CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
BPCA SUMMARY REVIEW

NDA	19-537
Date of Submission	August 4, 2003
Brand name	Cipro®
Generic name	Ciprofloxacin HCl
Applicant	Bayer
Type of submission	Pediatric Supplemental NDA

1. Executive Summary

Bayer was issued a Written Request (WR) in October 2001 to satisfy the pediatric exclusivity requirements. As part of the WR, an efficacy and safety study was conducted in pediatric patients from 1 to 17 years of age with complicated urinary tract infections (cUTI) and/or acute pyelonephritis. In addition, a pharmacokinetic substudy of ciprofloxacin in these pediatric patients with cUTI and/or acute pyelonephritis was also conducted. The proposed indication is treatment of cUTI and/or acute pyelonephritis.

A population PK (POPPK) analysis was conducted using data from a total of 6 pediatric studies. These 6 studies included the efficacy study conducted to satisfy the WR requirement along with 5 other studies performed in pediatric patients with varied disease diagnoses. These studies included a variety of infections such as urinary tract infection, lower respiratory tract infection, skin and soft tissue infection, severe sepsis, acute invasive diarrhea and cystic fibrosis. The POPPK analysis was conducted with the following objectives:

- To estimate typical population pharmacokinetic parameters for ciprofloxacin in pediatric patients.
- To identify covariate, demographic and clinical factors that are significant predictors of variability in ciprofloxacin pharmacokinetic parameters.
- To provide a dosing recommendation for pediatric patients.

Plasma ciprofloxacin concentration-time data were available in 357 pediatric patients. The age of these patients ranged from 0.27 to 16.9 years. The body weight of these patients ranged from 4.2 to 73.5 kg. One hundred and five patients were male and 252 patients were female. Twenty-eight out of 357 patients had a history of cystic fibrosis and 207 out of 357 patients were being treated for complicated urinary tract infection / acute pyelonephritis. Population pharmacokinetic analyses were performed with the NONMEM software using the First-Order Conditional Estimation (FOCE) method.

The pharmacokinetics of oral ciprofloxacin was described by a two-compartment model with first order absorption and absorption lag time. The POPPK analysis identified cystic fibrosis, body weight and creatinine clearance as the significant covariates for the apparent clearance (CL/F) of ciprofloxacin. In addition, the effect of cystic fibrosis on the absorption rate constant (k_a) was also found to be a significant covariate.

The predicted exposure of ciprofloxacin derived from the population PK analysis compared to the exposure observed in adults is given in Table 1.

Table 1. Predicted ciprofloxacin exposure derived from the population PK analysis compared to the exposure observed in adults

Creatinine Clearance (mL/min)	Pediatric dose	Predicted AUC (μg-h/mL)	Adult dose	Observed AUC (μg-h/mL)
>50	15 mg/kg BID (po)	11.8	500 mg BID (po)	13.7
>50	9 mg/kg BID (iv)	12.1	400 mg BID (iv)	12.7

The population based estimates for ciprofloxacin half-life ($T_{1/2}$) ranged from approximately 4 to 5 hours in pediatric patients and was similar to that reported in adults (approximately 4 hours).

Based on the results of the efficacy study, the dosing regimen proposed for the treatment of cUTI and/or acute pyelonephritis is: (a) oral ciprofloxacin at doses of 10 to 20-mg/kg every 12 hours (maximum of 1500-mg per day) or (b) intravenous ciprofloxacin at doses of 6 to 10-mg/kg every 8 hours (maximum of 1200-mg per day) or intravenous ciprofloxacin at doses of 6 to 10-mg/kg every 8 hours (maximum of 1200-mg per day) followed by oral ciprofloxacin at doses of 10 to 20-mg/kg every 12 hours (maximum of 1500-mg per day).

2. Phase IV Commitments

No Phase IV studies are requested.

3. Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation III has reviewed the information included in the sNDA for ciprofloxacin in pediatric patients and has found it to be acceptable. The following dosing recommendation for ciprofloxacin in pediatric patients for use in complicated UTI infections and/or acute pyelonephritis, as used in the pivotal Phase III trial of Complicated Urinary Tract Infection (Study 100169), is proposed:

(a) oral ciprofloxacin at doses of 10 to 20-mg/kg every 12 hours (maximum of 1500-mg per day) or (b) intravenous ciprofloxacin at doses of 6 to 10-mg/kg every 8 hours (maximum of 1200-mg per day) or intravenous ciprofloxacin at doses of 6 to 10-mg/kg every 8 hours (maximum of 1200-mg per day) followed by oral ciprofloxacin at doses of 10 to 20-mg/kg every 12 hours (maximum of 1500-mg per day).

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