Medical Review

NDA No.: 19-915 (S-037)
Drug Name: Monopril® (fosinopril sodium)
Sponsor: Bristol-Myers Squibb
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EXECUTIVE SUMMARY
INTRODUCTION
Monopril® (fosinopril sodium, tablets of 10, 20 and 40 mg strength), NDA 19-915, is approved for the treatment of hypertension and the management of heart failure as adjunctive therapy when added to conventional therapy.

This medical review evaluates the results from two pediatric studies submitted by the sponsor, Bristol-Myers Squibb, in response to a written request for studies in pediatric hypertensive patients for fosinopril sodium. The sponsor provided full reports for the following studies: Protocol CV118-027 entitled "The Pharmacokinetics of Fosinopril in Children and Adolescents" a pharmacokinetics study of fosinoprilat, the active metabolite of fosinopril, and Protocol CV118-028 entitled "Study of Blood Pressure Reduction with Fosinopril in Children and Adolescents" a clinical study to assess the antihypertensive effect of fosinopril.

SUMMARY/CONCLUSIONS
The study Protocol CV118-028 had a randomized, double blind, placebo-controlled and dose-ranging design. Doses evaluated of fosinopril sodium, in the treatment of children and adolescents (age 6 to 16 years) with hypertension and high-normal blood pressure, included 0.1 mg/kg, 0.3 mg/kg and 0.6 mg/kg. In this study the sponsor used a tablet formulation of fosinopril with the following strengths: 1.25 mg, 2.5 mg, 5 mg, 10 mg, and 20 mg. Study medication was titrated up to the assigned target dose after the first week of study treatment. The fosinopril sodium doses that were used in this dose-ranging study were selected by determining the per kilogram dose of fosinopril for a 70 kg adult for both the lowest and highest doses approved for the treatment of hypertension. The sponsor selected trial design C, i.e., placebo withdrawal phase, to test the efficacy of fosinopril sodium as an antihypertensive drug in subjects within the pediatric age group. Thus, the study evaluated the effectiveness of a range of fosinopril doses in the treatment of male (65.6%) and female (34.4%) children [6 to 12 years of age, n=140 (55%)] and adolescents [13 to 16 years of age, n=113 (45%)] with hypertension or high-normal BP. The distribution (%) of races between placebo- and fosinopril-treated subjects in the double-blind placebo-controlled phase of study protocol CV118-028 was as follows: White 59.1% vs. 60.2%, Black 23.6% vs. 16.7%, Asian 2.4% vs. 1.9%, Hispanic 11.0% vs. 18.5%, Native American 0.8% vs. 0.0%, and Other 3.1% vs. 2.8%. Hypertension was defined as SeSBP or SeDBP $\geq$ 95th percentile for gender, age, and height, on at least 3 sequential occasions. High-normal BP was defined as SBP or DBP $\geq$ 90th percentile and $< 95^{th}$ percentile for gender, age, and height, on at least 3 sequential occasions and with any one of the following clinical conditions: diabetes mellitus (either Type I or Type II), or positive family history of hypertension, or any other condition for which, in the opinion of the investigator, the reduction of BP would be in the best interest of the child or adolescent. Based on the above definition the hypertensive status of the randomized population was as follows: Hypertension 85.8% and High Blood Pressure 14.2%. Two hundred and fifty three subjects

were randomized to three doses of fosinopril sodium, 0.1 mg/kg (n=83), 0.3 mg/kg (n=87) and 0.6 mg/kg (n=83), and were treated in a double-blind manner for 4 weeks. Thereafter they were re-randomized in a blinded fashion either to their previous treatment or to be withdrawn to placebo for a total of two more weeks of treatment. Changes in trough SeSBP from baseline at the end of treatment, with an assessment for trend with dose (i.e., a non-zero slope with dose), was the primary response variable. The pre-specified analysis was an intent-to-treat. For SeSBP and SeDBP, the adjusted mean changes from baseline were -10.9, -11.3, and -11.9 mmHg, and -4.5, -4.2, and -5.1 mmHg, respectively. Thus after 4 weeks of treatment the three regimen groups showed adjusted mean decreases from baseline which were similar. The test for trend across these regimen groups revealed no evidence of a dose-response relationship (p=0.53 and p=0.52, respectively). Without evidence of a dose-response relationship, the withdrawal phase provided the opportunity to establish that there was a positive drug effect. In the placebo group, the adjusted mean change for SeSBP represented a statistically significant (p = 0.013) withdrawal effect, which was 3.7 mmHg greater than the mean change in the fosinopril group. The adjusted mean change for SeDBP was 1.6 mmHg higher for the placebo group than for the fosinopril group (p = 0.104). Of note, none of the individual dose groups was significantly different than placebo in the randomized withdrawal phase.

