MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 12, 2005

FROM: Monika Houstoun, Pharm.D., Safety Evaluator
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THROUGH: Rosemary Johann-Liang, MD, Deputy Director
For Mark Avigan, M.D., C.M., Director
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TO: M. Dianne Murphy, M.D.
Director, Office of Pediatric Therapeutics (OPT), OIASI
Office of the Commissioner
and
Solomon Iyasu, M.D., M.P.H., Acting Deputy Director
Division of Pediatric Drug Development
Office of Counter-Terrorism and Pediatric Drug Development (OCTAP)

SUBJECT: One Year Post-Pediatric Exclusivity Postmarketing Adverse Event Review; PID# D040641
Drug: Avapro® (irbesartan) NDA# 20-757
Pediatric Exclusivity Approval Date: September 16, 2004

Executive Summary

The AERS database was searched for reports of adverse events occurring with the use of irbesartan in pediatric patients. Overall, AERS contains 2209 reports (raw count) for irbesartan. Pediatric reports represented 4 (raw count) of the total number of reports. No adverse event reports were obtained during the pediatric exclusivity period. This review did not highlight any significant safety concerns regarding the use of irbesartan in children.

Background:

Avapro (irbesartan) is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. To obtain pediatric exclusivity for Avapro, the sponsor conducted 2 studies: a multicenter, randomized, double-blind, 3 week dose ranging safety and effectiveness study of low, medium, or high doses of irbesartan in children with a placebo withdrawal period and a single-dose pharmacokinetic study in children aged 1-6 years. Only 2 subjects were enrolled before the second study was terminated. The dose ranging safety and effectiveness study

included specified age-groups (50% school aged) and a mix of black and non-black patients (10% black).

The current label includes pediatric specific information. Under Special Populations it states: 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.

In Precautions under Pediatric use it is labeled: Safety and effectiveness in pediatric patients have not been established. Pharmacokinetic parameters in pediatric subjects (age 6-16, n=21) were comparable to adults. At doses up to 150 mg daily for 4 weeks, AVAPRO (irbesartan) was well tolerated in hypertensive children and adolescents (see **CLINICAL PHARMACOLOGY: Special Populations**). Blood pressure reductions were comparable to adults receiving 150 mg daily; however, greater sensitivity in some patients cannot be ruled out (see **DOSAGE AND ADMINISTRATION: Pediatric Patients**). AVAPRO has not been studied in pediatric patients less than 6 years old.

In Dose and Administration under Pediatric Patients, the label reads: Children (<6 years): Safety and effectiveness have not been established. Children (6-12 years): An initial dose of 75 mg once daily is reasonable. Patients requiring further reduction in blood pressure should be titrated to 150 mg once daily (see **PRECAUTIONS: Pediatric Use**). Adolescent patients (13-16 years): An initial dose of 150 mg once daily is reasonable. Patients requiring further reduction in blood pressure should be titrated to 300 mg once daily. Higher doses are not recommended (see **PRECAUTIONS: Pediatric Use**).

AERS Search Results: Irbesartan

AERS Search includes all sources - U.S. & foreign

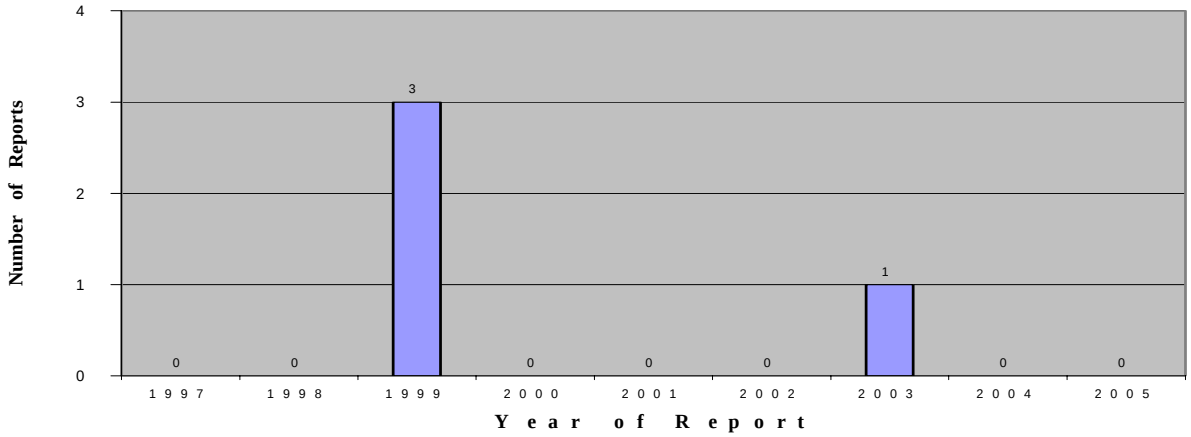
A. From marketing approval date, September 30, 1997, through AERS data cut-off date, October 16, 2005.

