Division of Cardio-Renal Drug Products (HFD-110)

Medical Review

NDA No.: 19851 (S-028)
Drug Name: Lotensin (bezanepril hydrochloride)
Sponsor: Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
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EXECUTIVE SUMMARY

Introduction

Lotensin® (benazepril HCl, tablets 5, 10, 20 and 40 mg strength), NDA 19851, is approved for the treatment of hypertension in adults.

This medical review evaluates the results of two pediatric studies submitted by the sponsor, Novartis Pharmaceuticals Corporation in response to a written request for studies in pediatric hypertensive patients for benazepril HCl. The sponsor provided full reports of the following studies: Protocol CIB824E US01 entititled "A multicenter study to evaluate the pharmacokinetics, dose-response, efficacy, and safety of benazepril in pediatric subjects" (the pharmacokinetic substudy of this protocol was not completed); and protocol CIB824E US03 entitled "A multicenter open-label, steady state study to evaluate the pharmacokinectics of benazepril in pediatric subjects"

The main review focused on the pivotal study of safety and efficacy (CIB824E US01) and the results from the open-label steady state pharmacokinectic study (CIB824E US03) were evaluated for additional data on safety.

Summary/Conclusion

The sponsor selected trial design D in which patients were force titrated to maximal tolerated doses and then randomly withdrawn to lower doses or placebo to test the efficacy of benazepril HCl as an antihypertensive drug in subjects within the pediatric age group. The CIB824E US01 is a three-phase study. It has a dose-escalation phase, a randomized, double blind, placebo-controlled phase and an-open label extended phase. It used a dose- ranging design. Doses of benazepril HCl evaluated in the treatment of pediatric subjects (age 6 to 16 years) with

hypertension included 0.1 mg/kg, 0.2 mg/kg, 0.3 mg/kg and 0.6 mg/kg. In this study the sponsor used a tablet formulation of benazepril with the following strengths: 5 mg, 10 mg, 20 mg, and 40 mg. In the first phase, study medication was titrated up from 5 or 10 mg (low dose) to 20 or 40 mg (high dose). The benazepril HCl doses used were selected by determining the per kilogram dose of benazepril for a 70 kg adult for both the lowest and highest doses approved for the treatment of hypertension. In the forced titration phase doses given depended on weight. Subjects 50 kg or lighter were titrated up from 5 to 20 mg and subjects weighing greater than 50 kg were titrated up from 10 to 40 mg in a matter of four weeks.

One hundred and seven subjects with hypertension were enrolled in this study. 58.9% were males and 41.1% were females, 43% were 7 to 12 years of age and 57% were 13 to 16 years of age. The distribution of races between placebo and benazepril-treated subjects in the double-blind placebo-controlled phase was as follows: White 57.6% vs. 52.6.2%, Black 21.1% vs. 26.3%, Oriental 6.1% vs. 5.3%, and Other 15.2% vs. 15.8%. Hypertension was defined as mean SeSBP or mean SeDBP equal to or greater than the 95th percentile for age, sex, and height while off antihypertensive medication during the screening period.

Eighty five subjects who completed and responded to the maximal dose of 40 mg of benazepril in the forced titrated phase were enrolled in the randomized, double-blind, withdrawal, placebo-controlled phase. Sixty six were randomized to one of three doses of benazepril HCl and 19 were randomized to placebo. Twenty four received low dose (0.1 or 0.2 mg/kg), 23 received medium dose (0.2 or 0.3 mg/kg), and 19 received high dose (0.3 or 0.6 mg/kg). All were treated in a double- blind manner for two weeks. The placebo group and the overall treated group are not significantly different. Changes in trough SeSBP between visit 5 (the first day on randomized regimen) and visit 7 (the end of the randomized phase), with an assessment for dose response was the primary response variable. The pre-specified analysis was an intent- to- treat. The withdrawal phase provided data to establish that there was a positive effect of benazepril on blood pressure in pediatric patients. In the placebo group the mean changes in SeSBP and SeDBP were greater than changes in the groups randomized to low, medium or high doses. Changes in SeSBP were + 7.5 mm Hg in placebo vs. + 4 mm Hg in the low dose group, + 1 mm Hg in the medium dose group and + 2.2 mm Hg in the high dose group. Changes in the same direction and of the same magnitude were observed for SeDBP. The difference in SeSBP change between placebo and medium dose was statistically significant. The difference in SeDBP change was statistically significant between placebo and both the medium and high doses. The test for dose-response showed positive slopes for both SeSBP and SeDBP but they were not statistically differentiable from zero ($p= 0.053$ and $p= 0.071$ respectively). In the placebo group the mean changes in SeSBP and SeDBP represented a statistically significant ($p = 0.023$ and $p = 0.010$ respectively) withdrawal effect. These changes were 5.18 mmHg and 5.16 mm Hg greater than the mean changes seen in the overall benazepril group.

