One Year Post-Exclusivity Adverse Event Review: Toprol® XL

Pediatric Advisory Committee Meeting
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Background Drug Information

- **Drug:** Toprol XL® (metoprolol succinate) extended release tablets
- **Therapeutic Category:** Beta-Blocker
- **Sponsor:** AstraZeneca
- **Indication:** Treatment of hypertension, angina pectoris, and heart failure

Background Drug Information

- Information for use in pediatric patients 6 years and older added to labeling
- Pediatric use limited (~ 0.1% of all prescriptions)[1]
- **Original Market Approval:** January 10, 1992
- **Pediatric Exclusivity Granted:** July 27, 2006

[1]Verispan, LLC: Vector One®: National (VONA) data extracted July 2007

Exclusivity Studies

- Exclusivity Studies: A randomized, placebo-controlled, dose ranging study with a pop PK analysis and a 52 week open-label extension study were conducted in pediatric patients aged 6 to 16 years.

Exclusivity Studies

The dose ranging study did not meet its primary end point (dose response for reduction in SBP).

Exclusivity Studies

- An analysis of the high and mid level doses against placebo demonstrated significant decrease in blood pressure.
- These pre-specified secondary end points demonstrated effectiveness:
  - Dose-response for reduction in DBP
  - 1.0 mg/kg vs. placebo for change in SBP
  - 2.0 mg/kg vs. placebo for change in SBP and DBP

Labeling Changes

- Exclusivity studies resulted in labeling with:
  - a description of the clinical study results and adverse event profile in the Pediatric Use section
  - A dosing recommendation for pediatric patients ≥ 6 years in the Dosage and Administration section if Toprol® XL is selected for treatment

Pediatric Adverse Events in 1-year Post Exclusivity Period

- Three reported cases with serious adverse events:
  - 2 y/o with accidental ingestion
  - In utero exposure of neonate (34 weeks gestation) with moderate heart murmur, bradycardia, and severe difficulty breathing.
  - Literature report of 12 y/o s/p renal transplantation on multiple medications developed severe anemia. Authors attributed anemia to irbesartan.

Pediatric Adverse Events Since Market Approval Prior to Exclusivity

1 reported death

- Neonate with in utero exposure delivered at 36 weeks gestation with limb deformities, pulmonary hypertension with PDA, abnormal kidney structure and Potter's facies. Developed respiratory failure and died on day 4. Mother was on several anti-hypertensives including Losartan.

Pediatric Adverse Events Since Market Approval Prior to Exclusivity

12 pediatric cases reported:

- Congenital abnormalities in patients with in utero exposure (3)
  - 3 day old with a patent foramen ovale
  - 10 month old with hip skeletal abnormality
  - 1 day old with multiple ulcers in the esophagus and stomach
- Accidental/Intentional overdose (3)

Pediatric Adverse Events Since Market Approval Prior to Exclusivity

- Pharmacy Dispensing Error (4)
  - Each error involved a different drug. No trend identified.
- Other (2)
  - 16 y/o with epigastric pain and elevated amylase. Underwent appendectomy and excision of an ovarian cyst.
  - 15 y/o with mild retinal vein occlusion.

Summary: metoprolol

- No safety signals identified since market approval unique to the pediatric population.
- Exclusivity studies resulted in labeling with dosing information, adverse event information, and a description of the clinical study results.
- Pediatric use limited (~ 0.1% of all prescriptions)[1]

1Verispan, LLC: Vector One®: National (VONA) data extracted July 2007

Summary: metoprolol

- This completes the one year post-exclusivity adverse event reporting.
- FDA recommends routine monitoring of AEs for metoprolol in all populations.

Does the Advisory Committee concur?

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