1. Raw counts of reports: Table 1 (parentheses denote U.S. origin report counts)

	All reports (US)	Serious(US)	Death(US)
All ages	2209 (934)	1599 (356)	126 (24)
Adults (≥17)[1]	1719 (598)	1381 (280)	109 (18)
Peds (0-16)[1]	4 (3)	3 (2)	0

[1] 482 AERS reports received without patient age reported

Figure 1: Reporting trend for pediatric reports from approval date, September 30, 1997 (bar graph of annual counts of reports):



2. Counts of top 20 reported event preferred terms for all ages, adults, and pediatric age groups. Events not described in the label are underlined.

   All ages: Renal failure acute[2] (118), hyperkalemia (116), dizziness (98), hypotension (89), drug interaction[3] (88), asthenia[4] (86), hyponatremia (85), diarrhea (80), blood creatinine increased (73), dyspnea (70), fatigue (70), malaise[5] (70), renal failure[2] (67), headache (66), hypertension (66), fall[6] (64), myalgia[7] (59), vomiting (56), confusional state (54), nausea (54)

   Adults: Renal failure acute[2] (117), hyperkalemia (98), dizziness (89), hypotension (78), drug interaction[3] (77), hyponatremia (76), asthenia[4] (73), diarrhea (69), malaise[5] (66), blood creatinine increased (64), fall[6] (62), dyspnea (59), hypertension (59), renal failure[2] (59), vomiting (53), fatigue (52), headache (51), confusional state (49), nausea (49), dehydration (46)

   Peds: Dyspnea (1), erythema multiforme[8] (1), papilloedema (1), paresthesia (1)

[2] Labeling includes Precautions for impaired renal function and Warnings for renal failure associated with fetal and neonatal injury
[3] Labeling contains Drug Interactions section noting no significant clinical pharmacokinetic or pharmacodynamic drug-drug interactions with several studied drugs
[4] Labeled for muscle weakness
[5] Fatigue is labeled
[6] Labeled for orthostatic hypotension and syncope
[7] Labeled for musculoskeletal pain, muscle cramp, and muscle ache
[8] Labeled for rash, pruritis, dermatitis, and urticaria

B. From Pediatric Exclusivity approval date, September 16, 2004 through AERS data cut-off date, October 16, 2005:

1. Raw counts of reports: Table 2 (parentheses denote U.S. origin report counts)

	All reports (US)	Serious (US)	Death (US)
All ages	660 (382)	328 (67)	30 (6)
Adults (≥17)[9]	445 (211)	271 (46)	25 (3)
Peds (0-16)[9]	0	0	0

2. Counts of top 20 reported event preferred terms for all ages, adults, and pediatric age groups. Events not described in the label are underlined.

   All ages: Dysgeusia (45), renal failure acute[2] (37), diarrhea (35), dizziness (35), drug interaction[3] (32), hyponatremia (30), hyperkalemia (25), headache (21), blood creatinine increased (20), hypotension (20), rash (20), renal failure[2] (20), myalgia[7] (19), pruritus (19), drug ineffective[10] (18), fatigue (18), malaise[5] (18), asthenia[4] (17), vomiting (17), anemia (15), blood pressure increased (15), confusional state (15), dehydration (15), dyspnea (15), hypertension (15)

   Adults: Renal failure acute[2] (37), dizziness (31), diarrhea (29), drug interaction[3] (29), hyponatremia (26), dysgeusia (22), hyperkalemia (19), hypotension (18), asthenia[4] (17), malaise[5] (17), renal failure[2] (17), vomiting (17), blood creatinine increased (15), dehydration (15), headache (15), pruritus (15), nausea (14), confusional state (13), drug ineffective[10] (13), hypertension (13), oliguria (13)

   Peds: n/a

Postmarketing hands-on review of all peds adverse event reports from all sources received during the one-year after a drug receives pediatric market exclusivity.

There were no pediatric adverse event reports found during the pediatric exclusivity period, from September 16, 2004 through October 16, 2005.

Summary

The AERS database was searched for reports of adverse events occurring with the use of irbesartan in pediatric patients. We focused on the 1-year period following the FDA approval of pediatric exclusivity for irbesartan, September 16, 2004 to October 16, 2005. There were no adverse event reports for pediatric patients during this time.

[9] 211 AERS reports received without patient age reported
[10] Labeled for hypertension

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HFD-960/Iyasu/S. Murphy/K. Phucas/D. Avant
HFD-950/D. Murphy//Crescenzi

Appendix

Limitations of the Adverse Event Reporting System (AERS)

AERS collects reports of adverse events from health care professionals and consumers submitted to the product manufacturers or directly to the FDA. The main utility of a spontaneous reporting system, such as AERS, is to identify potential drug safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

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/s/

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12/12/2005 12:50:19 PM
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