

MEMORANDUM

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

DATE: September 29th, 2004

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THROUGH: Mark Avigan, M.D., C.M.
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Office of Counter-Terrorism and Pediatric Drug Development, HFD-950

SUBJECT: One Year Post-Pediatric Exclusivity Postmarketing Adverse Event
Review, PID#D030409
Drug: Benazepril (Lotensin®), NDA#19-851
Pediatric Exclusivity Approval Date: July 2, 2003

Confidential: Contains IMS data; not to be used outside of the FDA without clearance from IMS.

Executive Summary

The AERS database was searched for reports of adverse events occurring with the use of benazepril in pediatric patients. Overall, AERS contains 1842 reports (raw count) for benazepril in all ages. Pediatric reports represented 5 (raw count) of the total number of reports. Three (raw count) of the 111 reports received during the pediatric exclusivity period, July 2, 2003 to August 2, 2004, involved pediatric patients. None of the pediatric cases reported fatal outcomes.

We reviewed 2 unique pediatric cases reported to the FDA during the pediatric exclusivity period. The first case described a hyperchloraemic metabolic acidosis with hypoaldosteronism in a child with nephrotic syndrome¹ and the second case described a possible accidental ingestion of benazepril. This review did not highlight any significant safety concerns regarding benazepril use in pediatric patients.

AERS Search Results: Benazepril

AERS search includes all sources- U.S. & Foreign

A. From marketing approval date (June 25, 1991) through AERS data cut-off date (August 2, 2004).

1. Counts of Reports: Table 1 (parentheses denote U.S. origin report counts)

Table 1: Raw counts of reports from marketing approval date through AERS data cut-off date			
	All reports (U.S.)	Serious (U.S.)	Death (U.S.)
All ages	1842 (1366)	973 (686)	97 (30)
Adults (≥17)	1394 (1009)	836 (575)	89 (29)
Peds (0-16)	5 (2)	5 (2)	0

Reporting trends for pediatric reports from approval date (June 25, 1991): see Table 2

Table 2: Reporting trend for pediatric reports from approval date (June 25, 1991)	
Year	Number of reports
1996	1
1997	1
2003	1
2004	2

2. Counts of top 20 reported event preferred terms for all ages, adults, and pediatric age groups since drug approval: see Table 3 (Events not previously described in the product label² are underlined; bolded events are unique to top 20 events in pediatric patients relative to adults)

Table 3: Counts of top 20 reported event preferred terms (from approval date)		
All ages (includes null ages)	Angioneurotic Oedema-224 Cough-214 Dizziness-104 Face Oedema-100 Tongue Oedema-98 Headache-88 Dyspnoea-83 Dermatitis-82 Asthenia-81 Hyperkalaemia-66	<u>Drug Ineffective-61</u> Renal Failure Acute-57 Nausea-54 <u>Hypertension-52</u> Blood Creatinine Increased-51 Hypotension-48 <u>Oedema Peripheral-48</u> <u>Diarrhoea-45</u> Alopecia-41 <u>Pruritis-39</u>
Adults (17+ years)	Angioneurotic Oedema-191 Cough-158 Tongue Oedema-90 Face Oedema-87 Dizziness-85 Dyspnoea-73 Headache-69 Asthenia-63 Hyperkalaemia-61 Dermatitis-60	Renal Failure Acute-56 Blood Creatinine Increased-43 <u>Hypertension-42</u> Nausea-41 Hypotension-39 <u>Diarrhoea-38</u> Drug Interaction-35 <u>Abdominal Pain-33</u> <u>Oedema Peripheral-33</u> Vomiting-32

Table 3: Counts of top 20 reported event preferred terms (from approval date)		
Pediatric patients (0-16 years)	<u>Anorexia-2</u> Asthenia-2 <u>Gastroenteritis-2</u> <u>Hyperchloraemia-2</u> <u>Hypoaldosteronism-2</u> <u>Metabolic Acidosis-2</u> Nausea-2 Somnolence-2 Vomiting-2 <u>Accidental Exposure-1</u>	<u>Adverse event-1</u> <u>Anion Gap Increased-1</u> Blood Creatinine Increased-1 Blood Electrolytes Abnormal-1 <u>Bradycardia-1</u> <u>Choking-1</u> Cough-1 <u>Crying-1</u> Fatigue-1 Fetal Disorder

B. From Pediatric Exclusivity approval date (July 2, 2003) through AERS data cut-off date (August 2, 2004):

1. Counts of reports: Table 4

Table 4: Raw counts of reports from pediatric exclusivity approval date through AERS data cut-off date			
	All reports (U.S.)	Serious (U.S.)	Death (U.S.)
All ages	111 (65)	97 (51)	19 (5)
Adults (≥17)	93 (48)	84 (39)	18 (4)
Peds (0-16)	3 (1)	3 (1)	0

