CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-571/S007

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 20-571/S007

Trade Name: Camptosar

Generic Name(s): (enalaprilat)

Sponsor: Pharmacia & Upjohn Company

Agent:

Approval Date: March 18, 1998

Indication: For the treatment of patients with metastatic 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/S007

Approval Letter(s)

MAR 18 1998

NDA 20-571/S-007

Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001

Attention: John S. Walker
Regulatory Affairs Manager

Dear Mr. Walker:

Please refer to your supplemental new drug application dated January 28, 1998, received January 29, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CAMPTOSAR Injection (irinotecan hydrochloride injection).

The User Fee goal date for this application is July 28, 1998.

The supplemental application (special supplement - changes being effected) with final printed labeling provides for a revised package insert with the following changes:

1. Revisions in the PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of the insert based on the study reports included in Attachment 3 that discuss the association between increased bilirubin levels and neutropenia being observed.

2. Revision in the ADVERSE REACTIONS section of the insert based on the summary of events in Attachment 4 regarding seven reports of serious colitis-type events from clinical studies with irinotecan hydrochloride.

3. In the DOSAGE AND ADMINISTRATION section of the insert, a table that clarifies the dosing interval for the first treatment course has been added.

4. The DOSAGE AND ADMINISTRATION section of the insert has been rearranged in a manner that the sponsor considers to be more useful to the prescriber and other health care providers.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for

use as recommended in the final printed labeling submitted on January 28, 1998. Accordingly, the supplemental application is approved effective on the date of this letter.

Should a letter communicating important information about this drug product (i.e., a Dear Doctor letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

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

If you have any questions, please contact Patrick Guinn, Project Manager, at (301) 827-1537.

Sincerely yours,

Robert J DeLap 3/17/98

Robert J. DeLap, M.D., Ph.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-571
HFD-150/Div. files
HFD-150/CSO/P.Guinn
HFD-150/RDeLap
HFD-150/RJustice
HFD-150/GWilliams
HFD-150/IChico
HFD-150/RBarron
HFD-150/RWood
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.

Drafted by: PGuinn/March 11, 1998

Initialed by: MPelosi for DPease/3-11-98
RBarron/3-11-98
RWood/3-12-98
IChico/3-16-98
GWilliams/3-16-98

F/T by: PGuinn/3-16-98
Final init. by: DPease/ D Pease 3-17-98

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-571/S007

Approved Labeling

Attachment 2 (4 pages)

Camptosar®
Injection

Pharmacia &Upjohn

irinotecan hydrochloride injection

For Intravenous Use Only

FPL dated 1/28/98
Submitted with SLR-007

Camptosar
Irinotecan
hydrochloride injection

0816907005

Camptosar
Irinotecan
hydrochloride injection

0816907005

WARNINGS

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

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

3. Severe myelosuppression may occur (see WARNINGS section).

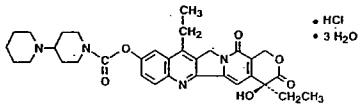
Camptosar
brand of irinotecan hydrochloride injection

DESCRIPTION

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

CAMPTOSAR is supplied as a sterile, pale yellow, clear, aqueous solution. It is available in two single-dose sizes: 2 mL-fill vials contain 40 mg irinotecan hydrochloride and 5 mL-fill vials contain 100 mg irinotecan hydrochloride. Each milliliter of solution contains 20 mg of irinotecan hydrochloride (on the basis of the trihydrate salt), 45 mg of sorbitol NF powder, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. CAMPTOSAR is intended for dilution with 5% Dextrose Injection, USP (D5W), or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion. The preferred diluent is 5% Dextrose Injection, USP.

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



Irinotecan Hydrochloride

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

CLINICAL PHARMACOLOGY

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

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

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

Pharmacokinetics

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

Over the dose range of 50 to 350 mg/m², the AUC of irinotecan increases linearly with dose; the AUC of SN-38 increases less than proportionally with dose. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of CAMPTOSAR.

