CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-571 SE8-021

Drug name:	CAMPTOSAR
Generic name:	Irinotecan
Formulation:	20 mg/ml solution for intravenous injection
Adult Indication:	Metastatic carcinoma of the colon or rectum
Pediatric Indication:	None
Current Submission:	Pediatric Supplement
Applicant:	Pfizer (agent for Pharmacia and Upjohn) 235 East 42nd Street New York NY 10017
OCPB Division:	Division of Pharmaceutical Evaluation I (HFD-860)
OND Division:	Division of Oncology Drug Products (HFD-150)
Submission Dates:	22-Dec-2003, 13-Feb-2004, 21-Jan-2004, 31-Mar- 2004
Primary Reviewer:	Roshni Ramchandani, Ph.D.
Pharmacometrics Team Leader:	Joga Gobburu, Ph.D.
Team Leader:	Brian Booth, Ph.D.
Type of Submission:	NDA-Supplemental

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1. Executive Summary

Irinotecan hydrochloride (CPT-11, CAMPTOSAR) is a prodrug derivative of camptothecin, an alkaloid obtained from plants such as the *Camptotheca acuminata* tree. Camptothecins are inhibitors of topoisomerase I.

In June 1996, the Food and Drug Administration (FDA) first approved irinotecan, under subpart H regulations for accelerated approval for the second-line treatment of patients with recurrent or progressive metastatic carcinoma of the colon or rectum. Subsequently, full approval was granted for the second-line treatment of metastatic colorectal cancer in October 1998. In April 2000, the FDA approved the use of irinotecan in combination with 5-FU and leucovorin, for first-line therapy for metastatic colorectal cancer.

The current submission includes phase 1 and phase 2 studies evaluating the safety, effectiveness and pharmacokinetics of irinotecan in pediatric patients with a range of malignancies. Six clinical studies (four phase 1 studies and two phase 2 studies) form the basis for full compliance with the CAMPTOSAR Written Request for Pediatric Studies, issued by the FDA on October 30, 2000. These trials provide information regarding the safety and pharmacokinetics (PK) of irinotecan using 3 different schedules of administration and document the activity of irinotecan in a range of pediatric malignancies. Two of the phase I studies evaluated daily x 5, q 3 weeks schedule (POG 9571 and P9871). Another study evaluated a [daily x 5] x 2, q 3 weeks (St. Judes Study). Schedule. A fourth study evaluated a schedule similar to the adult schedule of weekly x 4, q 6 weeks (H6957). For the two phase 2 trial the daily x 5, q 3 weeks schedule and [daily x 5] x 2, q 3 weeks were studied. The applicant met the requirements of the written request and Pediatric exclusivity was granted to the applicant on March 11, 2004.

Results of the pharmacokinetic analyses of irinotecan and its metabolites showed considerable variability in peak concentrations (Cmax) and area under the concentration curve (AUC) following single IV infusions of irinotecan at doses ranging from 50 mg/m^2 to 125 mg/m^2. As in adults, irinotecan appears to be metabolized to an active metabolite, SN38 (300 to 1000 fold more active than the parent), via carboxylesterase and to inactive metabolites, APC and NPC, via CYP 3A4. The mean ($\pm$ SD) clearance of irinotecan from 2 studies were 16.2 ($\pm$ 6.7) L/h/m^2 and 17.3 ($\pm$ 4.6) L/h/m^2. Concomitant use of enzyme-inducing anticonvulsants (EIACs) resulted in a significantly lower exposure to SN38, where there was a 67-70% reduction in dose-adjusted Cmax and AUC in patients receiving EIACs (n=5) compared to patients who were not receiving any anticonvulsants (n=13), although the data are limited.

Exploratory analysis conducted by the applicant did not show any correlations between irinotecan or SN38 exposure and measures of effectiveness (response rates) or toxicity (incidence of severe diarrhea or neutropenia). Exposure-response analysis of the data across all 6 studies conducted by the reviewer showed a trend for increased incidence of

severe (grade 3 or 4) diarrhea and severe (grade 3 or 4) neutropenia with an increase in exposure (AUC) of SN38 in pediatric solid tumor patients. However, this was not statistically significant. These trends were consistent with data in adult patients. A comprehensive characterization of the exposure-toxicity relationship would be critical in targeting of optimal exposures in future studies.

The phase 2 studies included in this supplemental application did not show effectiveness following irinotecan treatment in children with CNS and non-CNS solid tumors. The applicant is not recommending the use of irinotecan in children, however they would like to include information about the pharmacokinetics and safety of irinotecan in the label. The Office of Clinical Pharmacology and Biopharmaceutics recommends that information on the pharmacokinetics in the pediatric population should be included in the label.