2. Counts of top 20 reported event preferred terms for all ages, adults, and pediatric age groups: see Table 5 (Events not previously described in the product label are underlined; bolded events are unique to top 20 events in pediatric patients relative to adults)

Table 5: Counts of top 20 reported event preferred terms (from pediatric exclusivity date)		
All ages	Angioneurotic Oedema-12 <u>Pharmaceutical Product Complaint-11</u> Asthenia-10 Renal Insufficiency-10 Hypotension-9 <u>Medication Error-9</u> <u>Drug Interaction-8</u> Swelling face-8 <u>Anorexia-7</u> <u>Blood Pressure Increased-7</u>	Dyspnoea-7 Hyperkalaemia-7 <u>Oedema Peripheral-7</u> <u>Septic Shock-7</u> <u>Completed Suicide-6</u> Dizziness-6 <u>Pyrexia-6</u> <u>Toxic Epidermal Necrolysis-6</u> Alanine Aminotransferase Increased-5 <u>Coagulopathy-5</u>
Adults	Angioneurotic Oedema-10 Renal Insufficiency-10 <u>Pharmaceutical Product Complaint-9</u> Asthenia-8 <u>Drug Interaction-8</u> Swelling Face-8 <u>Blood Pressure Increased-7</u> Dyspnoea-7 Hyperkalaemia-7 Hypotension-7	<u>Oedema Peripheral-7</u> <u>Septic Shock-7</u> <u>Completed Suicide-6</u> Dizziness-6 <u>Pyrexia-6</u> <u>Toxic Epidermal Necrolysis-6</u> Alanine Aminotransferase Increased-5 <u>Anorexia-5</u> <u>Condition Aggravated-5</u> <u>General Physical Health Deterioration-5</u>

Table 5: Counts of top 20 reported event preferred terms (from pediatric exclusivity date)		
Pediatric patients	<u>Anorexia-2</u> Asthenia-2 <u>Gastroenteritis-2</u> <u>Hyperchloraemia-2</u> <u>Hypoaldosteronism-2</u> <u>Metabolic Acidosis-2</u> Nausea-2 Somnolence-2 Vomiting-2 <u>Accidental Exposure-1</u>	<u>Adverse Event-1</u> <u>Anion Gap Increased-1</u> Blood Electrolytes Abnormal-1 <u>Choking-1</u> Cough-1 <u>Crying-1</u> Fatigue-1 <u>Hypernatraemia-1</u> <u>Hypothalamo-Pituitary Disorders-1</u> <u>Renal Tubular Acidosis-1</u>

Postmarketing hands-on review of all peds adverse event reports from all sources received during the one-year after pediatric market exclusivity was granted

A. Demographic characteristics of two unduplicated pediatric reports regarding gender, age, indications, doses, and outcomes:

Table 6: Characteristics of pediatric cases (reports during the 1-year period after receiving pediatric market exclusivity)	
Gender	Male (2)
Age	2 yrs 4 yrs
Indication for which the drug was used	Nephrotic Syndrome (1) Possible accidental ingestion of benazepril (1)
Dose	0.3mg/kg/day (1) Unknown (1)
Serious outcomes	Deaths – 0 Hospitalization-1

B. Comments regarding labeling status of the top 20 adverse events and similarities to adult adverse event profile.

A hands-on review revealed that one of the three reports obtained for pediatric patients during the period of Pediatric Exclusivity was a duplicate report. If the preferred terms (PTs) for this duplicate report are removed from the pediatric section Table 5, then none of the PTs had counts of greater than 1. None of the 12 PTs appeared as a top 20 PTs for the adult population during either the period of Pediatric Exclusivity or the period from marketing to the end of the Pediatric Exclusivity period.

C. Comments and analysis of events not recognized for adult population.

Of the unrecognized (unlabeled) events for an adult population the events, accidental exposure, adverse event, choking and crying were all related to one case of a possible accidental ingestion of benazepril. This case will be discussed further in Section F below.

The remaining unlabeled events were specific to a second case discussed in Section F below.

D. Comments and analysis of events uniquely identified in children but not reported in adult population, including increased frequency of any expected events. Recommended actions, if appropriate, after consultation with HFD-960 and OND Review Division (HFD-110).

It is not possible to make a valid comment regarding increased frequency of reporting from the two reports for benazepril.

E. Summary and comment on death reports.

There were no reports of death occurring in pediatric patients for benazepril.

F. Summary of pediatric adverse event profile during period.

We received 2 unduplicated cases for pediatric patients during the pediatric exclusivity period.

