second concern was that factitious differences in response rate or time to tumor progression (TTP) might arise based only upon differences in the interval of assessment between the treatment arms.

In addressing the first concern, there appeared to be general consensus at the time of FDA/P&U discussions in October 1995 that comparison of the experimental regimen with a 5-FU/LV regimen that represented a US community standard was important. By the time Study 0038 was being designed, there had been considerable clinical testing of various doses, infusion time, schedules and methods of modulation of 5-FU. The distillation of these efforts lead to empiric development of two regimens of 5-FU/LV that have become widely adopted in the US for adjuvant treatment and for the therapy of metastatic disease. One method of administration has comprised the "Mayo Clinic" regimen of intensive-course 5-FU (approximately 425 mg/m²) plus low-dose LV (20 mg/m²) given daily for 5 days every 4-5 weeks. The other method was the "Roswell Park" regimen of weekly 5-FU (500-600 mg/m²) plus high-dose LV (500 mg/m²) for 6 weeks followed by a 2-week rest.

Two randomized clinical trials have directly compared each of these every-4-week and weekly regimens of 5-FU administration. Efficacy summaries for these trials are described in Table 1. In the most definitive study relevant in the first-line therapy of patients with metastatic colorectal cancer, the North Central Cancer Treatment Group compared these regimens in a randomized phase III trial involving the therapy of 372 patients [Buroker 1994]. Based on the response rate, TTP, and survival outcomes, the authors concluded that the two regimens were similarly effective but that the Mayo Clinic variation had less need for hospitalization to manage chemotherapy toxicity. In another direct comparison of these regimens as first-line therapy of metastatic colorectal cancer [Leichman 1995], the results again proved similar. In this trial, it was indicated that TTP was approximately 6 months in both regimens; as in the Buroker study, the degree of rigor applied in evaluating tumor progression was not detailed in the publication of this trial.

Table 1. Randomized Comparisons of the Mayo Clinic versus Roswell Park Regimens of 5-FU/LV for the First-Line Therapy of Metastatic Colorectal Cancer

Citation	Regimens	N	RR (%)	TTP (mo)	OS (mo)
Randomized Comparisons of the Mayo Clinic versus Roswell Park 5-FU/LV Regimens					
Buroker 1994	5-FU 425 mg/m ² Days 1-5 every 4-5 weeks LV, 20 mg/m ² , Days 1-5 every 4-5 weeks	183	35	5	9.3
	5-FU 600 mg/m ² weekly for 6 weeks every 8 weeks LV, 500 mg/m ² , weekly for 6 weeks every 8 weeks	179	31	6	10.7
Leichman 1995	5-FU 425 mg/m ² Days 1-5 every 4-5 weeks LV, 20 mg/m ² , Days 1-5 every 4-5 weeks	85	27* 17†	6	14
	5-FU 600 mg/m ² weekly for 6 weeks every 8 weeks LV, 500 mg/m ² , weekly for 6 weeks every 8 weeks	86	21* 14†	6	13

* Overall objective tumor response rate

† Confirmed objective tumor response rate (response confirmed on scan obtained \geq 4 weeks after initial response)

Results from another phase III study comparing high-dose to low-dose LV in the context of administering the Roswell Park regimen [Jäger 1996] became available shortly after the initiation of Study 0038. No appreciable differences in response rates for low- or high-dose LV were noted. While TTP was relatively long in this trial at 6.7 and 6.9 months, respectively, this endpoint was similar between the arms. Again, no information was provided about the circumspection with which evaluation of tumor progression was performed.

Table 2. Comparative Trial Involving High-Dose vs Low-Dose Leucovorin the Roswell Park 5-FU/LV Regimen for First-Line Therapy of Metastatic Colorectal Cancer

Citation	Regimens	N	RR (%)	TTP (mo)	OS (mo)
Jäger 1996	5-FU 500 mg/m ² weekly for 6 weeks every 8 weeks LV, 500 mg/m ² , weekly for 6 weeks every 8 weeks	143	18	6.9	12.5
	5-FU 500 mg/m ² weekly for 6 weeks every 8 weeks LV, 20 mg/m ² , weekly for 6 weeks every 8 weeks	148	22	6.7	12.7

In addition, a large meta-analysis by the Advanced Colorectal Cancer Meta-Analysis Project of 9 trials evaluated a total of 1381 patients who were randomized to receive treatment with either 5-FU or 5-FU plus LV. In this experience, the combination 5-FU/LV therapy produced an overall response rate of 23%, whereas the single-agent 5-FU therapy produced only an 11% rate. No difference in survival was noted between regimens that contained LV (median 11.5 months) and those that did not (median 11.0 months). These collective data regarding various 5-FU/LV regimens document a great deal of similarity in the efficacy outcomes for any of these methods of administering the two drugs.