Camptosar
brand of irinotecan hydrochloride injection

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

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

Dose (mg/m²)	Irinotecan					SN-38		
	C_{max} (ng/mL)	AUC_{0-24} (ng·hr/mL)	$t_{1/2}$ (hr)	V_{area} (L/m²)	CL (L/hr/m²)	C_{max} (ng/mL)	AUC_{0-24} (ng·hr/mL)	$t_{1/2}$ (hr)
125 (N=64)	1,660± 797	10,200± 3,270	5.8± 0.7	110± 48.5	13.3± 6.01	26.3± 11.9	229± 108	10.4± 3.1

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

Metabolism and Excretion: The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver. SN-38 subsequently undergoes conjugation to form a glucuronide metabolite, SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines in vitro. The disposition of irinotecan has not been fully elucidated in humans. The urinary excretion of irinotecan is 11% to 20%; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of CAMPTOSAR in two patients ranged from approximately 25% (100 mg/m²) to 50% (300 mg/m²).

Pharmacokinetics in Special Populations

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

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

Gender: The pharmacokinetics of irinotecan do not appear to be influenced by gender.

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

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

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

Drug-Drug Interactions

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

CLINICAL STUDIES

In phase 1 studies of CAMPTOSAR Injection, the maximum-tolerated dose as a single agent in the treatment of patients with solid tumors was 120 to 150 mg/m² when administered once weekly for 4 weeks, followed by a 2-week rest period. The dose-limiting toxicities were diarrhea and neutropenia. In one study, use of granulocyte colony-stimulating factor (G-CSF) appeared to increase the tolerated dose from 120 to 145 mg/m².

Data from three open-label, phase 2, single-agent clinical studies, involving a total of 304 patients in 59 centers, support the use of CAMPTOSAR in the treatment of patients with metastatic cancer of the colon or rectum that has recurred or progressed following treatment with fluorouracil (5-FU)-based therapy. These studies were designed to evaluate tumor response rate and do not provide information on actual clinical benefit, such as effect on survival and disease-related symptoms. In each study, CAMPTOSAR was administered in repeated 6-week courses consisting of a 90-minute intravenous infusion once weekly for 4 weeks, followed by a 2-week rest period. Starting doses of CAMPTOSAR in these trials were 100, 125, or 150 mg/m², but the 150 mg/m² dose proved poorly tolerated (unacceptably high rates of grade 4 late diarrhea and febrile neu-

nia). Study 1 enrolled 48 patients and was conducted under the auspices of a single investigator at several regional hospitals. Study 2 was a multicenter study conducted by the North Central Cancer Treatment Group. All 90 patients enrolled in Study 2 received a starting dose of 125 mg/m². Study 3 was a multicenter study that enrolled 166 patients from 30 institutions. The initial dose in Study 3 was 125 mg/m² but was reduced to 100 mg/m² because the toxicity seen at the 125 mg/m² dose was perceived to be greater than that seen in previous studies. All patients in these studies had metastatic colorectal cancer, and the majority had disease that recurred or progressed following a 5-FU-based regimen administered for metastatic disease.

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

	Study			
	1	2	3	
Number of Patients	48	90	64	102
Dose (mg/m²/wk x 4)	125*	125	125	100
Male (%)	54	64	50	49
Age <65 yr (%)	54	54	64	54
Ethnic Origin (%)				
White	79.2	95.6	81.3	91.2
African American	12.5	4.4	10.9	4.9
Hispanic	8.3	0.0	7.8	2.0
Oriental/Asian	0.0	0.0	0.0	2.0
Performance Status 0 (%)	60	38	59	44
Performance Status 1 (%)	38	48	33	51
Performance Status 2 (%)	2	14	8	5
Prior 5-FU Therapy (%)				
For Metastatic Disease	81.3	65.5	73.4	67.7
≤ 6 months after Adjuvant	14.6	6.7	26.6	27.5
> 6 months after Adjuvant	2.1	15.6	0.0	2.0
Classification Unknown	2.1	12.2	0.0	2.9
Primary Tumor (%)				
Colon	100	71	89	87
Rectum	0	29	11	8
...of Courses of ...SAR	3.5	3.0	3.0	3.0
...an Dose Intensity† (mg/m²/wk)	62	56	61	54
Objective Response Rate (%)‡ [95% CI]	20.8 [9.3, 32.3]	13.3 [6.3, 20.4]	14.1 [5.5, 22.6]	7.8 [2.6, 13.1]
Time to Response (median, months)	2.6	2.1	2.8	2.8
Response Duration (median, months)	6.4	5.9	5.6	6.2
Survival (median, months)	10.4	8.1	10.7	9.3

*Nine patients received 150 mg/m² as a starting dose; 2 (22.2%) responded to CAMPTOSAR.
† Total dose administered in a course ÷ 6 (number of weeks in a course).
‡ There were 2/304 complete responses; the remainder were partial responses.