- ISR#4277906-X; 2004; Italy:

This case was published in the literature and described a case of metabolic acidosis in a four year old male with a history of “minimal change nephrotic syndrome” from the age of 11 months¹. He had been taking benazepril (0.3mg/kg per day) for four months when he was admitted to hospital with fatigue, asthenia, metabolic acidosis, moderate hyperchloremia and normal Na⁺ and K⁺ values. His renal function was normal and a relapse of nephrotic syndrome was excluded. Suppression of hypothalamic-pituitary-adrenal axis function was suspected to be due to recent corticosteroid therapy, but this was ruled out. The patient was discharged with a diagnosis of metabolic acidosis secondary to gastroenteritis. The patient failed to recover and continued to experience anorexia and nausea and was readmitted two weeks later. Upon examination; metabolic acidosis, mild hyperchloremia, high urinary sodium and low potassium excretion was found. At first, proximal renal tubular acidosis was suspected, oral bicarbonate and saline solutions were administered, plasma pH improved, but clinical conditions, anorexia, nausea and vomiting got worse. Hypoaldosteronism was then suspected due to the metabolic acidosis, abnormal urinary electrolyte levels and the lack of recovery. Aldosterone levels were found to be below the level of detectability. The benazepril dose was reduced to 0.2mg/kg per day. After a few days the patient’s clinical condition improved and blood gases and electrolytes normalized. One week later benazepril was ceased altogether and after ten days aldosterone levels were found to be normal. The child completely recovered and proteinuria was still low 9 months after the event.

- ISR#4277906-X; 2003; United States:

This case reported a possible accidental ingestion of benazepril in a two year old male who may have taken one or more of three medications prescribed for his grandmother; rosiglitazone, benazepril and/or carisoprodol. At an unknown time after the possible ingestion, the child experienced choking, cough, and an “unspecified adverse event”. It was reported that the child had found a tablet on the floor at his grandmother’s house. No adverse reactions were reported other than that the child cried excessively and “fell asleep in the car on the way home”. The outcome of the events was not reported. The child had no reported medical history other than he was recovering from a recent “viral infection”.

Summary

The AERS database was searched for reports of adverse events occurring with the use of benazepril in pediatric patients. We focused on the 1-year period following the FDA approval of pediatric exclusivity for benazepril, July 2, 2003 to August 2, 2004. The adverse event preferred terms obtained for pediatric patients during this period were compared to those obtained for adults. Three (raw count) of the 111 reports received during the Pediatric Exclusivity period involved pediatric patients. One of the three cases was a duplicate report.

We reviewed 2 unique pediatric cases reported to the FDA during the Pediatric Exclusivity period. The first case described a hyperchloraemic metabolic acidosis with hypoaldosteronism in a child with nephrotic syndrome¹. Decreases in aldosterone are described in benazepril labeling, but hypoaldosteronism and metabolic acidosis are not present in the labeling for benazepril, or any of the ACE-inhibitors. No other reports of hypoaldosteronism or metabolic acidosis in pediatric patients were found in AERS during the period from marketing to the end of the Pediatric Exclusivity period (June 25, 1991 through AERS data cut-off date August 2, 2004). When looking *all* reports for *all* ages of patients using benazepril, the AERS database contains 2 (raw) reports of hypoaldosteronism and 8 (raw) reports of metabolic acidosis obtained during the period from marketing to the end of the Pediatric Exclusivity period. Although it is plausible that benazepril contributes to metabolic acidosis linked to hypoaldosteronism, the numbers of these reported cases is small.

The second case described a possible accidental ingestion of one or more tablets of benazepril, rosiglitazone and/or carisoprodol. From the available information it is not possible to determine whether benazepril was responsible for the events described in the report. The most concerning event is “choking”, but the description, severity and outcome of this event is not described within the report. The lack of information provided prevents reasonable analysis of this report.

From the available information we do not consider that there are any additional safety concerns at this time regarding the use of benazepril in the pediatric population. We will continue to monitor for adverse event reports in this patient group.

References

- 1) Bruno I, Pennesi M, Marchetti F. ACE-inhibitors-induced metabolic acidosis in a child with nephrotic syndrome. *Pediatr Nephrol.* 2003; 18:1293-1294.
- 2) Benazepril/Lotensin®-Novartis official labeling, August 2003 Edition (in effect from October 2003).

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Concur:

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Appendix

Standard Searches:

- A. Adults (17 yrs and above)
 - 1. All outcomes from AP date (no set criteria)
 - 2. Serious outcomes from AP date
 - 3. Death as an outcome from AP date
 - 4. All outcomes from PE date to present or any desired date
 - 5. Serious outcomes from PE date to present or any desired date
 - 6. Death as an outcome from PE date to present or any desired date

- B. Ages 0-16 yrs ONLY
 - 1. Same as above 1-6
 - 2. Retrieve case reports for hands-on review

Standard Printouts for Attachments:

- A. Adults (17 yrs and above)
 - 1. Frequency counts of all preferred terms (PT) in cases
 - 2. Frequency counts of all PT in cases with serious outcomes
 - 3. Frequency counts of all PT in cases with death as an outcome
 - 4. Frequency counts of cases by Gender and ages

- B. Ages 0-16 yrs ONLY
 - Same as above 1-4

Drug Product Information

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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9/29/04 03:50:37 PM
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