

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20571/S9

ADMINISTRATIVE DOCUMENTS

MEETING MINUTES

MEETING DATE: September 23, 1999

TIME: 1:00 p.m. **LOCATION:** WOC2/r 2064

NDA: 20-571

Meeting Request Submission Date: 8-18-99

Briefing Document Submission Date: 8-27-99

DRUG: Camptosar Injection (Irinotecan Hydrochloride Injection)

SPONSOR/APPLICANT: Pharmacia & Upjohn

TYPE of TELECON:

1. Guidance (pre sNDA)
2. Proposed Indication: metastatic colorectal cancer.

FDA PARTICIPANTS:

Robert Justice, M.D.	Acting Division Director	(at industry meeting only)
Julie Beitz, M.D.	Acting Deputy Director	(at pre-meeting only)
Grant Williams, M.D.	Clinical Team Leader	
Isagani Chico, M.D.	Clinical Reviewer	
Atiqur Rahman, Ph.D.	Biopharm Team Leader	(at industry meeting only)
Lydia Kieffer, Pharm.D.	Biopharm Reviewer	
David Smith, Ph.D.	Statistical Reviewer	(at pre-meeting only)
Loretta Arscott	Project Manager	

INDUSTRY PARTICIPANTS:

Langdon Miller, M.D.	Vice President, Clinical Development Oncology
Paula Locker, M.S.	Senior Clinical Trial Specialist, Clinical Development Oncology
Gary Elfring, M.S.	Senior Statistician
Larry Schaaf, Ph.D.	Scientist, Clinical Pharmacokinetics
Karin Weston	Regulatory Affairs Director
Christiane Vanderlinden, M.S.	Regulatory Affairs Manager
Gianfranco Rutili, M.D.	Camptosar Project Team Leader
Anna Petroccione, M.D.	Director, Biostatistics & Data Management
Nicoletta Pirota	Senior Statistician
Silvia Chiota, Ph.D.	Regulatory Affairs Director
Cosimo Scarafile, R.Ph.	Regulatory Affairs Manager

BACKGROUND:

September 21, 1999 Pre-meeting decision was to convey the reviewers' comments to the sponsor, giving the sponsor the option of canceling the 9-23-99 teleconference.

September 22, 1999 Conveyed responses to the sponsor via facsimile.

Sponsor responded by facsimile requesting that the teleconference remain as scheduled only to discuss FDA's additional comment regarding the Clinical Pharmacology and Biopharmaceutics comment.

TELECON OBJECTIVES:

To clarify and discuss the additional biopharmaceutical comments raised by the reviewer regarding the pharmacokinetic data on 5-FU and LV.

FDA COMMENT for DISCUSSION with DECISION REACHED:

Clinical Pharmacology and Biopharmaceutics Comment to Pharmacia & Upjohn:

Upon reviewing the publication, for Study 007 and according to the results, no 5-Fluorouracil (5-FU) or Leucovorin (LV) pharmacokinetic (PK) data was collected in order to determine if Irinotecan (CPT-11) alters the PK of 5-FU and LV.

The sponsor should provide information on the PK disposition of the proposed combination (CPT-11, 5-FU, and LV) at the proposed dose for all 3 medications upon submission of the sNDA.

Please refer to the March 8, 1999 FDA Meeting Minutes, questions 2 & 3.

Comment revised to:

Upon reviewing the publication, for Study 007 and according to the results, no 5-Fluorouracil (5-FU) or Leucovorin (LV) pharmacokinetic (PK) data was collected in order to determine if Irinotecan (CPT-11) alters the PK of 5-FU and LV.

The sponsor is recommended to provide information on the PK disposition of the proposed combination (CPT-11, 5-FU, and LV) at the proposed dose for all 3 medications upon submission of the sNDA.

Please refer to the March 8, 1999 FDA Meeting Minutes, questions 2 & 3.

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Pharmacia & Upjohn: Pharmacia & Upjohn will submit their application as it stands now.

Concurrence Chair: _____

Loretta Arscott
Project Manager

Attachments: Overhead not in briefing document

cc: Original NDA 20-571
HFD-150/Div File
/L.Arscott

TELECON MINUTES

**MEMORANDUM OF TELEPHONE CONVERSATION
DIVISION OF ONCOLOGY DRUG PRODUCTS**

DATE: August 18, 1999

SUBJECT: NDA 20-571, Camptosar Injection

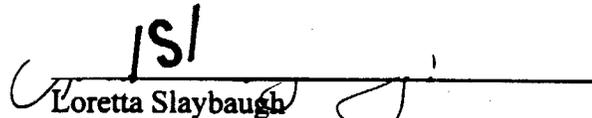
BETWEEN: Christiane A. Vanderlinden, Regulatory Manager, Pharmacia & Upjohn
and Loretta Slaybaugh, Project Manager, HFD-150

Discussion:

Pharmacia & Upjohn plans to submit an efficacy supplement to the division in the second half of October 1999; the supplement was originally scheduled to arrive in September 1999.