Study 0038 Design

The design of Study 0038 took these considerations into account. The Buroker data became available in the year before finalization of the protocol for Study 0038, and added impetus to the decision to use the Mayo Clinic regimen as the most relevant control. In addition, despite its weekly schedule, the Roswell Park regimen did not offer any obvious advantage in terms of matching the timing of assessment of response and TTP between the treatment and control

arms; indeed, the 8-week cycle length was actually more cumbersome than the 4-week cycle length of the Mayo Clinic regimen in this regard.

It was clear that there was general sentiment among US colorectal cancer experts that further variations in modulating thymidylate synthase were unlikely to achieve additional benefit. As a result, Dr. Leonard Saltz, who developed the Arm-B irinotecan/5-FU/LV combination, felt that the regimen could be modeled in part on existing regimens, but could also be practically designed to avoid serious overlapping toxicities. The regimen was derived from a phase I dose-escalation study that was conducted at the Memorial Sloan-Kettering Cancer Center [Saltz 1996]. The schedule was based on the weekly irinotecan schedule that had been most extensively studied in the United States as well as on extensive experience with the Roswell Park weekly administration of 5-FU/LV [Buroker 1994]. Criteria for dose-limiting toxicity and maximum tolerated dose were standard in order to limit the overall toxicity to a level that would not be substantially different from that seen with 5-FU/LV regimens employed in the therapy of colorectal cancer. In order to achieve this objective, the weekly LV dose was lowered from that used in the Roswell Park regimen, much as had been done in the Jäger trial [Jäger 1996]. A prior attempt to use high-dose LV in conjunction with 5-FU and irinotecan had failed due to excessive dose-limiting diarrhea [Parnes 1995]. The results of Dr. Saltz's phase I trial indicated that the MTDs were 125 mg/m² of irinotecan, 500 mg/m² of 5-FU, and 20 mg/m² of LV given weekly for 4 weeks every 6 weeks.

Evaluation of the doses and schedule in this experimental regimen relative to those that had been used in the studies described in Table 1 indicated that it was quite unlikely that the contribution from 5-FU/LV alone in the Arm B regimen would be more efficacious than either the Roswell Park or Mayo clinic regimens of 5-FU/LV. The planned weekly doses of both 5-FU and LV in this experimental regimen are lower than those used in the Roswell Park regimen. Moreover, the number of planned treatments given in a 12-week period is fewer, with only 8 planned treatments in Study 0038 Arm B versus 10 such treatments in the Roswell Park regimen. In the contrast between the experimental Arm B regimen and the Mayo Clinic method of administration in Arm C, it is also notable that the planned 5-FU dose intensity (333.3 mg/m²/week) in Arm B was substantially lower than that in Arm C (531.3 mg/m²/week). This design feature helped ensure that any positive effects observed with the combination irinotecan/5-FU/LV treatment could be definitively attributed to the addition of irinotecan.

It should further be observed that the study was designed to avoid any bias in reporting of the efficacy or safety results. Dose modification rules were designed to provide balanced attenuation of dose intensity in each arm of the study. Supportive care recommendations were applied to all treatment arms in order to promote a consistent approach to alleviating treatment-related adverse events. Early evaluation of tumor assessments was to be performed in a uniform fashion at 6-week intervals in all arms of the study even though the control arm schedule might normally have prompted reevaluation at 8-week time periods. Tumor assessments were obtained at 6, 12, 18, and 24 weeks, and then every 12 weeks until response or tumor progression. All patients with initial evidence of objective tumor response were to have the response confirmed 4-6 weeks after the first documentation of response. In order to more precisely determine time of progression, the investigators were encouraged to obtain radiologic assessments earlier if there is a strong clinical suspicion of progression of disease in order to either confirm or refute the clinical impression. Definitions of response

and TTP (with detailed censoring rules) were clearly stated in the protocol and were strictly followed in the interpretation of results.

