CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

Division of Pharmaceutical Evaluation I

NDA 19-915 **SUBMISSION DATE:** November 27, 2002
Supplement S_037

MONOPRIL® (fosinopril sodium)
Pediatric tablet strengths 1.25,2.5 ,5,10 and 20 mg
Bristol-Myers Squibb
Princeton, New Jersey REVIEWER: Peter H. Hinderling, MD

TYPE OF SUBMISSION: Pediatric Exclusivity Supplement S_037 to NDA 19-915

SUBMISSIONS:

Reference is made to the approved NDA 19-915 for Monopril® (fosinopril sodium) Tablets of 10, 20 and 40mg strength. Monopril® is indicated for the treatment of hypertension and as adjunct in the treatment of congestive heart failure.

Supplement S_037 to NDA 19-915 dated November 27, 2002, includes the results of Study Protocol No. CV 118027 entitled " The Pharmacokinetics of Fosinopril in Children and Adolescents" using an oral solution of fosinopril. Also included are the results from dissolution tests performed with the pediatric tablets used in the efficacy trial in children and adolescents.

SUMMARY OF FINDINGS

Fosinopril is an ACE inhibitor and indicated for the treatment of hypertension and as an adjunct therapy for heart failure in adults. The Written Request stipulated the need for the conduct of 2 studies, an efficacy and safety trial and a PK study to obtain pediatric exclusivity for the indication hypertension. The Written Request recommended the enrollment of infants, preschool children, school children, and adolescents of black and non-black origin in the pharmacokinetic trials and the use of age-appropriate formulations. When solid dosage formulations were to be used their bioavailability relative to the marketed product was to be known.

The Company performed 2 trials. An oral solution of fosinopril (0.3mg/kg) was used for the single dose PK study that enrolled 43 hypertensive infants, preschool children, school children and adolescents. Pediatric tablets that differ in the composition from the adult tablets were used in the efficacy and safety trial. The pediatric tablets were of strength 1.25, 2.5, 5, 10 and 20mg. The Company did not perform an in vivo study to compare the pediatric tablets with adult tablets and an oral solution.

In order to link the pediatric tablets with the adult tablets and the oral solution the Company provided data of in vitro dissolution tests of all the pediatric tablets performed in water in accord with the FDA approved method for fosinopril. In addition the Company performed dissolution tests at pH 1.2, 4.5 and 6.8 with the 5, 10 and 20mg pediatric tablets and provided summary data of earlier performed in vivo bioavailability studies comparing the performance of adult tablets of strength 20mg and 40mg with that of equipotent oral solutions. Based on the information submitted the Company requests a Biowaiver for the pediatric tablets used in the efficacy and safety trial.

The PK data provided characterize the PK in the pediatric population investigated and fullfil the requirements of the Written Request. The PK data showed an age dependency of the exposure parameters Cmax and AUC, whereas t1/2 was constant. The Cmax and AUC values increased with age. An age dependent increase in bioavailability is more plausible than a decrease in clearance with age. Because the efficacy and safety trial investigated school children and adolescents, only the PK information obtained in the older pediatric groups can be used in the label. The efficacy trial showed similar antihypertensive effects of the 3 tested doses 0.1mg/kg, 0.3mg/kg and 0.6mg/kg of the drug. Given the flat dose-response relationship an adjustment of the dose in the 6-12 year old age group is not justified.

The data on the tablet composition showing proportional similarity combined with the in vitro dissolution results allow bridging of the pediatric tablets of dose strength 5,10 and 20mg to the corresponding adult tablets. The data comparing the performance of the adult tablet of 20mg strength and the oral solution show biocomparability. Thus, the pediatric tablets of strength 5,10 and 20mg are linked to the adult tablets and, via the adult tablets, also to the oral solution. However, the pediatric tablets of dose strength 1.25 and 2.5mg are not proportionally similar to any of the adult tablets. Hence their bioavailability is not linked to the adult tablets and hence to the oral solution.

The Company intends to market the adult tablets of strength 10, 20 and 40 mg for use in the pediatric population. Given the fact that the body weight of a 6 year old child may be as low as 20kg, and considering the similarity of the antihypertensive effects of doses in the range between 0.1 and 0.6mg/kg found in the efficacy and safety study, administration of a full or half 10mg adult tablet corresponds to a 0.25-0.5mg/kg dose. These lowest doses exceed the effective dose of 0.1mg/kg dose clearly. The dose strengths proposed by the Company do not allow the required flexibility in the dosing of fosinopril in the youngest and possible sickest individuals of the target pediatric population of 6-16 years.

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RD Initialed by Patrick Marroum, Ph.D._____

Briefing held 2/5/03 (Hinderling, Marroum, Mehta, Gobbaru, Nguyen, Pelayo

cc: NDA 19-915, HFD-860 (Hinderling, Mehta, Sahajwallah and CDR (Biopharm)

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/s/

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