Pharmacia & Upjohn plans to request a sNDA meeting, the formal request and packages are expected to arrive within 10 days from today. They also request that the meeting be scheduled during the second week of September.

I advised Ms. Vanderlinden that the review team would need adequate time to review the package and that I would call her after discussing the meeting request with the team.


Loretta Slaybaugh
CSO/Project Manager, HFD-150

cc:
Orig. NDA 20-571
HFD-150/Div. File
HFD-150/LSlaybaugh

MEETING MINUTES

MEETING DATE: November 17, 1999 **TIME:** 2:30-3:30 p.m. **LOCATION:** cr-B

IND/NDA: sNDA 20-571/009

Submission Date: October 19, 1999

DRUG: Camptosar Injection (Irinotecan Hydrochloride Injection)

SPONSOR/APPLICANT: Pharmacia & Upjohn

TYPE of MEETING:

1. 30-Day Filing
2. **Proposed Indication:** Irinotecan as a component of first-line therapy for patients with metastatic colorectal cancer.

FDA PARTICIPANTS:

Richard Pazdur, M.D.	-	Division Director
Robert Justice, M.D.	-	Deputy Director
Rachel Behrman, M.D.	-	Deputy Director, ODEI
Grant Williams, M.D.	-	Medical Team Leader
Isagani Chico, M.D.	-	Medical Reviewer
Gang Chen, Ph.D.	-	Statistical Team Leader
David Smith	-	Statistical Reviewer
Atiqur Rahman	-	Biopharmaceutics Team Leader
Gurston Turner	-	Division of Scientific Investigations
Loretta Arscott	-	Project Manager
Sean Bradley	-	Project Manager

MEETING OBJECTIVES:

1. To determine filing status

DISCUSSION and DECISIONS REACHED:

1. **FILEABILITY:** The NDA will be filed. A Priority review has been granted.

2. DISCUSSION POINTS:

- a) **Medical:** *Financial Disclosure* – Linda Carter has advised P&U that they may have until December 3, 1999 to send in the financial disclosure documentation for the V303 (Europe) study. This will not be considered a RTF issue until receipt of documentation on or before December 3, 1999.

Working Meetings – Discussed scheduling 15-30 minute working meetings between clinical and statistical reviewer's during the review process.

Laptop – Unable to request a laptop from P&U, laptops can only be volunteered by the company.

To be conveyed to the sponsor:

Please specify the path to the electronic version of the package insert. If not submitted, please include the current, strikethrough and proposed final versions in MS Word.

The contribution of 5-FU/LV to the efficacy of arm B in study 0032 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.

- b) **Statistical:** Requested volumes and electronic data as well as documentation for the data.
- c) **Biopharm:** Would like to consult clinical on the dosing that will be recommended, may need additional information from the sponsor after this decision is made.

3. CONSULTS:

- a) **DSI:** The original request for the inspection of 5 domestic sites will be reduced to 3 domestic sites at the recommendation of Gus Turner. Gus indicated that the inspections may take place in December.

4. **ODAC:** March 16 or 17, 2000 (if being presented)

5. TEAM GOALS:

Medical, Statistics, and Biopharm. agreed on the review completion goal date of 02/26/00.

6. TEAM MEETINGS/GOAL DATES:

The following table is an outline of goal dates:

	DATE	DAY	TIME	ROOM	MEETING TYPE
a.	Jan. 25, 2000	Tuesday	11:00-12:00	WOC2-cr B	3-Mo team for (to determine labeling schedule and meetings, other issues)
b.	Feb. 16, 2000	Wednesday	REVIEWS COMPLETE (if possible) (to ODAC)		
c.	Feb. 22, 2000	Tuesday	11:00-12:00	WOC2-cr A	Or 4-mo team meeting (if needed)
d.	Mar. 06, 2000	Monday	2:00-4:00	WOC2-cr B	ODAC Practice
f.	Mar. 13, 2000	Monday	ACTION PACKAGE TO REVIEWERS & T.S.		
e.	Mar. 16 or 17	Thur/Fri	ODAC MEETING		
f.	Mar. 20, 2000	Thursday	ACTION PACKAGE TO PAZDUR		
g.	Mar. 23, 2000	Thursday	11:00-12:00	WOC2-cr B	Post ODAC meeting
h.	April 03, 2000	Monday	ACTION PACKAGE TO TEMPLE		

USER FEE DATE: April 20, 2000

OTHER ISSUES:

- a) Action Letter sign-off: TBD in mini-rounds
- b) R. Temple will want to see labeling, even if not signing off on letter.
- c) ODAC – Further discussion should take place, at the 3-month meeting, as to whether the submission will definitely be presented at the ODAC meeting.
- d) Drug shortage for Camptosar should not be an issue for this application since user fee date is not until April 20, 2000.
- e) EA – Chemistry has the environmental assessment, which was not included in the original submission.

