C\LINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

Division of Pharmaceutical Evaluation I

NDA 20757 **SUBMISSION DATES**: July 30, September 2,
Supplement SE5-034 October 1, 2004
Supplement Amendment SE 5-034 BB
Avapro ® (irbesartan) Tablets
Sanofi-synthelabo c/o Bristol-Myers Squibb Company
Princeton, NJ

Reviewer: Peter H. Hinderling, MD

TYPE OF SUBMISSION: Pediatric Exclusivity Supplement SE5-034 and Supplement Amendment SE5-034 BB to NDA 20757

EXECUTIVE SUMMARY

The results of the two bioequivalence studies indicate that the 18.75 mg and the 37.5 mg film coated tablets are bioequivalent to the PS tablets of the corresponding strengths.

The evidence provided by the results of the bioequivalence studies and in vitro dissolution testing links the to be marketed FC tablets, the clinical tablets used in the dose ranging study in the pediatric target population, and the marketed Avapro® tablets.

The accuracy of the LC/MS/MS method used in the two bioequivalence studies when assessed at the highest concentration of the QC samples exceeded the 15% limit. However, it is very unlikely that the observed small bias impacted the results.
The validation report of the LC/MS/MS method used in the two bioequivalence studies is acceptable.

The earlier submitted single and multiple dose pharmacokinetic study with extensive sampling enrolled 9 school children and 12 adolescents, predominantly males of African-American origin. The dose of irbesartan administered to the children was approximately 2mg/kg. The resulting exposure values were similar to those in adults. The data of the study were reviewed by OCPB/DPE1 in 2000 and found to be appropriate and the proposed labeling acceptable. It should be noted that in the pharmacokinetic study one dose level (2.0 mg/kg) was tested whereas in the efficacy and safety study a dose range of 0.5 mg/kg – 4.5 mg/kg was evaluated.

The results of the dose ranging study in hypertensive school children and adolescents indicated that irbesartan elicits a statistically significant antihypertensive effect in a hypertensive pediatric population. Irbesartan lowered the trough sitting systolic blood

pressure (primary endpoint) and the trough sitting diastolic blood pressure statistically significantly during the up-titration phase compared to baseline and during the withdrawal phase compared to placebo. During the up-titration phase respective decreases in the systolic blood pressure from baseline of -11.7, -9.3 and -13.2 mm Hg after doses of 0.5 mg/kg, 1.5 mg/kg and 4.5 mg/kg, were observed. The corresponding decreases in diastolic blood pressure were -3.8, -3.2, and -5.6 mmHg, respectively. During the withdrawal phase the difference in systolic and diastolic blood pressure between subjects receiving the active treatment and subjects on placebo was identically small, namely -2.3 mmHg. There was no dose-response relationship observed for the effect on systolic blood pressure. The antihypertensive effect of -2.3 mmHg measured is considered therapeutically insignificant by the Cardiorenal Division. Thus, irbesartan cannot be recommended for the indication treatment of hypertension in school children and adolescents.

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