

# **One Year Post Exclusivity Adverse Event Review: Benazepril**

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# Background Drug Information

- **Drugs:** Lotensin<sup>®</sup> (benazepril HCL); Lotensin HCT<sup>®</sup> (benazepril hydrochlorothiazide); Lotrel<sup>®</sup> (benazepril/amlodipine)
- **Therapeutic Category:** anti-hypertensive (ACE inhibitor)
- **Sponsor:** Novartis
- **Adult & Pediatric Indication:** Treatment of hypertension, age  $\geq 6$  years
- **Original Market Approval:** June 25, 1991 (Lotensin<sup>®</sup>); May 19, 1992 (Lotensin HCT<sup>®</sup>); March 3, 1995 (Lotrel<sup>®</sup>)
- **Pediatric Exclusivity Granted:** July 2, 2003

# Drug Use Trends in Outpatient Settings: Benazepril

- Decrease in prescriptions dispensed for single ingredient benazepril products from 8.8 million (8/01-7/02) to 7.2 million (8/03-7/04) for all ages<sup>1</sup>
- Less than 0.1% of benazepril and combination products prescribed for ages 1-16 years<sup>2</sup>
- Based on IMS Health, NDTI™, no pediatric use for benazepril or benazepril/hydrochlorothiazide (HCTZ) reported during past three years<sup>3</sup>
- Estimated 5,000 mentions of benazepril/amlodipine in 12-16 y.o. group for Dx of “essential hypertension unspecified” during 8/03-7/04<sup>3</sup>

<sup>1</sup>IMS Health, National Prescription Audit *Plus*™, On-Line, Aug 2001 – Jul 2004, Data Extracted Sep 2004

<sup>2</sup>Caremark Dimension Rx™ On-Line, Aug 2001 – Jul 2004, Data Extracted Sep 2004

<sup>3</sup>IMS Health, National Disease and Therapeutic Index™, CD-Rom, Aug 2001 - Jul 2004, Data Extracted Sep 2004

# Pediatric Exclusivity Studies: Benazepril

- Pharmacokinetics (PK)
- Efficacy and Safety
  - Forced Dose Titration
  - Randomized Withdrawal
  - Open Label

# Pediatric Exclusivity Studies: PK (3 studies)

## Study 1:

- Bioavailability of extemporaneously compounded suspension compared to tablet in 30 healthy adults
- Bioequivalence demonstrated

## Study 2:

- PK of benazepril and benazeprilat studied after a single dose in 30 healthy children, aged 0.7 to 16.9 years
- Mean clearance (CL) values for benazepril in children were larger than in adults.
- Mean CL of benazeprilat in school age children was twice that of healthy adults, and mean CL in adolescents was 27% greater than in healthy adults.

# Pediatric Exclusivity Studies: PK (3 studies) (cont.)

## Study 3:

- Open label, steady state PK study in 57 pediatric patients, aged 1 month to 16 years, given multiple daily doses for 5 days
- Mean CL of benazepril was higher in study patients compared to healthy children and adults.
- Mean CL of benazeprilat in children 6-12 years old was more than twice that of healthy adults; in adolescents, it was 27% higher than that of healthy adults.
- Terminal elimination half-life of benazeprilat in pediatric patients (6-16 years) was one-third that observed in adults.

# Pediatric Exclusivity Studies: Efficacy and Safety

- 107 hypertensive patients, 7-16 years of age, were studied in forced dose titration phase for 4 weeks.
- Hypertension defined as mean systolic blood pressure (SBP) or mean diastolic blood pressure (DBP)  $\geq 95^{\text{th}}$  % for height, age, gender, off anti-hypertensive medications
- Doses ranged from 0.1-0.6 mg/kg, maximum total dose 40 mg, in tablet form



# Pediatric Exclusivity Studies: Efficacy and Safety (cont.)

- 85 patients who responded to therapy during the forced titration phase enrolled in a 2-week randomized, double-blind, withdrawal, placebo-controlled study.
- Primary efficacy endpoint: change from baseline trough SBP during drug withdrawal phase
  - Increases in mean changes of SBP and DBP in placebo group were greater than changes in all three benazepril dose groups (low, medium and high).
  - SBP and DBP in placebo group increased by 4 to 6 mm Hg more than in drug groups.
  - No dose-response observed



# **Pediatric Exclusivity Studies: Efficacy and Safety (cont.)**

- 70 patients were enrolled in 26 week open-label extended phase with 64 completions.
- This study phase provided additional safety data.