In the intent-to-treat analysis of the pooled data across all three studies, 193 of the 304 patients began therapy at the recommended starting dose of 125 mg/m². Among these 193 patients, 2 complete and 27 partial responses were observed, for an overall response rate of 15.0% (95% Confidence Interval [CI], 10.0% to 20.1%) at this starting dose. A considerably lower response rate was seen with a starting dose of 100 mg/m². The majority of responses were observed within the first two courses of therapy, and all but one of the responses were observed by the fourth course of therapy (one response was observed after the eighth course). The response duration (median) for patients beginning therapy at 125 mg/m² was 5.8 months (range, 2.6 to 15.1 months).

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS

Diarrhea:

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

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

Myelosuppression:

Deaths due to sepsis following severe myelosuppression have been reported in patients treated with CAMPTOSAR. Therapy with CAMPTOSAR should be temporarily discontinued if neutropenic fever occurs or if the absolute neutrophil count drops below 500/mm³. The dose of CAMPTOSAR should be reduced if there is a clinically significant decrease in the total white blood cell count (<2000/mm³), neutrophil count (<1000/mm³), hemoglobin (<8 gm/dL), or platelet count (<100,000/mm³) (see DOSAGE AND ADMINISTRATION). Routine administration of a colony-stimulating factor (CSF) is not necessary, but physicians may wish to consider CSF use in individual patients experiencing significant neutropenia.

Pregnancy:

CAMPTOSAR may cause fetal harm when administered to a pregnant woman. Radioactivity related to ^{14}C-irinotecan crosses the placenta of rats following intravenous administration of 10 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about 3 and 0.5 times, respectively, the corresponding values in patients administered 125 mg/m²). Administration of 6 mg/kg/day intravenous irinotecan to rats (which in separate studies produced an irinotecan C_{max} and AUC about 2 and 0.2 times, respectively, the corresponding values in patients administered 125 mg/m²) and rabbits (about one-half the recommended human dose on a mg/m² basis) during the period of organogenesis, is embryotoxic as characterized by increased post-implantation loss and decreased numbers of live fetuses. Irinotecan was teratogenic in rats at doses greater than 1.2 mg/kg/day (which in separate studies produced an irinotecan C_{max} and AUC about 2/3 and 1/40th, respectively, of the corresponding values in patients administered 125 mg/m²) and in rabbits at 6.0 mg/kg/day (about one-half the recommended weekly human dose on a mg/m² basis). Teratogenic effects included a variety of external, visceral, and skeletal abnormalities. Irinotecan administered to rat dams for the period following organogenesis through weaning at doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights in the offspring. There are no adequate and well-controlled studies of irinotecan in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with CAMPTOSAR.

PRECAUTIONS

General

Care of Intravenous Site:

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

Premedication with Antiemetics:

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

Treatment of Early Diarrhea:

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

Patients at Particular Risk:

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

The use of CAMPTOSAR in patients with significant hepatic dysfunction has not been established. In clinical trials, CAMPTOSAR was not administered to patients with serum bilirubin >2.0 mg/dL, or transaminase >3 times the upper limit of normal if no liver metastasis, or transaminase >5 times the upper limit of normal with liver metastasis.

However, patients with even modest elevations in total serum bilirubin levels (1.0 to 2.0 mg/dL) have had a significantly greater likelihood of experiencing first-course grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50% versus 17.7%; $p<0.001$). Patients with abnormal glucoronidation of bilirubin, such as those with Gilbert's syndrome, may also be at greater risk of myelosuppression when receiving therapy with CAMPTOSAR. An association between bilirubin elevations and an increased risk of late diarrhea has not been observed.

Information for Patients

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

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

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

Patients should be alerted to the possibility of alopecia.

