CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-671/S-004

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CAMERON

Clinical Pharmacology and Biopharmaceutics NDA Review

NDA 20,671/004 **Submission Date:** December 5, 1997

Type of Submission: Supplemental NDA for efficacy

Drug Name: Hycamptin® (topotecan HCl) MAY 29 1998

Formulation: Injectable 4 mg (free-base) single-dose vial

Sponsor: SmithKline Beecham Pharmaceuticals
Philadelphia , PA

Reviewer: Lydia V. Kieffer, Pharm.D.

SYNOPSIS

This efficacy supplement was submitted by the sponsor to support the use of topotecan for the treatment of patients with small cell lung cancer after failure of first-line chemotherapy. Topotecan is currently approved for the treatment of patients with metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy. The same dose and regimen used for ovarian cancer (1.5 mg/m^2 per day via a 30 minute intravenous infusion on days 1 to 5 of a 21-day cycle) will be used for the sought indication.

New information provided in section 6 of the NDA include: methodology of assays to include a one-step assay used in the small cell lung cancer population pharmacokinetic study; updated information on the metabolism of topotecan; and population pharmacokinetics in the targeted population (study 181). Four assays were submitted however, only one will be reviewed in this report (100MND/1) because it was the assay utilized by the sponsor in the analysis of topotecan for the population pharmacokinetic analysis (study 181). The new metabolism information will not be discussed in this review. Those results were from a study in the rat and dog to investigate the biotransformation of oral dosing; which has no relevance in this submission because the injectable form of topotecan is indicated. Two separate pharmacokinetic analysis were performed on the data in study 181: one by The Eastern cooperative Oncology Group (ECOG), which performed this study and used a pharmacokinetic/pharmacodynamic relationship approach, and the other by the sponsor in the form of a population modeling pharmacokinetic analysis approach in which different covariates were explored to evaluated their effect on the fit of the final pharmacokinetic model.

Analytical Methods

Pharmacokinetic Study in Targeted Population

A phase II open-label, multicentre study (U.S. and South Africa) in chemotherapy and radiation therapy naïve patients with extensive small cell lung cancer was conducted to evaluate the efficacy and toxicity of topotecan (administered as 2 mg/m^2/day over a 30 minute infusion X 5 days every 3 weeks) as an induction regimen followed by salvage chemotherapy with etoposide plus cisplatin. A secondary objective was designed to find topotecan pharmacokinetic correlates with toxicity, response, and various physiologic and demographic characteristics to include hepatic and/or renal function. Thirty-three patients underwent plasma sample collection for pharmacokinetic analysis.

Plasma samples of topotecan were obtained on day 1 of cycle 1. Sample times were at baseline (immediately prior to the first dose on day 1); 15 minutes after the start of the 30 minute infusion; and at eight, fifty, and 300 minutes after the end of the infusion. Two pharmacokinetic evaluations of the study were performed; one by ECOG, and the other by the sponsor. ECOG analysis included pharmacokinetic parameter estimations performed for AUC and Cmax for total topotecan, topotecan lactone in plasma, and topotecan lactone in tissue. The sponsor performed a pharmacokinetic population analysis of the study in which plasma samples were assayed for total topotecan only.

The ECOG's analysis resulted in the following observations: survival fractions of WBC and ANC seemed to correlate with AUC and Cmax of total topotecan and topotecan lactone in plasma; there seemed to be a trend between platelet count survival fraction and all the pharmacokinetic variables; and there appeared to be no correlation between response and the pharmacokinetic variables. It was unclear what assay methodology was used for the analysis of this portion of the pharmacokinetics.

The sponsor's pharmacokinetic model utilizing the NONMEM program was parametized for systemic clearance (CL), volume of the central compartment (V1), inter-compartmental clearance (Q), and volume of the tissue compartment (V2). A combined constant coefficient of variation (CCV) and an additive error model were representative of the random residual error. An exponential error model best described inter-individual variability.

The final model was best described as two-compartment model with zero order input and first order elimination from the central compartment for topotecan. Final values for the model (Table 12) are attached in the appendix. See figure 11 of the appendix for the distribution of the six estimated pharmacokinetic parameters. Skewness to the right for distributions of AUC and Cmax of topotecan lactone in tissue were observed which the sponsor believes may have been due to "out-liers" and may be an artifact of the pharmacokinetic model used. Removal of outlier data points resulted in a significant reduction in the objective function (drop of 108.599) with a minor improvement in parameter precision for all model parameters. However, the model describing residual error was not improved .

Covariates with significant impact on topotecan pharmacokinetics were systemic clearance (0.476 L/min) correlation with creatinine clearance, and volume of distribution at steady-state (94.4 L) in the peripheral compartment (V2) correlating to weight. Differences in the clearance and volume of distribution at steady-state were observed between the SCLC patients and the ovarian population (CL = 0.28 L/min, and V_{ss} = 60-70L) previously submitted in the original NDA. However, phase I findings reported previously (CL = 0.23 to 0.467 L/min, and V_{ss} = 70 to 80 L) were similar to the SCLC pharmacokinetic parameters in question and the SCLC population parameters (i.e. half-life = 2.3 hours) were still within the range reported in the labeling for the ovarian population (half-life = 2 to 3 hours). The sponsor believes that the differences may be partially explained by the differences in prior therapy received between the two populations. The ovarian population had received prior chemotherapeutic therapy versus a chemotherapy and radiation therapy naïve population for the SCLC study. As a result in similarity, the sponsor is not seeking any changes to the Clinical Pharmacology and pharmacokinetic portion of the labeling. Please refer to appendix for additional study information.

Reviewer's comments:

The sponsor believes that the differences observed in the clearance and volume of distribution at steady-state may be partially explained by the differences in prior therapy received between the two populations. The ovarian population had received prior chemotherapeutic therapy versus a chemotherapy and radiation therapy naïve population for the SCLC study. However, other factors that may explain or may be accountable for the observed disparity are ***1)*** *the use of different assays for the SCLC study from the original NDA accounting for the differences in estimation of clearance and volume of distribution at steady-state;* ***2)*** *the difference in topotecan doses from this study (was 2 mg/m^2/day over a 30 minute infusion X 5 days every 3 weeks as an induction regimen) and the current dose (1.5 mg/m^2 per day via a 30 minute intravenous infusion on days 1 to 5 of a 21-day cycle) in the labeling (which is intended to stay the same) may explain the disparity of the pharmacokinetic differences observed (i.e., clearance);* ***3)*** *or it may be due to the gender differences in the studies (22 males and 11 females for this study versus the ovarian study from the previous submission) having an impact on the pharmacokinetic differences observed.*

COMMENTS

General:

1. It was unclear what assay methodology was used for ECOG's pharmacokinetic analysis of this study. Four assays were submitted with the application; but which, if any were used for ECOG's portion of the pharmacokinetic analysis is not stated. Please clarify which assay or assays were used to quantitate total topotecan and topotecan lactone in plasma and in tissue.

2. The original NDA had insufficient data to provide a dosage adjustment recommendation in patients with severe renal impairment. The sponsor should submit adequate information to address that population and deficiency.

Labeling:

- No changes to the label seem necessary from the observations of the new pharmacokinetic data in the SCLC population.

RECOMMENDATION

The submission has adequately addressed the Office of Clinical Pharmacology and Biopharmaceutics' requirements. The general and labeling comments need to be sent to the sponsor.

/S/ 5-29-98

Lydia V. Kieffer, Pharm.D.
Reviewer
Division of Pharmaceutical Evaluation I

/S/ 5/29/98

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cc: Orig 20,671
HFD-150/Division File
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