## Reviews / Information Included in this NDA Review.

<table>
<thead>
<tr>
<th>Review Type</th>
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<tr>
<td>Approval Letter</td>
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<td>Approvable Letter</td>
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<td>Final Printed Labeling</td>
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<td>Medical Review(s)</td>
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<td>EA/FONSI</td>
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<td>Pharmacology Review(s)</td>
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<td>Statistical Review(s)</td>
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<td>Microbiology Review(s)</td>
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<td>Clinical Pharmacology/ Biopharmaceutics Review(s)</td>
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<td>Administrative Document(s)</td>
<td>X</td>
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<tr>
<td>Correspondence</td>
<td>X</td>
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<tr>
<td>Bioresearch Monitoring</td>
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</table>
Trade Name: Camptosar Injection

Generic Name(s): (irinotecan hydrochloride injection)

Sponsor: Pharmacia & Upjohn Company

Agent:

Approval Date: January 15, 1998

Indication: For the treatment of patients with carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU based therapy.
CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-571/S-006

Approval Letter(s)
N 20-571/S-006

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

Attention:  John S. Walker
Regulatory Manager

Dear Mr. Walker:

Please refer to your supplemental new drug application dated July 18, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Camptosar Injection (irinotecan hydrochloride injection).

The User Fee goal date is for this application is January 21, 1998.

The supplemental application provides for the addition of a new chiral HPLC method to determine the enantiomeric purity of the active ingredient and which will also serve as an identification test for the finished product. Additionally, the supplement provides for tightening of the impurity specifications in response to the commitment outlined in the approval letter of June 5, 1997, allowing marketing of the 2 mL fill presentation.

We have completed the review of this supplemental application and it is approved as of the date of this letter.

However, we request you submit complete analytical data, such as a certificate of analysis, proof of structure, etc., on the (R)-enantiomer reference material as an NDA supplemental new correspondence.

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

Sincerely yours,

Rebecca H. Wood, Ph.D.
Chemistry Team Leader
Division of Oncology Drug Products, (HFD-150)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

KHW 1-15-98
cc: Orig. NDA 20-571
    Div. File/HFD-150
    HFD-150/RHWood
    HFD-150/RPBarron
    HFD-150/PQuinn
    HFD-150/JSimmons
    HFD-358/JCook

Drafted by: RBarron/January 14, 1997
Final:

Approved (AE) (AP)
CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-571/S-006

Chemistry Review(s)
CHEMIST'S REVIEW

1. ORGANIZATION
   HFD-150 DODP

2. NDA NUMBER
   20-571

3. NAME AND ADDRESS OF APPLICANT (City and State)
   Pharmacia & Upjohn Company
   7000 Portage Road
   Kalamazoo, MI 49001-0199

4. AF NUMBER

5. SUPPLEMENT (S) NUMBER(S) DATES(S)

6. NAME OF DRUG
   Camptosar® Injection

7. NONPROPRIETARY NAME
   Irinotecan hydrochloride injection

8. SUPPLEMENT PROVIDES FOR:
   1) a new chiral HPLC method, with validation data, to determine enantiomeric purity and serve as an identification test and 2) new tighter impurity specifications for the drug product. This supplement also fulfills the commitments outlined in the approval letter dated 5-JUN-1997 for SCP-003 for the marketing of a 2 mL fill vial.

9. AMENDMENTS DATES

10. PHARMACOLOGICAL CATEGORY
    Antineoplastic agent

11. HOW DISPENSED
    RX __ OTC ___

12. RELATED IND/NDA/DMF

13. DOSAGE FORM(S)
    Injection

14. POTENCY
    20 mg/mL

15. CHEMICAL NAME AND STRUCTURE
    (4S)-4,11-dihydropyranol[3',4',6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)dione hydrochloride hydrate

   See USAN for structure

16. RECORDS AND REPORTS
    CURRENT YES NO
    REVIEWED YES NO

17. COMMENTS
    See REVIEW NOTES on Page 2 & ff.

18. CONCLUSIONS AND RECOMMENDATIONS
    Approval is recommended. However, the applicant should provide complete information per the draft letter on the (r)-enantiomer standard utilized in the new chiral method.

cc:
   Orig. NDA 20-571
   HFD-150/Div File
   HFD-150/P Guinn
   HFD-150/RBarron
   HFD-150/RWood
   R/D init. by

19. REVIEWER NAME
    Robert P. Barron

   SIGNATURE

   DATE COMPLETED 1/13/96
CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-571/S-006

Administrative/Correspondence
May 1, 1998

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
Supplemental Correspondence to S-006

Dear Sir or Madam:

Please refer to our supplement (S-006) dated July 18, 1997, which added a chiral HPLC method to determine the enantiomeric purity of the active ingredient. The assay also serves as an identification test for the finished product. Please also refer to your approval letter of January 15, 1998 for supplement 006 which requested additional analytical data on the method.