MEDICAL OFFICER 30-DAY FILING MEETING REVIEW
(sNDA 20-571/SE1-009)

FILING DATE: October 20, 1999
DATE OF REVIEW: November 17, 1999
SUBJECT: Day 30 Report for sNDA 20-571 SE1-009(CPT-11)
FROM: Isagani Chico, MD, Medical Officer

This efficacy supplement application is for irinotecan as component of first-line treatment of patients with metastatic colorectal cancer. The action on this NDA will be based on data from two large, multicenter, and randomized phase III trials (Study 0038 and V303), supported by pharmacokinetics data from Study 0007.

PIVOTAL PHASE III TRIALS

PROTOCOL	ARM	DOSE (mg/m ²)	PATIENTS (n)	COMMENTS
Study 0038 P&U US, Can, Aus, NZ	A: CPT-11 42d course	125 wkly x 4, then 2 wks rest	231	<ul style="list-style-type: none"> - prior adjuvant tx >12 m (10% of pts) - no pelvic RT, 15% pts w/ rectal CA - Stratified by age, PS, prior FU, time from dx - 1^o endpoint: TTP - 110/198 (56%) in Arm C received CPT-11 after tx - significant improvement in RR, TTP, TTF - QOL, PS and weight data collected
	B: CPT-11/ 5-FU/LV 42d course	125 wkly x 4/ 500/20 wklyx4 then 2 wks rest	226	
	C: 5-FU/LV 28d course	425/20 daily x 5	226	
V303 RPR Europe, Israel, SA	A ₁ : CPT-11/ 5-FU/LV 7w course	80 wkly x 6 2300 over 24 ^o x 6 500 over 2 ^o	145	<ul style="list-style-type: none"> - prior adjuvant tx > 6 m (25% of pts) - pelvic RT ok, 35-45% pts w/ rectal CA - Stratified by study center - 1^o endpoint: Response Rate - 3/4 of patients used A1/B1 - 58/187 (31%) in Arm B received CPT-11 after tx - significant improvement in RR, TTP, TTF - significant improvement in survival - QOL, PS and weight data collected
	A ₂ : CPT-11/ 5-FU/LV 6w course	180 on d1 x3w 400-600/22 ^o d1-2 200/2 ^o d1-2 x3w	53 Total: 198	
	B ₁ : 5-FU/LV 7w course	2300 over 24 ^o x 6 500 over 2 ^o	143	
	B ₂ : 5-FU/LV 6w course	400 then 600/22 ^o 200/2 ^o x3 w	44 Total: 187	

Study 0007 (Supportive Trial) is a Phase 1 clinical and PK study of the Saltz regimen. The main objective of the PK endpoint was to determine the effect of 5-FU/LV on the PK of CPT-11 and SN-38 and to determine the effect of the order of administration on CPT-11 PK and toxicity when given on a weekly schedule.

This study provides important information on the PK of CPT-11, however, the FDA and the sponsor have discussed about looking at the effect of CPT-11 on 5-FU PK in the first few patients enrolled in Study 0038 (1996). It might be useful to have this information; however, a stronger rationale (maybe clinical?) may be needed to require it. The medical reviewer will be sensitive to the possibility of enhanced 5-FU/LV toxicity, dose modifications, etc. during the review.

Contents of the NDA Submission:

Electronic:

- 2 CDs containing CRF and CRF tabulations (SAS transport file),
purged in the Electronic Document Room
- Proposed revised Package Insert (MS Word)
- Primary PK data (MS Excel)

The efficacy variables for statistical analysis were tabulated, coded and decoded in a separate hyperlinked table. (Looks great!)

Paper:

1. Financial Disclosure Statements:

- Certification for investigators in Study V303 was not submitted.
- Certifications were only obtained from _____ investigators
Dr. Leonard Saltz (who established the safety of the Saltz regimen used in one of the arms in Study 0038) submitted a statement showing absence of conflict.

The FDA gave P&U until December 3, 1999 to submit the disclosure statements for the investigators of Study V303. According to the draft guidance, the applicant may submit a statement documenting its efforts in place of the certification or disclosure statement if they are unable to obtain the information from investigators of a study conducted outside the U.S.