It was recognized that this circumspection in documenting tumor progression might potentially influence the results of the trial. In determining the sample size, it was assumed that the control arm would experience a 5-month median TTP. This figure was derived from the cooperative group trials suggesting a 6-month median TTP [Buroker 1994, Leichman 1995] and information from rigorously conducted phase II studies of first-line, single-agent CPT-11, which suggested a 4.2-month TTP [Dietz 1995a, Dietz 1995b]. Accounting for variations in the rigor of measurement of progression, the 5-month estimate was considered reasonably likely to reflect what could be expected of first-line therapy in Arms A and C of the current study.

Study 0038 and Study V303 Results

Beyond the design issues, the actual results of Study 0038 and also of Study V303, clearly indicate that irinotecan must be responsible for the incremental benefits associated with Arm B irinotecan/5-FU/LV therapy.

Table 3 summarizes the projected and actual dose intensities of irinotecan and 5-FU over the entire course of treatment for the as-treated population, by treatment arm. When considering the actual median dose intensities of each agent, these values were lower than the planned dose intensities. These data confirm that less 5-FU per unit time was administered in the Arm B than in Arm C, strongly supporting the critical contribution of Arm-B irinotecan in improving response rates and prolonging time to tumor progression.

Table 3. Dose Intensity (mg/m²/wk) Over the Entire Study
 (As-Treated Population)

Treatment Arm	No. of Pts	Irinotecan			5-FU		
		Projected	Median	Range	Projected	Median	Range
B*	225	83.3	59.6	20.8-85.5	333.3	236.4	83.1-341.1
C†	219	—	—	—	531.3	457.0	242.6-548.2
A‡	223	83.3	62.2	19.3-86.8	—	—	—

Source: Appendix 13, Table 8.4.1

- * Irinotecan/5-FU/leucovorin
- † 5-FU/leucovorin
- ‡ Irinotecan alone

Assessment of efficacy outcome in both Studies 0038 and V303 also confirms the critical role of irinotecan in improving tumor control. In this regard, the designs and results of the 2 trials were very complimentary. Where Study 0038 confirmed that a combination of irinotecan/5-FU/LV could provide better outcomes than a widely employed US regimen of bolus 5-FU/LV, Study V303 entirely isolated the effect of adding irinotecan, independent of 5-FU schedule.

As shown in Table 4, remarkable consistency across the studies was observed when examining the major efficacy outcome measures. In Studies 0038 and V303, the confirmed objective tumor response rates with the irinotecan/5-FU/LV combination arms (39.4% and 34.8%) were 1.5-2 times those in the 5-FU/LV control arms (20.8% and 21.9%); these results were highly statistically significant in both trials. The endpoint of TTP was significantly improved with combination therapy (medians, 7.0 and 6.7 months) over 5-FU/LV alone

(medians, 4.3 and 4.4 months). TTF was also consistently and significantly enhanced by combination irinotecan/5-FU/LV treatment vs 5-FU/LV in Study 0038 and in V303 (medians, 5.4 and 5.3 months vs 3.7 and 3.8 months, respectively).

Table 4. Efficacy Results of Two Phase III, Randomized, Controlled Studies of First-Line Therapy of Colorectal Cancer

Efficacy Endpoint	Study 0038 (Intent-to-Treat Population)			Study V303 (Full-Analysis Population)	
	Irinotecan 5-FU/LV	5-FU/LV	Irinotecan	Irinotecan 5-FU/LV	5-FU/LV
	Arm B N = 231	Arm C N = 226	Arm A N = 226	Arm A N = 198	Arm B N = 187
Confirmed Objective Tumor Response Rate (%)	39.4	20.8	18.1	34.8	21.9
	(p<0.001)†			(p<0.005)†	
Median TTP (months)	7.0	4.3	4.2	6.7	4.4
	(p=0.004)*			(p<0.001)*	
Median TTF (months)	5.4	3.7	3.2	5.3	3.8
	(p=0.001)*			(p=0.001)*	
Median Survival (months)	14.5	12.6	12.0	16.8	14.0
	(p=0.097)*			(p=0.028)*	

*Log-rank tests.

†Chi-square tests.

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

It is important to reiterate that these studies were very well conducted, with extensive internal or external review of response and time to tumor progression in each patient. This level of scrutiny is generally not possible in cooperative group trials. Thus the results of Studies 0038 and V303 almost certainly offer a conservative view of the outcomes in both treatment and control arms relative to those obtained in antecedent studies. This contention is supported by examination of industry-sponsored regulatory trials involving comparison of new thymidylate synthase inhibitors (eg, uracil/tegafur [UFT], capecitabine, raltitrexed) with Mayo Clinic 5-FU. In these trials, the Mayo Clinic control arms had response rates in the range of 9-18% and median TTP values of 3.3-5.1 months [Cocconi 1998, Carmichael 1999, Pazdur 1999, Twelves 1999].