Laboratory Tests

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

Drug Interactions

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

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

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

specifically been attributed to lymphocytopenia.

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

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

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

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

Drug-Laboratory Test Interactions

There are no known interactions between CAMPTOSAR and laboratory tests.

Carcinogenesis, Mutagenesis & Impairment of Fertility

Long-term carcinogenicity studies with irinotecan were not conducted. Rats were, however, administered intravenous doses of 2 mg/kg or 25 mg/kg irinotecan once per week for 13 weeks (in separate studies, the 25 mg/kg dose produced an irinotecan C_{max} and AUC that were about 7.0 times and 1.3 times the respective values in patients administered 125 mg/m^2) and were then allowed to recover for 91 weeks. Under these conditions, there was a significant linear trend with dose for the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas. Neither irinotecan or SN-38 was mutagenic in the in vitro Ames assay. Irinotecan was clastogenic both in vitro (chromosome aberrations in Chinese hamster ovary cells) and in vivo (micronucleus test in mice). No significant adverse effects on fertility and general reproductive performance were observed after intravenous administration of irinotecan in doses of up to 6 mg/kg/day to rats and rabbits. However, atrophy of male reproductive organs was observed after multiple daily irinotecan doses both in rodents at 20 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about 5 and 1 times, respectively, the corresponding values in patients administered 125 mg/m^2) and dogs at 0.4 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about one-half and 1/15th, respectively, the corresponding values in patients administered 125 mg/m^2).

Pregnancy

Pregnancy Category D—see WARNINGS.

Nursing Mothers

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

Pediatric Use

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

ADVERSE REACTIONS

US Clinical Trials

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

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

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

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

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

Hematology: CAMPTOSAR commonly caused neutropenia, leukopenia (including lymphocytopenia), and anemia. Serious thrombocytopenia was uncommon. Neutropenic fever (concurrent NCI grade 4 neutropenia and fever of grade 2 or greater) occurred in 3.0% of the patients; 5.6% of patients received G-CSF for the treatment of neutropenia. NCI grade 3 or 4 anemia was noted in 6.9% of the patients. Blood transfusions were given to 9.9% of the patients. The frequency of grade 3 and 4 neutropenia was significantly higher in patients who received previous pelvic/abdominal irradiation than in those who had not received irradiation (48.1% versus 24.1%; p = 0.0356). Patients with total serum bilirubin levels of 1.0 mg/dL or more also have had a significantly greater likelihood of experiencing first-course grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50% versus 17.7%; p<0.001). There were no significant differences in the frequency of grade 3 and 4 neutropenia by age or gender.

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

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

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

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

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

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

Non-US Clinical Trials

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

OVERDOSAGE

In US phase 1 trials, single doses of up to 345 mg/m^2 of irinotecan injection were administered to patients with various cancers. Single doses of up to 750 mg/m^2 of irinotecan have been given in non-US trials. The adverse events in these patients were similar to those reported with the recommended dosage and regimen. There is no known antidote for overdosage of CAMPTOSAR. Maximum supportive care should be instituted to prevent dehydration due to diarrhea and to treat any infectious complications.

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

DOSAGE AND ADMINISTRATION

Starting Dose and Dose Modifications

The usual recommended starting dose of CAMPTOSAR Injection is 125 mg/m^2 (see First 6-week Dosing Schedule table). In patients with a combined history of prior pelvic/abdominal irradiation and modestly elevated total serum bilirubin levels (1.0 to 2.0 mg/dL) prior to treatment with CAMPTOSAR, there may be a substantially in-

creased likelihood of grade 3 or 4 neutropenia. Consideration may be given to starting CAMPTOSAR at a lower dose (eg 100 mg/m²) in such patients (See PRECAUTIONS). Definite recommendations regarding the most appropriate starting doses in patients who have pretreatment total serum bilirubin elevations above 2.0 mg/dL are not yet available, but it is likely that lower starting doses will need to be considered in such patients.

After initiation of treatment with CAMPTOSAR, subsequent doses should be adjusted to as high as 150 mg/m² or to as low as 50 mg/m² in 25 to 50 mg/m² increments depending upon individual patient tolerance of treatment (see Recommended Dose Modifications table).