1.1 Recommendations

1. There appears to be a correlation between the incidence of severe (grade 3 or 4) diarrhea and SN38 AUC as well as severe (grade 3 or 4) neutropenia and SN38 AUC. However, this relationship was not statistically significant. Pharmacokinetic data was not collected in the majority of the patients. Knowledge of the exposure-toxicity relationship for irinotecan and SN38 would be critical in targeting optimal exposures (b)(4)----------

2. Genotypic differences in UGT1A1, a phase 2 enzyme involved in the glucuronidation of SN38, can result in a decreased rate of elimination of SN38 leading to elevation of SN38 levels and an increased risk of severe toxicity in patients with the less-efficient isoform. Thus, we recommend that you evaluate the relationship between UGT1A1 genotypes on the exposure of SN38 as well as on toxicity:

    (In existing data collected from the phase 2 trial already conducted and/or (b)(4)----------

3. Labeling Changes for Irinotecan (#1)

<u>Current Applicant Label</u>

PRECAUTIONS

Pediatric Use

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

(b)(4)----------

(b)(4)----------

FDA Proposed Labeling:

The following text should be included under the 'PRECAUTIONS' section under the 'Pediatric Use' subsection.

(b)(4)----------

Current Applicant Label

CLINICAL PHARMACOLOGY
Pharmacokinetics in Special Populations
Pediatric

~~*Pediatric:* Information regarding the pharmacokinetics of irinotecan is not available.~~

b)(4)----------

(b)(4)

FDA Proposed Labeling:

The applicant proposed text under the 'CLINICAL PHARMACOLOGY' section in the 'Pharmacokinetics in Special Populations' subsection under 'Pediatric' from lines 117 to 129 in the annotated proposed label, should be deleted.

1.2 Phase IV Commitments

None (not applicable).

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The pharmacokinetics of irinotecan and its metabolites were examined in six studies (four phase 1 and two phase 2 studies) conducted in pediatric solid tumor (including CNS tumors) patients. Results of the PK analyses show considerable variability in peak concentrations and AUC following single IV infusions of irinotecan at doses ranging from 50 mg/m^2 to 125 mg/m^2. The PK of irinotecan and SN38 showed substantial inter-patient and intra-patient variability as observed in adults. As in adults, irinotecan appears to be metabolized to an active metabolite, SN38, via carboxylesterase and to inactive metabolites, APC and NPC, via CYP 3A4.

The mean ($\pm$ SD) clearance of irinotecan from 2 studies (phase 1 study H6957 and phase 2 study P9761) were 16.2 ($\pm$ 6.7) $L/h/m^2$ and 17.3 ($\pm$ 4.6) $L/h/m^2$, and mean elimination

half-life was 3.9 and 4.7 hours, respectively. The clearance of irinotecan was correlated with body size metrics (body weight and body surface area) in pediatric patients, and did not appear to differ between male and female patients or between patients who had been heavily pretreated vs. those who had been less-heavily pretreated prior to irinotecan treatment. Concomitant use of enzyme-inducing anticonvulsants (EIACs) resulted in a significantly lower exposure to SN38, where there was a 67-70% reduction in dose-adjusted Cmax and AUC in patients receiving EIACs (n=5) compared to patients who were not receiving any anticonvulsants (n=13). The significance of this interaction and labeling recommendations for the use of anticonvulsants in combination with irinotecan will be addressed in another supplement (s022) submitted by the applicant.

Exploratory analysis conducted by the applicant did not show any correlations between irinotecan or SN38 exposure and measures of effectiveness (response rates) or toxicity (incidence of severe diarrhea or neutropenia). Exposure-response analysis of the data across all 6 studies conducted by the reviewer also does not indicate a significant correlation between incidence of severe (grade 3 or 4) diarrhea or severe (grade 3 or 4) neutropenia and exposure (AUC) of SN38 in the pediatric solid tumor patients. However, the proportion of pediatric patients with grade 3 and 4 diarrhea as well as grade 3 and 4 neutropenia appears to increase with an increase in SN38 AUC. This is in accordance with data in adult patients. A comprehensive characterization of the exposure-toxicity relationship would be critical in targeting of optimal exposures in future studies. The Agency recommends that the applicant collect PK data, using optimal sparse sampling for an appropriate duration post-dose, to ensure reliable estimation of SN38 AUC in all future studies. The collected data should be analyzed to examine the exposure-response relationship for measures of toxicity of irinotecan.

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Roshni Ramchandani, Ph.D.
Clinical Pharmacology Reviewer
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation I

Concurrence:

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Brian Booth, Ph.D.
Acting Clinical Pharmacology Team Leader
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation I

Concurrence:

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Joga Gobburu, Ph.D.
Pharmacometrics Team Leader
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation I

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/s/

Brian Booth

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