One Year Post-Exclusivity Adverse Event Review:

Brinzolamide Ophthalmic Suspension

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Background Drug Information

- **Drug:** Azopt® (brinzolamide ophthalmic suspension)
- **Therapeutic Category:** Carbonic anhydrase inhibitor
- **Sponsor:** Alcon
- **Indication:** for the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension or open-angle glaucoma
- **Original Market Approval:** April 1, 1998
- **Pediatric Exclusivity Granted:** June 28, 2006
- **Pediatric Drug Use:** 2.6% (4,467) of all patients receiving an outpatient prescription from a US retail pharmacy from July 2006 to June 2007[1]

[1] *Verispan, LLC: Total Patient Tracker, data extracted 8-24-07*

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Pediatric Adverse Events

- No pediatric cases during the post-exclusivity period (1 adult case was mislabeled as pediatric)
- One foreign pediatric case since market approval
  - 14 year old female developed dizziness, headache, abdominal discomfort, circulatory collapse, and unconsciousness after several months use of brinzolamide.
  - Treated with volume replacement. Regained consciousness without need for other treatment. EEG and blood tests were normal.
  - Resumed drug use later without difficulties.

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Systemic Effects of Brinzolamide

- Carbonic anhydrase (CA) II inhibition results in decreased aqueous humor secretion and IOP in the eye and decreased HCO_3 reabsorption in the proximal renal tubule.
- Brinzolamide distributes almost entirely in red blood cells (RBC) due to its high affinity for CA II.
- Brinzolamide saturation of RBC CA II results in a level of CA II inhibition below that expected for renal effects.
- <u>Conclusions</u>:
  - It is unlikely that ocular brinzolamide TID in pediatric patients with normal renal function will result in systemic CA II inhibition.
  - Other factors (e.g., impaired renal function) may increase systemic brinzolamide concentrations and CA II inhibition, causing a diuretic effect.

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Foreign Case Report of Systemic Effects of Dorzolamide

- Neonate with bilateral Peter's anomaly on ocular dorzolamide for 7 days developed metabolic acidosis.
- Treated with antibiotics and bicarbonate for 3 days but remained acidotic and unwell. Dorzolamide was discontinued 5 days later with next-day resolution of the acidosis.
- Negative blood, urine, stool, throat, and nasal cultures. Normal anion gap, electrolytes, liver function tests, and urinalysis. Renal ultrasound and DMSA scan revealed a normal functioning single kidney.
- Conclusions: Factors such as prematurity, low birth weight, renal tubular immaturity, and one functioning kidney may have led to poor dorzolamide elimination and higher systemic concentrations.

Br. J. Ophthalmol. 2003; 87; 1052-1053

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Summary: Brinzolamide Ophthalmic Suspension

- This completes the one year post-exclusivity adverse event reporting.
- FDA recommends routine monitoring of brinzolamide for adverse events in all populations.
- If the FDA identifies additional pediatric cases suggesting systemic absorption of brinzolamide, these cases will be presented to the Advisory Committee.
- Does the Advisory Committee concur?

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