# Pediatric Exclusivity Studies: Safety (n=107)

- No deaths
- Serious Adverse Events (SAEs) (n=9)
  - Renal failure and transplant rejection, urinary tract infections, increased creatinine with history of kidney transplant, hypertensive crisis, bowel obstruction, severe sleep apnea, severe depression
- Discontinuations due to AEs (n=9)
  - Angioedema, abnormal liver function, abnormal blood creatinine, kidney transplant rejections, aggravated cough, rash, hypertensive crisis, hyperactivity/insomnia

# Labeling Changes Resulting from Exclusivity Studies

- Clearance of benazeprilat (active metabolite) in 6-12 y.o. twice that of healthy adults; clearance in 12-16 y.o. is 27% higher than healthy adults
- No dose response observed among drug-treated patients
- Recommended starting daily dose 0.2 mg/kg; daily dose of  $>0.6$  mg/kg not studied
- Treatment not recommended in pediatric patients  $<6$  years or with glomerular filtration rate  $<30$  mL/min

# Labeling Changes Resulting from Exclusivity Studies (cont.)

- Pediatric AEs similar to adults
- Long-term effects of drug on growth and development have not been studied.
- Instructions for preparation of suspension available in label

# Adverse Event Reports since Market Approval: Benazepril Monotherapy

## 06/25/91 - 08/02/04

- Total number of reports, all ages<sup>†\*</sup>:
  - 1,842 reports (1,366 US)
    - 973 serious (686 US)
      - 97 deaths (30 US)
- Pediatric reports<sup>\*</sup>:
  - 5 reports (2 US)
    - All serious
      - No deaths

<sup>†</sup>Includes reports with unknown age

<sup>\*</sup>Counts may include duplicate reports

# Most Common Adverse Events since Market Approval

- **Pediatric\***: anorexia, asthenia, gastroenteritis, hyperchloremia, hypoaldosteronism, metabolic acidosis, nausea, somnolence, vomiting
- **Adult**: angioneurotic edema, cough, lingual edema, facial edema, dizziness, dyspnea, headache, asthenia, hyperkalemia

Underlined events = Unlabeled events

\*All underlined events on this slide are from one case

# Adverse Event Reports during the One-Year Post-Exclusivity Period: Benazepril Monotherapy 07/02/03 - 08/02/04

- Total number of reports, all ages<sup>†\*</sup>:
  - 111 reports (65 US)
    - 97 serious (51 US)
      - 19 deaths (5 US)
- Pediatric reports<sup>\*</sup>:
  - 3 reports (1 US)
    - All serious
      - No deaths

<sup>†</sup>Includes reports with unknown age

<sup>\*</sup>Counts may include duplicate reports

# **Pediatric Adverse Events: Unduplicated Pediatric Reports (n=2)**

1. Four y.o. male with hypertension due to nephrotic syndrome; hyperchloremic metabolic acidosis secondary to hypoaldosteronism found after 4 months of benazepril 0.3 mg/kg/d; improvement after reduction in dose to 0.2 mg/kg and complete recovery after drug discontinued
2. Two y.o male with resolving viral infection; possible accidental ingestion of benazepril, rosiglitazone and carisoprodol (doses of medications unknown), with choking, cough, crying followed by sleep; outcome unknown

# Summary: Benazepril

- No pattern discernible in pediatric AEs for benazepril monotherapy
- No AEs found for combination products during exclusivity period
- This completes the one-year post-exclusivity AE monitoring as mandated by BPCA.
- FDA recommends routine monitoring of AEs for this drug in all populations.
- Does the Advisory Committee concur?

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