All doses should be administered as an intravenous infusion over 90 minutes (see Preparation of Infusion Solution). The recommended treatment regimen (one treatment course) is once weekly treatment for 4 weeks, followed by a 2-week rest period. The first treatment course is shown in the following table. Thereafter, additional courses of treatment may be repeated every 6 weeks (4 weeks on therapy, followed by 2 weeks rest). Provided intolerable toxicity does not develop, treatment and additional courses of CAMPTOSAR may be continued indefinitely in patients who attain a response or in patients whose disease remains stable. Patients should be carefully monitored for toxicity.

First 6-Week Dosing Schedule for CAMPTOSAR for a Patient Experiencing No Toxicity Requiring Dosing Delays

Week (day)	1 (1)	2 (8)	3 (15)	4 (22)	5 (29)	6* (36)
Treatment (given on first day of weeks 1–4)	one 90-min IV infusion	one 90-min IV infusion	one 90-min IV infusion	one 90-min IV infusion	rest	rest

* The second 6-week course of treatment may begin week 7 (day 43).

The table below describes the recommended dose modifications during a course of therapy and at the start of each subsequent course of therapy. These recommendations are based on toxicities commonly observed with the administration of CAMPTOSAR. Therapy with CAMPTOSAR should be interrupted in grade 3 or 4 late diarrhea occurs (see PRECAUTIONS, Information for Patients) or when other intolerable toxicity is observed. Dose modifications for hematologic toxicities other than neutropenia (eg, leukopenia, anemia or thrombocytopenia, and platelets) during a course of therapy and at the start of a subsequent course of therapy are the same as recommended for neutropenia. Dose modifications for nonhematologic toxicities other than diarrhea (nausea, vomiting, etc) during a course of therapy are the same as those recommended for diarrhea. At the start of a subsequent course of therapy, the dose of CAMPTOSAR should be decreased by 25 mg/m², compared to the initial dose of the previous course, for other NCI grade 2 or by 50 mg/m² for other grade 3 or 4 nonhematologic toxicities. All dose modifications should be based on the worst preceding toxicity. A new course of therapy should not begin until the granulocyte count has recovered to ≥1500/mm³ and the platelet count has recovered to ≥100,000/mm³ and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicity. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing CAMPTOSAR.

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

Preparation & Administration Precautions

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

Preparation of Infusion Solution

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

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

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

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

Recommended Dose Modifications†

A new course of therapy should not begin until the granulocyte count has recovered to ≥1500/mm³, and the platelet count has recovered to ≥100,000/mm³, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing CAMPTOSAR.

Toxicity NCI Grade* (Value)	During a Course of Therapy†	At the Start of the Next Courses of Therapy† (After Adequate Recovery), Compared to the Starting Dose in the Previous Course
No toxicity	Maintain dose level	↑ 25 mg/m² up to a maximum dose of 150 mg/m²
Neutropenia		
1 (1500 to 1999/mm³)	Maintain dose level	Maintain dose level
2 (1000 to 1499/mm³)	↓25 mg/m²	Maintain dose level
3 (500 to 999/mm³)	Omit dose, then ↓ 25 mg/m² when resolved to ≤ grade 2	↓25 mg/m²
4 (<500/mm³)	Omit dose, then ↓ 50 mg/m² when resolved to ≤ grade 2	↓50 mg/m²
Neutropenic fever (grade 4 neutropenia & ≥grade 2 fever)	Omit dose, then ↓ 50 mg/m² when resolved	↓50 mg/m²
Other hematologic toxicities	Dose modifications for leukopenia, thrombocytopenia, and anemia during a course of therapy and at the start of subsequent courses of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.	
Diarrhea		
1 (2-3 stools/day > pretx‡)	Maintain dose level	Maintain dose level
2 (4-6 stools/day > pretx)	↓25 mg/m²	Maintain, if the only grade 2 tox§
3 (7-9 stools/day > pretx)	Omit dose, then ↓ 25 mg/m² when resolved to ≤ grade 2	↓25 mg/m², if the only grade 3 tox
4 (≥ 10 stools/day > pretx)	Omit dose, then ↓ 50 mg/m² when resolved to ≤ grade 2	↓50 mg/m²
Other nonhematologic toxicities		
1	Maintain dose level	Maintain dose level
2	↓25 mg/m²	↓25 mg/m²
	Omit dose, then ↓ 25 mg/m² when resolved to ≤ grade 2	↓50 mg/m²
	Omit dose, then ↓ 50 mg/m² when resolved to ≤ grade 2	↓50 mg/m²

…al Cancer Institute Common Toxicity Criteria.
… dose modifications should be based on the worst preceding toxicity.
‡ Pretreatment.
§ Toxicity.