The additional analytical work has now been completed. The attached summary and study reports provide documentation on the chemical structure and chiral assignment of the (R)-enantiomer, and also summarize the basis for purity assignment of the reference material. This information supports the continued use of lot ___ as a reference material for the chiral assay, with an assigned purity of ___.

If you have questions related to this submission, please contact me at ___ or address correspondence to mailstop 0636-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

John S. Walker
Regulatory Affairs Manager

JSW:SEH
Enclosures

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

Telephone (616) 835-4000
Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001
Attention: John S. Walker
Regulatory Affairs Manager

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Camptosar Injection
NDA Number: 20-571
Supplement Number: S - 006
Date of Supplement: July 18, 1997
Date of Receipt: July 25, 1997

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research, HFD-150
Attention: Document Control Room - 17B-20
5600 Fishers Lane
Rockville, MD 20857

Patrick Quinn
Chief, Project Management Staff
Division of Oncology and Pulmonary Drug Products
July 18, 1997

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)

Supplement

Dear Sir or Madam:

Please refer to your Approval Letter of June 5, 1997 for a new 2 mL fill presentation of Camptosar Injection. Please also refer to our facsimile of June 4, 1997 and to our letter of June 10, 1997 in which we committed to submit information in conjunction with approval of the new presentation. The Approval Letter states this information should be submitted as a supplement for prior approval.

As committed to in our previous correspondence, validation data for the chiral HPLC assay (TA 0716) are provided in Attachment 1. The technical report of Attachment 1 demonstrates that TA 0716 is suitable for use as a limits test for determination of the chiral purity of Camptosar Injection. The assay produces adequate resolution of the (R)-enantiomer of irinotecan hydrochloride for the drug peak as well as formulation components. The method was also shown to be linear over a range of the limit level. Finally, the limit of detection is about than the registration limit for the (R)-enantiomer.

We have also committed to propose new impurity registration specifications. Attachment 2 contains proposed impurity limits which decrease the allowable levels of Total Impurities, as well as the individual impurities
If you have any questions regarding the contents of this submission, please contact me at _______. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

[Signature]

John S. Walker
Regulatory Manager
Regulatory Affairs

JSW:law
Field Copy Statement

In accord with CFR §314.70(a), this is to certify that a field copy of this Chemistry, Manufacturing and Controls section/supplement to NDA 20-571 dated July 18, 1997 has been provided to the Detroit District Office.

PHARMACIA & UPJOHN COMPANY

[Signature]
John S. Walker
Regulatory Manager
Regulatory Affairs
SUMMARY

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**PUBLIC HEALTH SERVICE**  
**FOOD AND DRUG ADMINISTRATION**

**USER FEE COVER SHEET**

*Reports Clearance Officer, PHS*  
Hubert H. Humphrey Building, Room 215-B  
200 Independence Avenue, S.W.  
Washington, DC 20201

*Att.: FDA*

Please DO NOT RETURN this form to either of these addresses.

*See Instructions on Reverse Before Completing This Form.*

<table>
<thead>
<tr>
<th>1. PRODUCT NAME</th>
<th>CAMPTOSAR Injection</th>
</tr>
</thead>
</table>

5. **DOES THIS APPLICATION CONTAIN CLINICAL DATA?**  
   - [ ] YES  
   - [X] NO  
   **IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.**

6. **USER FEE I.D. NUMBER**

7. **LICENSE NUMBER/IND NUMBER**

3. **IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.**
   - [ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92  
   - [ ] AN INSULIN PRODUCT SUBMITTED UNDER 506  
   - [ ] THE APPLICATION IS SUBMITTED UNDER 505(b)(2)  
   - [ ] FOR BIOLOGICAL PRODUCTS ONLY  
   - [ ] A CRUDE ALLERGENIC EXTRACT PRODUCT  
   - [ ] AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT  
   - [ ] BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92  
   - [ ] AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

9. **a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION?**  
   - [ ] YES  
   - [ ] NO  
   **(See reverse if answered YES)**

   **b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?**  
   - [ ] YES  
   - [ ] NO  
   **(See reverse if answered YES)**

---

**This completed form must be signed and accompany each new drug or biologic product, original or supplement.**

**SIL.**  
**Signature of Authorized Company Representative**

Daniel G. Mannix, Ph.D.

