CLINICAL REVIEW

Drug name:	Avapro®
Generic Name:	Irbesartan
Formulation:	Tablets
Pediatric Indication:	Pediatric hypertension
Current Submission:	Pediatric efficacy supplement
Applicant:	Sanofi-Synethelabo c/o Bristol-Myers Squibb P.O. Box 4000 Princeton, NJ 08543-4000
OND Division:	Division of Cardio-Renal Drug Products (HFD-110)
Medical Reviewer:	Abraham M. Karkowsky, M.D., Ph.D.
Review Completion Date:	October 26, 2004

Irbesartan, an angiotensin II receptor blocker, is approved for the treatment of adult hypertension and for the treatment of nephropathy associated with Type-2 adult diabetic patients.

The current application attempts to expand the hypertension indication to the treatment of pediatric patients. The application consists of a single three-week dose-response study followed by a placebo-controlled 2-week withdrawal period in pediatric patients. For safety, there was a 6 month open-label extension of those enrolled into this study. Also submitted in this application was an analysis of adverse events in two "use" databases.

Those enrolled into the placebo-controlled study were of either gender between the ages of 6 to 16 years old (inclusive) with hypertension, defined as a sitting diastolic or systolic blood pressure $\geq 95^{th}$ percentile adjusted for age, gender and height. Patients whose blood pressure is greater than the 90^{th} percentile were eligible for enrollment if they had diabetes, a strong positive family history of hypertension or who the investigator believes treatment is in the best interest of the patient. Approximately 50% of the population was between 6 and 12 years; and 50% between 12 to 16 years. Females, who have experienced menarche and are potentially fertile, need a negative pregnancy test for enrollment.

Subjects were randomized to receive a single daily dose approximating 0.5, 1.5 or 4.5 mg/kg. The approximations were made to accommodate dosing with the currently marketed (75, 150 and 300 mf) and additional 18.75 and 37.5 mg dose strengths.

The demonstration of efficacy relied on demonstrating a positive effect on the relationship between dose and decrease in sitting systolic blood pressure. Since there was no placebo group a non-significant slope could reflect one of two possibilities. The first possibility is that the drug as administered is relatively inactive in this population. The second possibility is that the dose selection only captured the flattened portion of the dose-response curve. To differentiate between the two possibilities, the protocol allowed for a placebo-controlled withdrawal period. The anticipation is that if the dose range was poorly chosen, the difference between those randomized to ongoing therapy compared to those who were withdrawn to placebo would be statistically different. A caveat, however, is that the magnitude of difference between the placebo-withdrawn and maintained on-therapy to be quite large.

The study enrolled 318 pediatric patients with hypertension; approximately 106 patients per dose group, from sites in the Unites States, Eastern and Western Europe and the former Soviet Union. The slope for the trough sitting systolic blood pressure versus dose, the primary metric of the study was flat, indicating that none of the doses appeared to differ in their effect on sitting systolic blood pressure. Although there was a statistically significant difference comparing those remaining on treatment to those randomized to placebo (the withdrawal portion of the study), the effect size was small (-2.3 mm Hg). Since this withdrawal portion of the study was to differentiate the situation where the doses chosen reflect the flat portion of the dose response curve and reflect the maximal drug effect, the small effect upon withdrawal appears unlikely to be a true or meaningful blood pressure effect. The doses chosen for study in pediatric patients when normalized to adult weights were approximately those approved for adults.

There is, consequently, insufficient information to conclude that Irbesartan at a dose of 0.5 to 4.5 mg/kg/day (maximum dose 300 mg), as a once daily regimen, is effective in pediatric patients who are hypertensive or who are borderline hypertensive with other confounding factors (such as diabetes).

With respect to safety, there were no deaths. Of the eight adverse events leading to discontinuation during double-blind and placebo-withdrawal portions of the study, the events appear to be manifestations of vasodilation and included hypotension, syncope, headache and dizziness. There was one case of Erythema multiforme, which potentially could be related to the use of Irbesartan. A second adverse event of diabetic ketoacidosis occurred in a patient with Type-2 diabetes. With respect to overall adverse events, the most frequent were common events in this population.

Group means for laboratory values were only slightly changed. The dose-response effect in alkaline phosphatase indicates a drop in the value but inversely related to dose. Creatinine kinase was increased in all three dose groups but did not appear to decrease with re-randomization to placebo. The majority of the laboratory abnormalities of clinical significance which were documented during the double-blind, placebo-withdrawal or open label period either were subsequently shown to normalize, or per sponsor did not appear to be associated with adverse events.

Regulatory actions:

The sponsor was granted pediatric exclusivity for this study and exclusivity appears warranted. Since there is inadequate information for an indication in pediatrics and since pharmacokinetic information on a non-approved pediatric population is usually not included in applications not approved for this population, that section containing pediatric pharmacokinetics has been deleted.

Labeling:

Under (CLINICAL PHARMACOLOGY, Special Populations) the following was deleted**:**

Pediatric: The pharmacokinetics of Irbesartan were studied in hypertensive children (age 6-12, n=9) and adolescents (age 13-16, n=12) following single and multiple daily doses of 2 mg/kg (maximum dose of 150 mg per day) for 4 weeks. Accumulation with repeated doses was limited (18%) in both age groups. Clearance rates, AUC values, and C_{max} values were comparable to adults receiving 150 mg daily. Irbesartan pharmacokinetics have not been investigated in patients <6 years of age.

Under (PRECAUTIONS, Pediatric Use), the following was inserted:

Irbesartan, at a dose up to 4.5 mg/kg/day, once daily, does not appear to be useful in the treatment of hypertension in pediatric patients age 6 and above despite a dosing regimen that gives plasma concentrations of irbesartan similar to those found active in adults.

A. Recommendations:

The sponsor was granted pediatric exclusivity for this study and exclusivity appears warranted. Since there is inadequate information for an indication in pediatrics and since pharmacokinetic information on a non-approved pediatric population is usually not included in applications not approved for this population, that section containing pediatric pharmacokinetics has been deleted.

B. Phase IV Commitments:

None.

C. Summary of Clinical Findings.

The dose ranging portion of the study did not find a statistically significant effect of irbesartan at doses ranging from 0.5 to 4.5 mg/kg on sitting systolic blood pressure. The change from baseline for sitting systolic blood pressure the three dose groups was -11.7, -9.3 and -13.2 mm Hg, for the 0.5, 1.5 and 4.5 mg/kg dose groups, respectively. The p-value for slope was not significant (> 0.1). The corresponding effect for sitting diastolic blood pressure for the three doses was -3.8, -3.2 and -6.6 mm Hg.

All subjects were then randomized to a two week period, either remaining on the randomized Irbesartan dose or switched to corresponding placebo. The effect was analyzed comparing all those remaining on the dose of irbesartan with all those who were withdrawn to placebo. The placebo-subtracted differences were -2.3 mm Hg for both systolic and diastolic blood pressure, with those remaining on Irbesartan having the lower blood pressure. Since the purpose of the placebo-withdrawal period was to evaluate the blood pressure effect if the dose range that was chosen for this study only captured the flat part of a dose-response curve, the magnitude of blood pressure effect upon withdrawal would approximate the maximum effect of Irbesartan at this dose schedule. The small effect, even if real, would not make irbesartan a useful regimen for pediatric patients in the dose range of 0.5 to 4.5 mg/kg, as a single daily dose.

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Abraham Karkowsky
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