Consults

Study sites and patient distribution list was faxed to DSI and the audit discussed with Gus Turner on Nov 10. Only US sites will be considered. The following five sites were proposed:

TOTAL: 184 patients (27%) I think these sites are excellent for consideration since academia, private practice, an HMO and a CCOP are represented. Gus Turner recommended auditing only three sites since this is a sNDA.

Medical/Review Issues:

1. The proposed indication for CPT-11 as "a component of first-line treatment of patients with metastatic colorectal cancer" may be too broad and may need to be modified. This indication assumes that chemotherapy other than 5-FU (although unlikely) may be used in combination with CPT-11. Since there is no standard 5-FU regimen for first line treatment, it also assumes that any 5-FU regimen may be used.
2. The current approved indication for CPT-11 is, "for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial therapy." If approved as a component of first line therapy, the indication for second line treatment may need to be modified to say, "except for patients already treated with CPT-11 as component of first line treatment", since the efficacy of CPT-11 in this setting is unknown.
3. The EORTC-QLQ-C30 was used in both studies. This consisted of 30 questions that were retrospectively converted into 15 subscales. These include 2 global health, five functional, and nine symptom subscales. The statistical plan for data analysis was not prospectively defined. The applicant presented an extensive analysis of QOL in their study report but proposed to include only certain mean and baseline comparisons in the proposed label. The FDA statistical and medical reviewers should probably identify the most clinically relevant endpoints on which longitudinal analyses can be done and possibly included in the label. The applicant should also be asked to identify and perform longitudinal analyses on subscales, which they believe are most clinically relevant. We may be able to cross validate our results by doing this.

MEETING MINUTES

MEETING DATE: March 8, 1999 TIME: 11:00 am LOCATION: Conf. Rm. G

IND []
NDA 20-571

Meeting Request Submission Date: Jan. 12, 1999
Briefing Document Submission Date: Jan. 20, 1999
Additional Submission Dates: Mar. 2, 1999

DRUG: CAMPTOSAR (irinotecan hydrochloride injection) Injection

SPONSOR/APPLICANT: Pharmacia & Upjohn

TYPE of MEETING:

1. pre-sNDA
2. Proposed Indication: First-line therapy of metastatic colorectal cancer

FDA PARTICIPANTS:

Dr. Temple - Office Director (pre-meeting only)
Dr. Behrman - Deputy Director
Dr. Justice - Acting Division Director
Dr. Beitz - Acting Deputy Director
Dr. Williams- Medical Team Leader
Dr. Chico- Medical Officer
Dr. Smith - Biometrics Reviewer
Dr. Kieffer- PK Reviewer
Mr. Guinn- Project Manager

INDUSTRY PARTICIPANTS:

Langdon Miller, MD - Vice President, Clinical Development Oncology, P&U USA
Paula Locker, MS - Senior Clinical Trial Specialist, Clin. Development Oncology, P&U USA
Gary Elfring, MS - Senior Statistician, P&U USA
Larry Schaaf, PhD - Senior Scientist, Clinical Pharmacokinetics, P&U USA
Lillian Neff, BA - Senior Medical Writer, Clinical Development, P&U USA
John Walker, MS - Regulatory Affairs Manager, P&U USA
Karin Weston - Regulatory Affairs Director, P&U USA
Silvia Chioato, PhD - Regulatory Affairs Director, P&U Italy
Nicoletta Pirota - Senior Statistician, P&U Italy
Kiyoshi Terada, PhD - General Manager, Medicine Department, Yakult Honsha Co., Japan
Amy S. Domanowski - Senior Director, Regulatory Affairs, Daiichi USA

MEETING OBJECTIVES:

To discuss Pharmacia & Upjohn's plans for a Camptosar supplemental NDA (sNDA) for first-line therapy of metastatic colorectal cancer.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. P&U proposes to submit the results of protocol M/6475/0038 in an sNDA as evidence of the efficacy and safety of irinotecan for the treatment of patients with previously untreated colorectal cancer. If the results of this study demonstrate a significantly longer TTP in patients who were treated with the combination of irinotecan/5-FU/LV than in those who were treated with standard 5-FU/LV, P&U believes that this study will provide sufficient evidence of the clinical benefits of irinotecan therapy. Given the past concurrence between the FDA and P&U regarding the design and endpoints of protocol M/6475/0038, will the FDA accept protocol M/6457/0038 as the basis for approval for a first-line indication for irinotecan when given in combination with 5-FU/LV?
 - Refer to the Meeting Minutes from 5-1-96: "Dr. Murgo noted that survival should also be included as a primary endpoint. The sponsor will analyze the data for survival in the same way planned for TTP."
 - The statistical review includes the following comments: "Survival is commonly used as a primary endpoint for colorectal studies because of the difficulty inherent in measuring TTP in this disease. The primary endpoint used for approval of 5-FU/LV 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."
 - Study 0038 alone could serve as an adequate basis of approval if a survival advantage is shown.
 - Absent a survival advantage in Study 0038, data from Study V303 will probably be needed to demonstrate the effectiveness of CPT-11.
 - For time to progression (TTP) to be considered, there is a need for a confirmatory study, such as V303.
2. A single-agent irinotecan arm (Arm A) was included in the study in order to document irinotecan clinical effects in the setting of a large, prospective, multicenter trial; there was the general expectation that clinically similar outcomes to those obtained with first-line 5-FU would be obtained in light of the existing phase II data regarding use of single-agent