Study protocol CV118-027 assessed the PK of fosinoprilat in 43 hypertensive patients[1] from four pediatric age groups: infants and toddlers (1 month to 2 years, n=10), pre-schoolchildren (>2 years to 6 years, n=14), school-age (>6 years to 12 years, n=10) and adolescents (>12 years to 16 years, n=9). The study had a multicenter, open-label, and single-dose (0.3 mg/kg fosinopril) design. Fosinopril was administered as an oral solution of fosinopril sodium reconstituted with water and diluted with simple syrup. Cmax, and AUC increased with age. There was a marked correlation between both Cmax and AUC and age, body weight and body surface area. On average drug exposure for children up to 6 years of age were ~60% less than those seen in older children. It is not understood whether the noted difference is due to an increase in fosinoprilat clearance and/or a decrease in fosinopril absorption. Cmax and AUC values of fosinoprilat in pediatric patients from 6 to 16 years of age were comparable to those seen in adult patients receiving 20 mg of fosinopril solution. Tmax and T-Half were not significantly affected by age.

Safety outcomes in the sponsor's report included reported adverse events, changes in vital signs, physical examination findings and laboratory test abnormalities. The safety data provided in this submission have been derived from studies protocol CV118-027 and CV118-028. The safety data from the latter study, the major contributor to our understanding of the safety profile of fosinopril sodium in subjects within the pediatric age groups (age 6 to 16 years), come from the double-blind (4 weeks, n=253), double-blind placebo controlled (2 weeks, n=235), and long-term open-label extension (52 weeks) periods. In the double-blind phase of the study 105 and 127 subjects were exposed to fosinopril sodium and placebo, respectively. A total of 209 subjects were enrolled in the long-term open-label, and the mean duration of exposure to any fosinopril sodium dose was 166.9 days (ranging from 1 day to 365 days). No deaths were reported during the studies and there were no cases of angioedema. Overall, with the caveat of few patients evaluated and the short-term exposure, fosinopril appears safe and well tolerated in hypertensive patients within the pediatric age groups age 6 to 16 years, with an adverse event profile similar to that observed in adult patients with hypertension. However, whether the long-term administration of fosinopril to patients within the four pediatric age groups studied would affect their growth and development, including sexual maturation, cannot be determined from the available clinical data. In addition, the safety profile of fosinopril in hypertensive patients within the pediatric age groups 0 months to 16 years have not been studied by the sponsor.

In conclusion, albeit the clinical trial CV118-028 failed to demonstrate a dose-response relationship, the withdrawal phase provided the opportunity to establish that there was a positive drug effect in that a statistically significant difference in changes in SeSBP was demonstrated between the pooled results from

[1] Hypertensive children as determined by blood pressure consistently above the 95th percentile as defined by the 1996 update of the 1987 Task Force Report on Blood Pressure Control in Children criteria or children with blood pressure consistently above the 90th percentile with other risk factors, such as family history of hypertension, renal disease, target organ damage, diabetes mellitus Type I or bronchopulmonary dysplasia.

the fosinopril groups and placebo group (p=0.0132). Thus, the therapeutic dose range of fosinopril remains indefinable. The long-term safety of fosinopril is not adequately characterized.

RECOMMENDATIONS

Because of the aforementioned deficiencies, including those identified in the Clinical Pharmacology and Biopharmaceutics review, this supplemental application is deemed approvable.