Camptosar
brand of irinotecan hydrochloride injection

HOW SUPPLIED

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

CAMPTOSAR Injection is available in single-dose amber glass vials in the following package sizes:

2 mL	NDC 0009-7529-02
5 mL	NDC 0009-7529-01

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

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

Caution: Federal law prohibits dispensing without prescription.

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
2. AMA Council Report. Guidelines for handling parenteral antineoplastics. JAMA 1985; 253(11): 1590-2.
3. National Study Commission on Cytotoxic Exposure. Recommendations for handling cytotoxic agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.
4. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. Med J Australia 1983;1:426-8.
5. Jones RB, et. al. Safe handling of chemotherapeutic agents: a report from the Mount Sinai Medical Center. CA-A Cancer J for Clinicians, 1983; Sept./Oct., 258-63.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on handling cytotoxic and hazardous drugs. Am J Hosp Pharm 1990; 47:1033-49.
7. OSHA work-practice guidelines for personnel dealing with cytotoxic (antineoplastic) drugs. Am J Hosp Pharm 1986;43:1193-1204.

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Revised December 1997 816 907 005A
692053

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-571/S007

Administrative/Correspondence

ORIGINAL

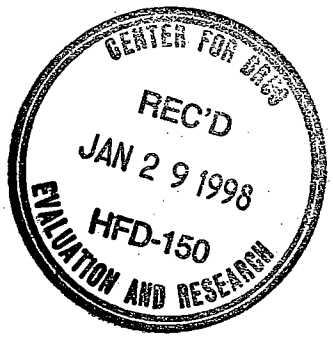
Pharmacia & Upjohn

Office of:
John S. Walker
Regulatory Affairs Manager

Mailstop: 0636-298-113
Telephone: ———
Fax: ———

NDA NO. 20-571 REF. NO. SLR-007
NDA SUPPL FOR Label

January 28, 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)

Changes Being Effected Supplement

Dear Sir/Madam:

In accordance with CFR 314.70(c) we are submitting a Changes Being Effected Supplement to the above referenced NDA. The package insert for CAMPTOSAR Injection has been revised to provide additional safety information and to further clarify dosage and administration for this product. Twenty copies of final printed labeling of the package insert (copy code 816 907 005) are provided in Attachment 1. Package insert revisions are shown in the mock-up provided in Attachment 2.

The revisions to the package insert include the following:

- An association between increased bilirubin levels and neutropenia has been observed. Attachment 3 contains the study report that discusses this association. This information affects the PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of the insert.

- Through July 1997, Pharmacia & Upjohn has received seven reports of serious colitis-type events from clinical studies with irinotecan hydrochloride. Attachment 4 contains a summary of these events. This event has been included in the ADVERSE REACTIONS section of the insert.

- Pharmacia & Upjohn has also received several inquiries regarding the Camptosar dosing regimen and the interval between dosing. For some health care providers, the current insert apparently is not entirely clear as to whether a standard course of therapy involves 42 days versus 35 days. Consequently, we have added a table that clarifies the dosing interval for the first treatment course to the DOSAGE AND ADMINISTRATION section.

- Because of the additional information added to the DOSAGE AND ADMINISTRATION section, we rearranged this section in a manner that we consider to be more useful to the prescriber and other health care providers.

Please be advised that the Agency and Pharmacia & Upjohn have had several communications regarding modifications to the company tradedress. Based on the Agency's letter of November 21, 1997, we intend to implement a modification of the tradedress as soon as possible (Attachment 5).