irinotecan in this clinical situation. Results from this arm (Arm A) of the study will not be formally compared with those of Arm C (standard 5-FU/LV regimen). However, if the TTP, response rate, and survival are clinically similar between Arms A and C, irinotecan may offer a reasonable alternative to 5-FU/LV as first-line therapy. P&U proposes that single-agent irinotecan therapy also be approved as part of the first-line labeled indication. Does the FDA believe that the data from study M/6475/0038 and those of the supportive phase II trials can potentially be sufficient to also allow registration of irinotecan as single-agent first-line treatment?

- No. It is unlikely that this trial can demonstrate non-inferiority. Furthermore, a single non-inferiority study will not be adequate.
3. Data from study M/6475/0007 indicate that the pharmacokinetics of irinotecan are essentially unaffected by coadministration of 5-FU and LV.
- Concurrence with this statement is not possible at this time because this data has not been submitted.
 - This data will be submitted by Pharmacia & Upjohn.

P&U proposes not to delay the sNDA submission in order to analyze the population pharmacokinetic data from protocol M/6475/0038 but rather to submit these results as a separate study report at a later time. Is this proposal acceptable?

- If results from Study 007 are insufficient to demonstrate that no drug interaction between the compounds being co-administered exists, then the data from Study 0038 will be of great relevance.
 - If you propose to make any label changes or claims, then the data from Study 0038 will need to be submitted.
 - If you propose to make a link to safety or efficacy, then the data from Study 0038 will need to be submitted.
 - The data would not need to be submitted unless it is relevant to the 3 points listed above.
4. P&U can potentially provide additional written information from an RPR-sponsored, phase III, controlled study (protocol V303) of combination irinotecan, 5-FU, and LV therapy in patients with previously untreated colorectal cancer as part of the sNDA if these results become available prior to the planned submission of the data from protocol M/6475/0038. In order not to delay the submission of the sNDA, P&U proposes to provide these supportive

data at a later time if they can be obtained and are considered relevant by the FDA. Since protocol V303 used regimens that are different from the regimen that will be recommended in the US, the results of this study may be supportive of those of protocol M/6475/0038 but will have no effect on the proposed CAMPTOSAR package insert. Would the FDA be interested in submission of the written report for this study as a potential amendment to the sNDA?

- Regardless of the difference in CPT-11 and 5-FU infusion schedules used in Study V303, submission of the protocol, full study reports, electronic data listings and primary data is recommended. Results from this study could provide independent substantiation of the safety and efficacy of CPT-11/5-FU/LV combination in first-line treatment of colorectal cancer. See #1.
 - The data from these two studies should be submitted at the same time. We trust that you will be able to negotiate an agreement with RPR to provide all documentation on study V303 in the same manner as they did in studies V301 and V302 for the second-line NDA application.
 - Pharmacia & Upjohn will negotiate with RPR regarding Study V303 and will submit a proposal to the FDA as to what data will be included. (A copy of the protocol and blank CRFs for Study V303 will be appended to the submission)
 - Pharmacia & Upjohn should also submit a financial disclosure statement for investigators in Study V303. However, this may not be necessary if the study cut-off date is before February 1, 1999.
5. Are the proposed contents of the sNDA acceptable?
- The proposed format appears to be acceptable for filing.
 - Primary data for first-line are not needed but you should submit summary reports on single agent Phase 1 and 2 studies.
 - Since these study reports have already been submitted, summaries would be acceptable.
6. Are the analysis display plan and proposed tabular displays of efficacy and safety data (in Appendix D) for protocol M/6475/0038 acceptable?
- Yes
7. Will both Access and SAS data sets be required by the FDA for protocol M/6475/0038?

- Data sets in Access need not be submitted if SAS datasets in SAS transport file (non-compressed) format is made available for the Medical Reviewer.
 - We encourage submission of the electronic data through our Electronic Document Room according to the guidance.
 - If providing population PK on 0038, then we would like it submitted electronically in EXCEL.
 - Additional Formatting Questions:
 - a. P&U proposes that electronic datasets in SAS or Access format be submitted to fulfill the CRT requirements for Item 11 and that domain and patient profiles not be provided with the sNDA. Does FDA concur with this proposal?
 - Yes
 - b. Are SAS datasets in Windows 95 (rather than SAS Transport format) acceptable?
 - SAS Transport Files (non-compressed) are preferable.
8. Given the importance of the data, is a priority (ie, 6-month) review considered feasible by the FDA?
- The official decision is made between 30-60 days after submission of the full NDA and is based upon the results.