**Title**  
**Director, Regulatory Affairs**

**Date**

7/18/97

ORM FDA 3397 (12/93)
### Application to Market a New Drug for Human Use or an Antibiotic Drug for Human Use

**Title 21, Code of Federal Regulations, 314**

**NOTE:** No application may be filed unless a completed application form has been received (21 CFR Part 314).

**NAME OF APPLICANT**
Pharmacia & Upjohn Company

**ADDRESS**
7000 Portage Road
Kalamazoo, Michigan 49001

**DATE OF SUBMISSION**
May 1, 1998

**TELEPHONE NO.** (Include Area Code)
(616) 833-8263

**NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER** (if previously issued)
20-571

#### DRUG PRODUCT

<table>
<thead>
<tr>
<th>ESTABLISHED NAME (e.g., USP/USAN)</th>
<th>PROPRIETARY NAME (if any)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan Hydrochloride Injection</td>
<td>CAMPTOSAR® Injection</td>
</tr>
</tbody>
</table>

**CODE NAME (if any)**
- CPT-11
- U-101440E

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

**DOSEAGE FORM**
Injection

**ROUTE OF ADMINISTRATION**
Intravenous

**STRENGTH(S)**
20 mg/mL

#### PROPOSED INDICATIONS FOR USE

Treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy.

#### INFORMATION ON APPLICATION

**TYPE OF APPLICATION (Check one)**
- [ ] THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50)
- [ ] THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

**NAME OF DRUG**

**HOLDER OF APPROVED APPLICATION**

**TYPE SUBMISSION (Check one)**
- [ ] PRESUBMISSION
- [ ] ORIGINAL APPLICATION
- [ ] RESUBMISSION
- [ ] AN AMENDMENT TO A PENDING APPLICATION
- [ ] SUPPLEMENTAL APPLICATION

**SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(3)(ii))**

**PROPOSED MARKETING STATUS (Check one)**
- [ ] APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx)
- [ ] APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

---

**IND Nos:** 35229

**DMF Nos:** blank
USER FEE DATA ENTRY/VALIDATION FORM

NDA #20-5711 DOCUMENT ID/LETTER DATE DF-0000 7-18-87
APPLICANT NAME: Pharmacia & Upjohn
PRODUCT NAME: Camptosar Injection

FORM MUST BE COMPLETED ASAP

1. **YES**  User Fee Cover Sheet Validated?

   NOTE TO DOCUMENT ROOM:
   PLEASE MAKE THE FOLLOWING CHANGES TO THE COMIS DATA ELEMENTS

   _______________________________________________________________
   _______________________________________________________________
   _______________________________________________________________
   _______________________________________________________________
   _______________________________________________________________

   2. **YES NO**  CLINICAL DATA?
   [Check YES if contains study reports or literature reports of what are
   explicitly or implicitly represented by the applicant to be adequate and well
   controlled trials. Clinical data do not include data used to modify the
   labeling to add a restriction that would improve the safe use of the drug
   (e.g., to add an adverse reaction, contraindication or warning to the
   labeling).]
   REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL
   DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION?

   3. **YES NO**  NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (OTHER THAN
   BUNDLING)? IF YES, list ALL NDA numbers, review divisions & indicate those for
   which application fees apply.
   NDA # DIVISION    FEE NO FEE
   N________ ________    FEE NO FEE

   4. **YES NO**  BUNDLING POLICY APPLIED CORRECTLY? NO DATA ENTRY REQUIRED
   FOR ELEMENT
   [Check YES if application is properly designated as one application or is
   properly submitted as a supplement instead of an original application. Check
   NO if application should be split into more than one application or submitted
   as an original instead of a supplement. IF NO, list resulting NDA numbers, and
   review divisions.]
   NDA # DIVISION    NDA # DIVISION
   N________ ________    N________ ________

   5. **P S**  PRIORITY OR STANDARD?

   6. CSO SIGNATURE/DATE 8/11/92
   SCSO CONCURRENCE SIGNATURE/DATE

COPY DISTRIBUTION: ORIGINAL TO ARCHIVAL AFTER DATA ENTRY, ONE COPY EACH TO
DIVISION FILE AND CDDB, ASSOCIATE DIRECTOR FOR POLICY HFD-5

S. CR 9/1/92
27 Page(s) Withheld

X § 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling