CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-588/s016

Drug name:	Gleevec®
Generic name:	Imatinib mesylate
Formulation:	100 and 400mg tablets
Pediatric Indication:	Treatment of newly diagnosed pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia.
Current Submission:	Pediatric supplement
Applicant:	Novartis Oncology One Health Plaza East Hanover, NJ 07936
OCP Division:	Division of Clinical Pharmacology V (HFD-860)
OND Division:	Division of Drug Oncology Products (HFD-150)
Submission Dates:	27-March-2006, 06-June-2006, 07-July-2006
Primary Reviewer:	Julie M. Bullock, Pharm.D.
Pharmacometrics Team Leader:	Joga Gobburu, Ph.D.
Team Leader:	Brian Booth, Ph.D.

I. Executive Summary

The sponsor collected intensive pharmacokinetic samples in the phase 1 studies STI571A 0103 and STI571A 03 001, and sparse sampling was gathered in study STI571A 2108. Both phase 1 studies evaluated a range of doses in pediatric patients to obtain a dose that had similar exposure to adults. The phase 2 study, enrolled 53 pediatric patients with newly diagnosed CML at a dose of 340 mg/m^2/day. Thirty-three of these patients were included in the pharmacokinetic sparse sampling. With the completion of the three trials above the applicant has met the requirements of the Pediatric Written Request.

The results of the intensive PK sampling in studies 0103 and 03 001 indicate that the pharmacokinetics in pediatrics in adults are similar based on similar values for clearance (pediatrics 6.38 ± 48% L/hr/m^2, adult 5.78 ± 32% L/hr/m^2). Sparse samples were collected in the Phase 2 study and were analyzed using a one-compartment model previously developed for adult patients. Briefly, the pharmacokinetic parameters estimated from the model were comparable to those found in previous studies with pediatric patients with intensive PK sampling.

No significant relationships were found between measures of Gleevec exposure and grade 3/4 toxicity.

The incidence of grade 3/4 toxicities was generally less than the incidence of grade 1/2 toxicities for all the common adverse events reported. No significant relationships were found between measures of Gleevec exposure (AUC, average dose, and average dose intensity) and measures of response (cytogenetic and hematologic response) in this population. This may be due to the limited number of patients enrolled and the number of responses that were missing, not assessed, or not available at 3 months when cytogenetic response was assessed.

A. Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the Clinical Pharmacology section of NDA 21-588 and finds it to be acceptable. No labeling changes were made to the clinical pharmacology sections of the label, and no additional changes are being added by OCP.

B. Phase IV Commitments

None.

C. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Sparse samples were collected on the first day of treatment for 33 of the 55 patients enrolled in the Phase 2 study. The pharmacokinetics were evaluated using a one-compartment model with first order elimination which had previously been used to characterize adult pharmacokinetics. The clearance and volume models used body weight (in kg), hemoglobin (Hgb), and white blood cell count (WBC) for covariates as these had previously been found to be significant covariates in the adult models. The Cmax and AUC estimated from the data in the current submission were similar to those

reported in studies 0103 and 03 001.

The results of the current study also confirmed the findings of the previous review, namely that, the AUC_{0-24} of a 340 mg/m^2/day dose in pediatrics provides comparable exposure to the approved adult dose of 400 mg/day.

Exposure response analyses were performed with these data to characterize the relationships between AUC_{0-24} or average daily intensity and effectiveness (cytogenetic response, hematological response) or toxicity. Based on the limited data available, no significant correlation between AUC or dose intensity of Gleevec and the endpoints of effectiveness or toxicity could be concluded.

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