Additional Comments:

1. Please provide a listing of all study sites and investigators, total number of patients enrolled and the number of responders in each site and each arm.
 - Guidance Document provided at the meeting.
2. The NDA submission should include a section containing financial disclosure for clinical investigators.
3. If available, please include post-treatment therapies. This may be important if TTP is the only positive finding.
 - Pharmacia & Upjohn will include this data in the NDA submission.

ACTION ITEMS:

1. Data from study M/6475/0007 will be submitted by Pharmacia & Upjohn.
2. Pharmacia & Upjohn will negotiate with RPR regarding Study V303 and will submit a proposal to the FDA as to what data will be included. (A copy of the protocol and blank CRFs for Study V303 will be appended to the submission)
3. Pharmacia & Upjohn should also submit a financial disclosure statement for investigators in Study V303. However, this may not be necessary if the study cut-off date is before February 1, 1999.
4. The minutes from this meeting will be forwarded to Pharmacia & Upjohn once they are finalized.

The meeting was concluded at 12:20pm. There were no unresolved issues or discussion points.

 /S/
Patrick Guinn, Project Manager
Minutes preparer

3/12/99

Concurrence Chair: /S/
Isagani/Chico, M.D.
Medical Officer

3/12/99

Guinn

MEETING MINUTES

DATE: December 11, 1997 **TIME:** 11:00 a.m. - 12:30 p.m. **LOCATION:** Conf.Rm.G

IND **NDA 20-571** Meeting Request Submission Date: October 2, 1997
Briefing Document Submission Date: November 11, 1997

DRUG: Camptosar Injection, CPT-11 (irinotecan HCl)

SPONSOR/APPLICANT: Pharmacia & Upjohn

TYPE of MEETING:

1. Pre-sNDA
2. Proposed Indication: Full Approval from accelerated approval status for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-fluorouracil (5-FU)-based therapy.

FDA PARTICIPANTS:	INDUSTRY PARTICIPANTS:
Dr. Krook -- ODAC Consultant (pre-meeting)	Dr. L.Miller -- V.P., Clin.Devel., USA
Dr. R.Temple -- Office Director, ODE 1	Dr. R.Petit -- Assoc. Dir., Clin. Devel.,USA
Dr. R.DeLap -- Division Director, DODP	Ms. P.Locker -- Sr. Clin. Trial Specialist,USA
Dr. R.Justice -- Deputy Director (pre-meeting)	Mr. G.Elfring -- Sr. Statistician,USA
Dr. G.Williams -- Medical Team Leader	Dr. L.Schaaf -- Clin. PK,USA
Dr. I.Chico -- Medical Reviewer	Mr. J.Walker -- R.A. Manager, USA
Dr. R.Davis -- Medical Fellow (pre-meeting)	Dr. D.Mannix -- R.A. Director, USA
Dr. Hoberman -- Biometrics Reviewer (pre-meeting)	Dr. R.Eccel -- CPT-11 Project Leader, Italy
Dr. A.Rahman -- PK Team Leader (pre-meeting)	Dr. S.Chioato -- R.A. Manager, Italy
Mr. P.Guinn -- Project Manager	Dr. P.Herait --Dir. Clin. Research RPR, France
	Dr. K.Terada -- Gen. Manager, Yakult Honasha Co., Japan

BACKGROUND:

At the time of approval, Pharmacia & Upjohn agreed to carry out a study of CPT-11 vs. 5FU/Leucovorin vs. CPT-11 plus 5FU/Leucovorin in first line therapy of colorectal cancer as a condition of accelerated approval of the refractory disease claim (note, we allowed them to study a different disease post-approval (primary treatment) instead of what was approved (refractory disease) because we thought controlled superiority trials in refractory disease would not be do-able.