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 Q Walker

John S. Walker
Regulatory Affairs Manager

JSW:law

Attachments

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

Form Approved: OMB No. *0910-0297*
Expiration Date: *November 30, 1996.*

USER FEE COVER SHEET

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

PHARMACIA & UPJOHN COMPANY
7000 Portage Road
Kalamazoo, MI 49001

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

PHARMACIA & UPJOHN COMPANY
7000 Portage Road
Kalamazoo, MI 49001

Robert A. Paarlberg
Director, External Affairs

3. TELEPHONE NUMBER *(Include Area Code)*
616-833-0646

4. PRODUCT NAME
NDA 20-571 CAMPTOSAR® Injection

DOES THIS APPLICATION CONTAIN CLINICAL DATA? ☐ YES ☒ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

5. USER FEE I.D. NUMBER

7. LICENSE NUMBER/NDA NUMBER.

8. 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) *(See reverse before checking box.)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ 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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
John S. Walker	Regulatory Affairs Manager	2/11/98

FORM FDA 3397 (12/93)

16.1

USER FEE DATA ENTRY/VALIDATION FORM Ver.3(2/17/9

NDA # 20571 DOCUMENT ID/LETTER DATE 1-28-98 SLR007

APPLICANT NAME Pharmacia + Upjohn

PRODUCT NAME Camptosar

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 labelling 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 fo which application fees apply.

NDA #	DIVISION		
N_____	_____	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, an review divisions.]

NDA #	DIVISION	NDA #	DIVISION
N_____	_____	N_____	_____

5. P (S) PRIORITY OR STANDARD?

Patricia Keegan 2/12/98
6. CSO SIGNATURE/DATE

Dun Reed 2-13-98
SCSO CONCURRENCE SIGNATURE/DATE

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

16-1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-571/S-007

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, Michigan 49001

FEB 10 1998

Attention: John S. Walker
Regulatory Affairs Manager.

Dear Mr. Walker:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: CAMPTOSAR (Irinotecan Hydorchloride Injection)

NDA Number: 20-571

Supplement Number: S-007

Date of Supplement: January 28, 1998

Date of Receipt: January 29, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on March 30, 1998 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

(if via U.S. Postal Service)

FDA/CDER
Division of Oncology Drug
Products, HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

(if via courier)

FDA/CDER
Division of Oncology Drug Products,
HFD-150
1451 Rockville Pike
Rockville, Maryland 20852

Sincerely,

Patrick Griesmer

for Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products, HFD-150
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-571/S-007
HFD-150/Div. Files
HFD-150/CSO/

filename: C:\WPWIN61\TEMPLATE\FDA\N20571

SUPPLEMENT ACKNOWLEDGEMENT

MAR 11 1998

CSO REVIEW OF LABELING

NDA 20-571/SLR-007 (Special Supplement-Changes Being Effected with FPL)

Drug: Camptosar (irinotecan hydrochloride injection)

Applicant: Pharmacia & Upjohn

Submission Date: **January 28, 1998**

Receipt Date: **January 29, 1998**

Review Date: **March 10, 1998**

Provisions of Special Supplement - Changes Being Effected SLR-007 with FPL:

This January 28, 1998 submission provides a revised package insert with the following changes:

1. Revisions in the PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of the insert based on the study reports included in Attachment 3 that discuss the association between increased bilirubin levels and neutropenia being observed.

2. Revision in the ADVERSE REACTIONS section of the insert based on the summary of events in Attachment 4 regarding seven reports of serious colitis-type events from clinical studies with irinotecan hydrochloride.

3. In the DOSAGE AND ADMINISTRATION section of the insert, a table that clarifies the dosing interval for the first treatment course has been added.

4. The DOSAGE AND ADMINISTRATION section of the insert has been rearranged in a manner that the sponsor considers to be more useful to the prescriber and other health care providers.

Review and Discussion:

The revisions as outlined in Attachment 2, have been made based on the information provided in the attachments of this supplement. The following revisions were outlined in Attachment 2:

1. In the PRECAUTIONS section, under Patients at Particular Risk subsection, a third paragraph has been added as follows:

   However, patients with even modest elevations in total serum bilirubin levels (1.0 to 2.0

mg/dL) have had a significantly greater likelihood of experiencing first-course grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50% versus 17.7%; $p<0.001$). Patients with abnormal glucoronidation of bilirubin, such as those with Gilbert's syndrome, may also be at greater risk of myleosuppression when receiving therapy with CAMPTOSAR. An association between bilirubin elevations and an increased risk of late diarrhea has not been observed.

