



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

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From: Monika Houstoun, Pharm.D.  
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Subject: Review of Serious Adverse Event cases in Pediatric Patients  
(follow up to 1 year Post Exclusivity BPCA review)

Drug Name(s): Benazepril (Lotensin)

Application: NDA 19-851

OSE RCM #: 2007-2126

## 1 INTRODUCTION

The Office of Pediatric Therapeutics requested a follow up review of adverse events reported in pediatric patients taking benazepril, an angiotensin-converting enzyme (ACE) inhibitor, from the AERS database. Events of interest included known labeled adverse events associated with ACE inhibitors: angioedema, cough, hypotension, renal disturbance, hyperkalemia, and fetal exposures.<sup>1,2</sup> The previous DDRE 1-year Post-Pediatric Exclusivity Postmarketing Adverse Event Review identified 2 pediatric cases; one case described hyperchloraemic metabolic acidosis with hypoaldosteronism in a child with nephrotic syndrome and the second case described a possible accidental ingestion of benazepril. The review did not highlight any significant safety concerns regarding benazepril use in pediatric patients.<sup>3</sup>

## 2 AERS SEARCH AND RESULTS

A search of AERS was performed on November 8, 2007 to identify all cases reported in those  $\leq 17$  years of age in association with benazepril use. Six reports were identified. Of these, two cases were presented in the previous OSE review<sup>3</sup>. There was one duplicate. The remaining three cases<sup>4</sup> are reviewed below.

### Congenital Abnormalities

*ISR 1899096; 1997 (France):* A mother was treated during her first pregnancy trimester with benazepril, bromazepam, prednisone, fenofibrate, verapamil, hydroxychloroquine, labetalol, lysine acetylsalicylate, calproate, and fluindione. A baby girl was delivered prematurely (gestational age not reported) via cesarean section secondary to fetal distress and bradycardia. The baby was hospitalized for one month in the neonatology unit with hypotrophy, premature jaundice, and “surfactant pulmonary troubles”. A favorable outcome was reported. A transfontanelar echography performed at 2 weeks of age showed white substance anomaly which was not “retrieved on control” one month later.

*ISR 5107887; 2006 (US):* Report received from an attorney regarding a female patient who was receiving benazepril/hydrochlorothiazide for hypertension for years and became pregnant with her first child. She continued taking benazepril/hydrochlorothiazide until she was deemed to be almost 8 weeks pregnant at which time she was prescribed methyldopa, which she continued throughout her pregnancy. She gave birth via cesarean section to a baby boy at gestational age of 36 weeks and 4 days. The baby was born with complicated life threatening heart defects including tricuspid “atresis”, transposition of great vessels, interrupted aortic arch type B, muscular ventricular septal defect, and a small right ventricle. The baby also had unilateral renal agenesis with a single dysplastic kidney. The baby died on day 19 of life; cause of death was pulmonary hemorrhage and

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<sup>1</sup> Medical pharmacology at a glance, M J Neal. Blackwell Publishing, 2005.

<sup>2</sup> Lotensin® (benazepril hydrochloride) product labeling revised 3/2007.

<sup>3</sup> 1-year Post-Pediatric Exclusivity Postmarketing Adverse Event Review, Benazepril, September 29, 2004, Daniela C. J. Saunders, PID # D030409.

<sup>4</sup> Two of the three cases were submitted prior to the 2004 OSE review pediatric exclusivity period.

congenital heart disease. No additional information about the mother, medical history or other concomitant medications was reported.

#### Other Adverse Events

*ISR 1826278; 1996 (US):* A 1 year old male received benazepril 5 mg QD for treatment of hypertension for 9 days. Increased serum creatinine and potassium were reported. This case reported an outcome of hospitalization (initial or prolonged). No additional information was provided.

### **3 DISCUSSION**

Two of the cases identified were submitted to the FDA prior to the DDRE pediatric exclusivity review period; there was only one new pediatric case submitted since August 2004. Two cases of congenital abnormalities in children born to mothers who had taken benazepril were identified; one case involved multiple concomitant medications. It is impossible to ascertain from these cases whether benazepril played a contributory role. In the remaining case, it is difficult to draw any conclusion about the use of benazepril and the adverse event while there was so little information provided. Benazepril is labeled for elevation of serum creatinine and elevation of serum potassium.

None of the cases involving pediatric patients in AERS reported angioedema, cough, or hypotension.

### **4 CONCLUSIONS AND RECOMMENDATIONS**

In conclusion, this review did not identify any new serious unexpected events associated with benazepril use in pediatric patients. We will continue to monitor reports of adverse events associated with benazepril in pediatric patients.

**Signed:**

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**Safety Evaluator**

**Concur:**

*Cindy Kortepeter, Pharm.D.*

**Safety Evaluator Team Leader**

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/s/

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