Meeting Objectives:

1. To discuss the specific component requirements for the sNDA.
2. To discuss the appropriate method of presentation of information.
3. To discuss the requirements to attain Full Approval status from Accelerated Approval status.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. RPR has recently completed two Phase 3, randomized clinical trials comparing second-line irinotecan to BSC (Protocol V301) and also to infusional 5-FU based therapy (Protocol V302) in patients whose disease has progressed following a prior 5-FU-containing regimen. Given the findings that irinotecan provides a survival advantage in these comparisons, can these studies form the basis of an sNDA to support transition from P&U's current accelerated approval status to full approval status?
 - ◆ Yes, if survival advantage is confirmed.
2. P&U intends to submit an sNDA consisting of the elements discussed in Section 7.0 of the Briefing Document. Does the FDA agree that these sNDA components are adequate?
 - ◆ No, this should include primary electronic data for RPR studies 301 and 302 (all information on Case Report Forms which have been recorded in an electronic database). Specific information was provided in an addendum to the minutes.
 - ◆ CRF's of deaths and dropouts of studies 301 and 302 will be included at this point of submission of the sNDA
 - ◆ Point 4 on page 67 of the meeting package, regimen in package insert, will depend upon review of the data.
 - ◆ If you feel it is acceptable for different doses to be used, then you should list them in the proposed package insert.
 - ◆ Providing the two RPR studies is sufficient for submitting the sNDA. However, it would be advisable to submit the other Pharmacia & Upjohn studies (24 and 37), as soon as the information is available (e.g., supplemental labeling changes).

- ◆ You should rely primarily on the RPR data. However, you should evaluate the U.S. data for dose modification information and early deaths. The electronic data for the 2 Pharmacia & Upjohn studies (24 and 37) does not need to be submitted at the same time and would not necessarily hold up the submission of the sNDA.

- 3. Because the two RPR studies demonstrate a survival advantage for irinotecan in treatment of second-line colorectal cancer, would a priority review of the sNDA be considered by the FDA?
 - ◆ Yes.

- 4. Is an ODAC review of this sNDA seen as necessary by the FDA?
 - ◆ Yes, most likely.

- 5. P&U Protocol M/6475/0038 was originally intended to serve as a confirmatory trial leading to full approval of the second-line colorectal cancer indication. Assuming that full approval of Camptosar for second-line treatment of colorectal cancer is considered feasible based on results from RPR studies V301 and V302, P&U Protocol M/6475/0038 takes on a different purpose than originally intended.
 - a. Pharmacia & Upjohn proposes that completion of Protocol M/6475/0038 is no longer a condition of accelerated approval. Does the FDA concur?
 - ◆ Yes, however, we still recommend that you complete it.

 - b. There had been discussion related to having an independent review of response and TTP performed in all 660 Protocol M/6475/0038 patients. Given the different focus of this protocol, we currently plan not to perform such an independent review. Does the FDA concur?
 - ◆ Individual investigator assessment on CRF's instead of an outside independent review is acceptable. An outside independent review might be helpful but is not a requirement.

Additional Comment:

- ◆ Please submit all completed clin/pharm study results (especially study 0062) in the sNDA submission.

- ◆ When the completed report becomes available, it will be submitted (may be after

the sNDA is submitted).

ACTION ITEMS: (Include description, identify person responsible and due date.)

1. Medical and statistical teams will review the amendment and will determine a timeframe in which this will be addressed and how (e.g., telecon, FAX, meeting).
2. Patrick Guinn will check into who to contact for the User Fee Requirement.
3. Future communication of Data Format will be addressed by each review discipline.

The meeting was concluded at 12:30 p.m. There were no unresolved issues or discussion points.

/S/

Patrick Guinn, Project Manager
Minutes preparer

Concurrence Chair:

/S/

Isagahi Chico, M.D., Medical Officer

12/18/97

0149-009

NOV 23 1999

Memo: 45-day filing review

Subject: NDA 20-571 SE1-009, CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

Submission Date: October 19, 1999

Drug Name: CAMPTOSAR® (Irinotecan HCl) Injection

Formulation & Strength: Injection, 20 mg/mL

Sponsor: Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199

Reviewer: Z. John Duan, Ph.D.

Type of Submission: New Drug Application Supplement

BACKGROUND

Irinotecan is a topoisomerase I inhibitor and a derivative of camptothecin. Pharmacia & Upjohn Company have submitted this supplemental NDA to seek an approval for irinotecan (when given in combination with 5-fluorouracil (5-FU) and leucovorin (LV)) as first-line therapy for patients with metastatic colorectal cancer.

In support of the application, the applicant has submitted two pivotal phase III studies and one supporting pharmacokinetic study, Study 0007.

Section 6 of the NDA contains two study reports and 8 related literature publications and references. The two studies are listed as a tabular summary in the **Appendix**. In addition, summaries regarding bioanalytical assay descriptions and validations are also presented.

The studies demonstrate that the pharmacokinetics of irinotecan and its active SN-38 metabolite are not substantially altered by coadministration of 5-FU and LV. However, there is no information about the influences of other components on the pharmacokinetics of 5-FU.

RECOMMENDATION

The Human Pharmacokinetics and Bioavailability section of this NDA appears to be

filable from Clinical Pharmacology and Biopharmaceutics perspective. However, we would like to request the following information from the applicant.