While the statistical analysis in Study 0038 focused on the comparison of the irinotecan/5-FU/LV experimental therapy (Arm B) with the standard 5-FU/LV regimen (Arm C), the results with irinotecan alone (Arm A) are also noteworthy. The similarity of outcome in all endpoints when inspecting the results for Arm A and Arm C is remarkable and suggests that application of either single-agent CPT-11 or "single-agent" 5-FU/LV provides approximately comparable degrees of tumor control. This similarity is reassuring because it suggests that the 2-week-shorter course length in Arm C of the trial is not a cause for concern in the assessment of differences in TTP and TTF among the study arms.

Moreover, the results with irinotecan alone in Arm A have clear implications for understanding the probable incremental benefit provided by the 5-FU/LV in Arm B. When considering tumor control variables of response rate and TTP, it appears that the addition of

5-FU/LV to CPT-11 in Arm B increases response rate by 21.3% (Arm B 39.4% - Arm A 18.1%) and TTP by a median of 2.8 months (Arm B 7.0 months - Arm A 4.2 months). When considered in conjunction with the results obtained in Arm C, these data strongly suggest that it is very unlikely that the benefits documented in the comparison of Arm B to Arm C are due to an improved method of administering 5-FU/LV in Arm B and are critically related to the contribution of irinotecan.

Summary

In overall summary, the validity of the comparison of Arms B and C of Study 0038 is clearly documented by several lines of evidence. Data obtained from other randomized trials of 5-FU/LV regimens, considerations applied in the design of Study 0038, the confirmatory results provided by Study V303, and the outcomes noted in Study 0038 Arm A all provide compelling reassurance of the strength of the results. It is clear that the incremental benefits offered by irinotecan/5-FU/LV in Arm B of 0038 must be ascribable to irinotecan.

**APPEARS THIS WAY
ON ORIGINAL**



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November 19, 1999

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)

Desk Copy

Dear Sir or Madam:

In response to recent FAX (November 18, 1999) from Ms. Loretta Arscott, Pharmacia and Upjohn (P&U) is pleased to provide the following requested documentation.

1. **Medical - Please specify the path to the electronic version of the package insert. If not submitted, please include the current, strikethrough and proposed final version in MS-WORD.**

Apart from the two CDs containing Item 11 and 12, the original electronic submission of October 19, 1999 also included two 3.5" diskettes (one with the proposed PI, and the other with PK data). A new set of these two CDs and one diskette is now included. The following Camptosar Injection PI versions (with file names) are on this diskette.

- a. Current PI (see campcur.pdf file)
- b. Strikethrough (see camppi.pdf file)
- c. Proposed (1stlinepir.doc; MS-Word): Provides changes envisioned in the current PI.

2. Unfortunately, we are unable to provide MS-Word versions of the items 'a' and 'b' noted above at this time, because approved inserts are stored in our system as only 'pdf' files. No specific definition of a path should be needed.
3. **Statistical - Please send all volumes pertaining to statistical data as well as the electronic data (CDs) and documentation for the electronic data (definitions, explanation between variable names).**

All 29 volumes (Item 8/10) are provided as 'desk copy' for use by the statistical reviewers. For both studies, a pdf file named "Define" provides "Dataset Descriptions" and "Variable Definitions". The file is located in the folder for the study (by study no.) on the CD with CRT's. Please advise if this information is sufficient.

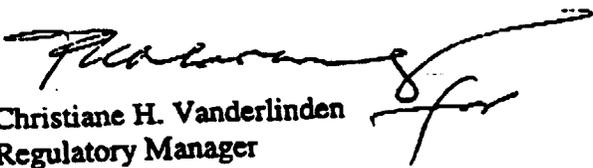
The electronic media have been scanned with Virus Scan Software from Network Associates (Windows NT ver 4.0.3a) to verify it is free of viruses. P&U wishes to recommend that the Division may wish to take additional precautions of re-scanning at their end.

We would also like to take this opportunity to apologize for our oversight in not having the duplicate set of Items 8/10 included in our original sNDA submission. Hopefully, it has not been a major inconvenience.

If you have questions related to this submission, please contact me at (616) 833-4355 or address correspondence to mailstop 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY


Christiane H. Vanderlinden
Regulatory Manager
Regulatory Affairs

CHV:mlw

cc: Loretta Arscott (FAX: 301 594 0499)