2. In the ADVERSE REACTIONS section, under the Gastrointestinal subsection, the following statement has been added as follows:

   Colonic ulceration, sometimes with gastrointestinal bleeding, has been observed in association with administration of CAMPTOSAR.

3. In the ADVERSE REACTIONS section, under the Hematology subsection, the following statement has been added as follows:

   Patients with total serum bilirubin levels of 1.0 mg/dL or more also have had a significantly greater likelihood of experiencing first-course grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50% versus 17.7%; $p<0.001$).

4. In the DOSAGE AND ADMINISTRATION section, the following has been deleted:

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

   Has been replaced with the following:

   The usual recommended starting dose of CAMPTOSAR Injection is 125 mg/m^2 (see First 6-week Dosing Schedule table). In patients with a combined history of prior pelvic/abdominal irradiation and modestly elevated total serum bilirubin levels (1.0 to 2.0 mg/dL) prior to treatment with CAMPTOSAR, there may be a substantially increased likelihood of grade 3 or 4 neutropenia. Consideration may be given to starting CAMPTOSAR at a lower dose (e.g., 100 mg/m^2) in such patients (See PRECAUTIONS). Definite recommendations regarding the most appropriate starting doses in patients who

have pretreatment total serum bilirubin elevations above 2.0 mg/dL are not yet available, but it is likely that lower starting doses will need to be considered in such patients.

After initiation of treatment with CAMPTOSAR, subsequent doses should be adjusted to as high as 150 mg/m^2 or to as low as 50 mg/m^2 in 25 to 50 mg/m^2 increments depending upon individual patient tolerance of treatment (see Recommended Dose Modifications table).

All doses should be administered as an intravenous infusion over 90 minutes (see Preparation of Infusion Solution). The recommended treatment regimen (one treatment course) is once weekly treatment for 4 weeks, followed by a 2-week rest period. The first treatment course is shown in the following table. Thereafter, additional courses of treatment may be repeated every 6 weeks (4 weeks on therapy, followed by 2 weeks rest). Provided intolerable toxicity does not develop, treatment and additional courses of CAMPTOSAR may be continued indefinitely in patients who attain a response or in patients whose disease remains stable. Patients should be carefully monitored for toxicity.

First 6-Week Dosing Schedule for CAMPTOSAR
for a Patient Experiencing No Toxicity Requiring Dosing Delays

Week (day)	1 (1)	2 (8)	3 (15)	4 (22)	5 (29)	6* (36)
Treatment (given on first day of weeks 1-4)	one 90-min IV infusion	one 90-min IV infusion	one 90-min IV infusion	one 90-min IV infusion	rest	rest

*The second 6-week course of treatment may begin week 7 (day 43).

Additional Changes Identified (but not noted in Attachment 2):

1. In the DESCRIPTION section, second paragraph, the following sentence has been added:

   ... aqueous solution. **It is available in two single-dose sizes: 2 mL-fill vials contain 40 mg irinotecan hydrochloride and 5 mL-fill vials contain 100 mg irinotecan hydrochloride.** Each milliliter ....

2. In the HOW SUPPLIED section, second paragraph, the following information has been added:

   ... available in single-dose **amber glass vials in the following package sizes:**
   2 mL NDC 0009-7529-02
   5mL NDC 0009-7529-01

Recommended Regulatory Action:

I have compared the FPL approved with SLR-004 March 7, 1997 with the FPL submitted January 28, 1998. I have noted, in this review, the revisions that were made to the package insert. Therefore, I conclude this FPL for SLR-007 as amended is acceptable contingent on the review of the revisions by the Medical Officer and the Chemist.

Conclusion:

This final printed labeling (FPL) submitted with SLR-007 is acceptable.

3/10/98
Patrick Guinn
Project Manager

Concurrence: for
3/11/98 Dotti Pease
Chief Project Manager

Isagani Mario Chico 3/16/98
Isagani Chico, M.D.
Medical Officer

Robert Barron
Chemist

Attachments: FPL approved with SLR-004 3-7-97
FPL submitted 1-28-98 with SLR-007

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