1. Full reports for the studies submitted, such as study M/6475/0007 and the Phase I European clinical and pharmacokinetic study, including original protocol, clinical output and adverse events, etc.
2. Information regarding the influences of other components in the combination therapy on the pharmacokinetics of 5-FU.
3. Information regarding the pharmacokinetic differences among the three dosing regimens listed in the DOSAGE AND ADMINISTRATION Section of the proposed package insert.
4. Detailed assay descriptions and validation reports specific to the studies submitted, i.e. study M/6475/0007 and the Phase I European clinical and pharmacokinetic study.

JSI
Atiqur Rahman, Ph.D. 11/23/99
Date

JSI
Z. John Duan, Ph.D. 11/23/99
Date

Team Leader
Division of Pharmaceutical Evaluation I

Reviewer
Division of Pharmaceutical Evaluation I

- CC: NDA 20-571 original
HFD-150 Division File
HFD-150 L Slaybaugh
HFD-150 I Chico
HFD-850 L Lesko
HFD-860 M Mehta, A Rahman, J Duan
HFD-340 Vishwanathan
CDR Biopharm

ITEM 13 & 14
PATENT INFORMATION AND CERTIFICATION

1. **Active Ingredient** Irinotecan hydrochloride
2. **Strengths** 20 mg/mL
(100 mg/5 mL and 40 mg/2 mL)
3. **Tradename** CAMPTOSAR® Injection
4. **Dosage Form** Injection
Route of Administration Intravenous
5. **Applicant Firm Name** Pharmacia & Upjohn
6. **NDA Number** 20-571
7. **Approval Date** June 14, 1996 (original NDA)
8. **Patent Information** Irinotecan hydrochloride is claimed *per se* in United States Patent 4,604,463, which expires August 20, 2007
9. **Patent Certification** Pharmacia & Upjohn hereby certifies that irinotecan hydrochloride is claimed *per se* in United States Patent 4,604,463 which expires August 20, 2007

Exclusivity Checklist

NDA: sNDA20-571				
Trade Name: Camptosar® Injection				
Generic Name: irinotecan hydrochloride injection				
Applicant Name: Pharmacia & Upjohn				
Division: Oncology Drug Products HFD-150				
Project Manager: Brenda J. Atkins				
Approval Date: April 20, 2000				
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	X
b. Is it an effectiveness supplement?	Yes	X	No	
c. If yes, what type? (SE1, SE2, etc.)	SE1			
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	X	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.				
Explanation:				
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:				
Explanation:				
d. Did the applicant request exclusivity?	Yes		No	X
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?				
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
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	X
if yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	X
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (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.	Yes		No	
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	Yes	X	No	

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.					
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).					
Drug Product	Camptosar® (irinotecan)				
NDA #	20-571				
Drug Product					
NDA #					
Drug Product					
NDA #					
2. Combination product.			Yes	No	X
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 <u>any one</u> 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).					
Drug Product					
NDA #					
Drug Product					
NDA #					
Drug Product					
NDA #					
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.					
PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS					
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	X	No
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.					
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			Yes	X	No

conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?				
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCKS.				
Basis for conclusion:				
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	X
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	X
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	X
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 #: 0038				
Investigation #2, Study #: V303				
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	X
Investigation #2	Yes		No	X
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:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
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	X
Investigation #2	Yes		No	X
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:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
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 #1 0038				
Investigation #2 V303				
Investigation #3				
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	Yes	X	No	
IND#:				
Explain:				
Investigation #2 V303	Yes		No	X
IND#:				
Explain: Study done in Europe not under IND				
Investigation #3	Yes		No	
IND#:				
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		No	
IND#:				
Explain:				
Investigation #2 V303	Yes	X	No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
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	X
If yes, explain:				

Signature of PM/CSO

Date:

Signature of Division Director

Date:

cc:

Original NDA

Division File

HFD-93 Mary Ann Holovac

/S/ April 17, 2000

/S/ Deputy Director 4/24/2000

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	<u>20571</u>	Trade Name:	<u>CAMPTOSAR (IRINOTECAN HCL TRIHYDROTE) IV</u>
Supplement Number:	<u>9</u>	Generic Name:	<u>IRINOTECAN HCL</u>
Supplement Type:	<u>SE1</u>	Dosage Form:	<u>INJ</u>
Regulatory Action:		Proposed Indication:	<u>FIRST LINE THERAPY IN TREATING PATIENTS WITH METASTATIC COLORECTAL CANCER</u>

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy Inadequate for ALL pediatric age groups
Formulation Status
Studies Needed
Study Status

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER,
BRENDA ATKINS

BS/
Signature

April 17- 2000
Date