The CIB824E US03 study assessed the PK of benazepril in fifty seven subjects ranging between one month and 16 years of age including 3 infant/toddlers, 9 preschool children, 19 school age children and 26 adolescents. There were 31 males and 26 females, and 32 were Caucasians, 19 were Black and 6 were Other. Doses ranged between 0.2 and 0.5 mg/kg in subjects six years of age or younger and these were administered as a suspension, and between 0.1 and 0.5 mg/kg in

older subjects in the form of tablets. Subjects received benazepril for at least five days with the goal of reaching a steady state distribution.

Safety outcomes in the sponsor's report included reported adverse events, changes in vital signs, examination findings and laboratory test abnormalities. The safety data provided in this submission have been derived from studies CIB824E US01 and CIB824E US03. Data from the CIB824E US01 pivotal study was the major contributor to our understanding of the safety profile of benazepril HCl in subjects 7 to 16 years of age. Safety was evaluated across all phases of the pivotal study for a total of 32 weeks. Four weeks in the force titrated open-label phase, two weeks in the randomized withdrawal, double-blind placebo-controlled phase and 26 weeks in long-term open-label extension phase. Seventy subjects volunteered to participate in the open-label extended phase and 64 completed it. In the randomize withdrawal phase of the study, 66 and 19 subjects were exposed to benazepril HCl and placebo, respectively. Comparison to placebo was meaningless because the duration of this phase was too short and the placebo group did not undergo a washout period.

No deaths were reported during the studies. The results demonstrated a number of safety concerns including angioedema and liver function changes. There were a total of 9 (8.4%) that discontinued as a result of adverse events. These AEs include one angioedema, one liver function abnormality, one blood creatinine abnormality, two kidney transplant rejections, one aggravated cough, one rash, one hypertensive crisis and one hyperactivity and insomnia.

Nine subjects (8.4%) developed serious adverse events. Five of these were related to the urinary apparatus including two acute renal failure and rejection of kidney transplants, one increased creatinine in patient with history of kidney transplant and two multiple hospitalizations for urinary tract infections. The remaining four serious adverse events include a hypertensive crisis that resolved after discontinuation of benazepril, one bowel obstruction, one severe sleep apnea and one severe depression.

Seven subjects (6.5%) developed clinically significant laboratory abnormalities while they were in the study. Three of these were liver function abnormalities. From screening to Visit 5 (the end of forced titration phase), the laboratory tests for which the percentage of subjects with a laboratory test that worsened exceeded the percentage of subjects whose values improved by at least 5% were AST (16.7% worsened; 7.6% improved), BUN (7.6% worsened; 1.5% improved), hematocrit (10.6% worsened; 1.5% improved), hemoglobin (10.6% worsened; 4.5% improved), and RBC count (12.1% worsened; 4.5% improved).

There were also two cases with severe increase in creatine phosphokinase. One was observed in a patient with musculoskeletal and connective tissue disease, and the other in a patient with increased liver enzymes and a history of cardiac disorders including mitral insufisciency.

Other adverse events include the ones commonly seen in association with the use of ACE inhibitors such as cough (9% in the dose escalation phase) and rash (6.5%) including two cases with urticaria. Others include headache, dizziness and GI disorders.

The effect of benazepril on growth, development and maturation in the studied population was not explored, and the safety profile of benazepril in hypertensive patients within the pediatric age groups 0 months to 6 years have not been studied in a design to assess safety in this age category.

In conclusion, the withdrawal phase showed that there was a positive drug effect in that a statistically significant difference in changes in SeSBP and SeDBP was demonstrated between placebo and the overall group that received benazepril (p=0.023 and p=0.010 respectively).

Benazepril seems to be associated with a number of safety concerns. It is difficult to conclude whether it was tolerated by pediatric subjects at the same level as it was by adults or whether it was tolerated as well as Monopril®[1] (another ACE inhibitor) was reported to have being in children. Benazepril in the adult population was studied in comparison to placebo. Monopril was studied in a somewhat healthier pediatric population (included patients who have high normal blood pressure) and it was assessed in comparison to placebo in a four-week long first phase of the pivotal study (protocol CV118-028). The placebo controlled phase of benazepril was only two weeks long and it followed a dose escalation phase that exposed study subjects to high doses without a washout period which rendered the placebo group not applicable for comparison of safety.

Given the lack of information confirming the diagnosis of some adverse events (the two cases with symptoms of angioedema that remained in the study), the lack of evidence of causality between benazepril and some of the observed adverse events (e.g. liver function abnormalities), and the small sample size studied and the absence of a comparative placebo group, the reviewer concludes the program under review is insufficient for the evaluation of safety of benazepril in the pediatric population.

RECOMMENDATION

Because of the aforementioned safety concerns and the insufficiency of the available data in evaluating the safety of benazepril in the pediatric population, this supplemental application is approvable with the condition that the sponsor further evaluates the incidence of the observed adverse events and the nature of the relationship of these adverse events to benazepril in pediatric patients.

[1] Monopril™,NDA 19-915/S-037, review by Dr. Juan Carlos Pelayo

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Salma Lemtouni

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