CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA:	**19,851 SE5 028 Submission Date:** April 28 2003
Drug Name:	Lotensin (benazepril hydrochloride) tablets
Applicant:	Novartis
Submission:	Pediatric Exclusivity Supplement
Reviewer:	Elena V. Mishina, Ph.D.

Background

Reference is made to the approved NDA 19,581 for Lotensin (benazepril hydrochloride) tablets. Benazepril and benazeprilat (active metabolite) inhibit angiotensin-converting enzyme (ACE). Lotensin® (benazepril hydrochloride) has been approved for the treatment of hypertension in the adult human population.
The applicant is seeking to obtain Pediatric Exclusivity for Lotensin, to evaluate the efficacy and safety of benazepril in pediatric population, and to provide the labeling changes related to the benazepril use in children. The recommended starting dose of Lotensin (benazepril HCl) in children is 0.2 mg/kg (up to a maximum of 10 mg) once daily. Dosage should be adjusted according to blood pressure response.

Current Submission

With this Application, NDA 19,851 SE5-028, the sponsor included 4 studies. These were:

Study Protocol US02 "A Pharmacokinetic Study to Assess the Comparative Bioavailability of a Pediatric Formulation of Lotensin (10 mg oral suspension) vs Lotensin (10 mg) Tablets",

Study Protocol US03A1 "A single center, single dose, open-label study to evaluate the pharmacokinetics of benazepril in pediatric subjects",

Study Protocol US03 "A multicenter open-label, steady state study to evaluate the pharmacokinetics of benazepril in pediatric subjects", and

Study Protocol US01 "A multicenter study to evaluate the pharmacokinetics, dose-response, efficacy, and safety of benazepril in pediatric subjects".

Summary of Findings

Study US02 compared a pediatric formulation of benazepril with the currently marketed tablet formulation in healthy adults. Lotensin ® (10 mg) administered orally as an extemporaneously compounded suspension was compared to Lotensin ® (10 mg) administered in tablet formulation. For benazepril, the 90% CI for the ratio of Cmax, AUC(0-t), and AUC(0-inf) were 86.72%- 111.95%, 84.38%-101.84%, and 81.48%-99.55%, respectively. For benazeprilat, the 90% CI for the ratio of Cmax, AUC(0-t), and AUC(0-inf) were 88.94%-112.49%, 90.8%-106.49%, and 89.69%-104.47%, respectively. Therefore, the 90% CI for geometric mean ratios of natural-log transformed Cmax, AUC(0-t), and AUC(0-inf) were all within the 80%-125%

range and the test and reference formulations were found to be bioequivalent with respect to both benazepril and benazeprilat.

The pharmacokinetics of benazepril and its active metabolite benazeprilat was determined following the administration of a single oral dose of benazepril hydrochloride in pediatric subjects (Study US03a1). Healthy subjects received the dose of Lotensin as a suspension (age range from 0.7 to 5.5 years) or a 5 or 10 mg tablet (age range from 6.5 to 16.9 years). The dose was individualized in the range of 0.1-0.5 mg/kg. The mean CL values of benazepril for all four pediatric groups were: 2.1, 3.8, 2.1, and 2.9 L/hr/kg respectively. These CL values were larger but of the same order of magnitude as calculated for adults after a 10 mg of Lotensin, Study US02 (1.45 L/hr/kg). The mean CL values for benazeprilat for all four pediatric groups were: 0.284, 0.364, 0.258, and 0.169 L/hr/kg. These CL values were larger than calculated for adults (0.132 L/hr/kg). The group of school age children had benazeprilat clearance twice faster than adults and adolescents' clearance values were 27% larger than the adults' clearance values.

Study US03 determined the pharmacokinetic of benazepril in pediatric patients at steady state. Four plasma samples were taken per patient at the specified time window of 4 hours covering the interval of 24 hours after dosing at Day 5. Population modeling was performed on the sparse plasma concentrations data separately for benazepril and benazeprilat. The sponsor concluded that the only significant covariate affecting clearance for both benazepril and benazeprilat is age. The model development is lacking the important part of model validation: after covariate adding one by one into the model, the sponsor did not perform deletion of the covariates from the model which was assumed to be final. Therefore, the appropriateness of the final model is not convincing. The graphic exploration of the data by the reviewer indicates that clearance depends on body weight. Body weight corrected clearance of benazepril was 10.7, 9.3, 6.3, and 3.4 L/hr/kg for each of four pediatric groups respectively. These values are higher than the same values calculated for the healthy children and for adults and are in agreement with the lower plasma concentrations profiles of benazepril found in the pediatric patients in comparison with healthy children. Therefore, the same dose of Lotensin produced lower exposure to benazepril in pediatric patients compared to healthy children and adults. Given the wide therapeutic index of benazepril, there will be no safety concern to use this drug in pediatric patients. Body weight corrected clearance of benazeprilat was 0.209, 0.363, 0.351, and 0.166 L/hr/kg for each of four pediatric groups respectively. These values were comparable with the same for healthy children. The plasma benazeprilat profiles were similar for both studies in pediatric patients and healthy children. The exposure to benazeprilat is about 10 times larger than the exposure to benazepril. Additionally, benazeprilat is much more potent ACE inhibitor benazepril. Therefore, although the exposure to benazepril was found to be smaller in pediatric patients, it might not compromise the efficacy of Lotensin.

The report of Study US01 did not include any of the pharmacokinetic data because the sponsor was not able to collect plasma samples from the patients in this study.

Elena Mishina, Ph. D.
Clinical Pharmacology Reviewer
Division Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

RD Initiated by Patrick Marroum, Ph. D.

CPB Briefing was held on October 9, 2003

Attendees: Drs. Sahajwalla, Marroum, Mishina

cc list: NDA 21,437, MehulM, MarroumP, MishinaE, HFD 110 BIOPHARM

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Elena Mishina
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Patrick Marroum
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