



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

Date: September 10, 2007

To: Lisa L. Mathis, M.D., OND Associate Director
Pediatric and Maternal Health Team
Office of New Drugs (OND), CDER
and
M. Dianne Murphy, M.D., Director
Office of Pediatric Therapeutics (OPT), OC

Thru: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation

From: Ronald Wassel, Pharm.D., Safety Evaluator
Division of Drug Risk Evaluation

Subject: 1-year Post-Pediatric Exclusivity Postmarketing Adverse
Event Review

Drug Name: Azopt[®] (brinzolamide)

Pediatric Exclusivity
Approval Date: June 28, 2006

Application
Type/Numbers: NDA # 20-816

Applicant/sponsors: Alcon

OSE RCM #: 2007-386

1. Executive Summary

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of brinzolamide in pediatric patients. Up to the "data lock" date of 7/28/2007, AERS contained 132 cases for brinzolamide (crude counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 0.75% of the total (1/132).

DDRE was asked to focus on the 1-year period following the approval of pediatric exclusivity, 6/28/2006 to 6/28/2007. We used an AERS data lock date of 7/28/2007, to allow time for reports received up to 6/28/2007, to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received a total of 16 cases (crude counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). There was one pediatric case; however, after further review it was determined that the age data was entered incorrectly and the patient was actually an adult. Therefore, there were no pediatric cases during the exclusivity period.

Otherwise, there was only one case with brinzolamide reported in a pediatric patient from 2004 in which the patient experienced headache, dizziness, loss of consciousness, circulatory collapse, and abdominal discomfort. However, the physician stated the relationship between product use and the symptoms was rather unlikely, and the patient continued to use the product without further problems.

A review from DAIOP's Clinical Pharmacology Team Leader stated that it is not likely that ocular administration of brinzolamide to pediatric patients with normal renal function will result in systemic inhibition of carbonic anhydrase.

Aside from the potential for increased systemic concentrations in patients with impaired renal function, this review does not reveal any other new safety concerns for the use of brinzolamide in pediatric patients. We will continue routine monitoring of adverse events in pediatric patients.

2. Products, Indications, Pediatric Labeling, and Pediatric Filing History

2.1 Products:

NDA 20-816 Suspension/Drops; Ophthalmic 1%

Approved 4/1/1998

2.2 Indications:

For the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension or open-angle glaucoma.

2.3 Pediatric labeling:

PRECAUTIONS/Pediatric Use

A three-month controlled clinical study was conducted in which AZOPT® (brinzolamide ophthalmic suspension) 1% was dosed only twice a day in pediatric patients 4 weeks to 5 years of age. Patients were not required to discontinue their IOP-lowering medication(s) until initiation of monotherapy with AZOPT. IOP-lowering efficacy was not demonstrated in this study in which the mean decrease in elevated IOP was between 0 and 2 mmHg. Five out of 32 patients demonstrated an increase in corneal diameter of one millimeter.

Note: The above mentioned study is described in the Precautions section because it demonstrated a lack of efficacy and, therefore, safety with an off-label, less frequent dose. Pediatric efficacy is extrapolated from efficacy demonstrated in adults when the correct dose is used. The current labeling does not prohibit the use of brinzolamide in pediatric patients. (Rhea Lloyd, Medical Officer, personal communication, 9/10/2007).

2.4 Pediatric Filing History:

The original Pediatric Written Request (WR) was issued on 10/15/99 and amended three times, on 11/17/2000, 5/16/03, and 8/30/2004. The pediatric efficacy supplement was approved on 9/28/2006 and pediatric exclusivity was granted on 6/28/2006.

3. AERS Search Results: Brinzolamide

3.1 Count of Reports: AERS Search including all sources – U.S. & foreign from marketing approval date (Table 1)

Table 1: Crude counts ¹ of AERS Reports for All Sources from Marketing Approval Date (4/1/1998) through 7/28/2007 (US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	69 (42)	25 (5)	1 (0)
Pediatrics (0-16 yrs.)	2 ³ (0)	1 (0)	0 (0)
Age unknown (Null values)	61 (58)	3 (1)	0 (0)
Total	132 (100)	29 (6)	1 (0)

¹ May include duplicates
² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, and congenital anomaly.
³ One patient was actually 66 years old (data entry error).

3.2 Count of Reports: AERS Search including all sources - U.S. & foreign from Pediatric Exclusivity approval date (Table 2)

Table 2: Crude counts¹ of AERS Reports for All Sources from date Pediatric Exclusivity was Granted (6/28/2006) through 7/28/2007 (US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	14 (1)	11 (1)	1 (0)
Pediatrics (0-16 yrs)	1 ³ (0)	0 (0)	0 (0)
Age unknown (Null Values)	1 (0)	1 (0)	0 (0)
Total	16 (1)	12 (1)	1 (0)

¹ May include duplicates
² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, and congenital anomaly.
³ Patient was actually 66 years old (data entry error).

4. Postmarketing Review of All Pediatric Adverse Event Reports received during the one-year after a drug receives pediatric market exclusivity

During the first 13 months after pediatric exclusivity was granted, AERS received a total of 16 cases for brinzolamide (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). One case (ISR # 5225711-X; Mfr. Control # FR-1160279) was retrieved in the pediatric age group; however upon further review it was determined that the age field in the AERS form had an incorrect entry (66 HR). The actual CIOMS report showed the correct age to be 66 years.

5. Review of all cases in pediatric patients since marketing

There was one case reported (ISR # 4416748-9; Mfr. Control # 28928) from Germany in a 14-year-old female that occurred in 2004. The narrative is as follows:

Clinical events: headache, dizziness, loss of consciousness, circulatory collapse, abdominal discomfort

Narrative: Ophthalmologist reports that a 14-year-old patient has used product since Jan 2004. About 4 weeks ago, she complained of dizziness and headache following use of product. On [redacted] the patient became unconscious and was admitted to the hospital. EEG and a blood test were carried out in the hospital with no diagnostic findings. Thyroid testing was performed, but results are not yet available.

On [redacted], the attending physician at the hospital stated the patient had regained consciousness by the time she arrived at the hospital, upon arrival she was administered a volume replacement infusion. No drugs or other therapeutic procedures were required. The physician stated the patient was hospitalized over several days not because treatment was required but for diagnostic purposes. She

stated the relationship between product use and the symptoms was rather unlikely but felt that the product was possibly a trigger factor.

Ophthalmologist stated on [] that the patient also experienced circulatory collapse and that she was hospitalized for diagnostic procedures from []. Ophthalmologist felt event was unlikely related to product.

Physician provided additional details on [] stating the patient also experienced sickness in the abdominal region.

The physician stated on [] that the long-term ECG and the thyroid test were without pathological findings. Patient continues to use product without any difficulties.

6. Summary/Recommendations

A review of AERS data found only one case with brinzolamide reported in a pediatric patient from 2004 in which the patient experienced headache, dizziness, loss of consciousness, circulatory collapse, and abdominal discomfort. However, the physician stated the relationship between product use and the symptoms was rather unlikely, and the patient continued to use the product without further problems.

An AERS search with dorzolamide (an agent in the same pharmacologic class) found no similar cases.

A review from DAIOP's Clinical Pharmacology Team Leader (Chuck Bonapace, email to Jennifer Harris, June 22, 2007) noted:

Based on the data from the review of NDA 20-816 and information in the label, it is not likely that ocular administration of 1 drop of brinzolamide ophthalmic suspension, 1% in each eye three times daily to pediatric patients with normal renal function will result in systemic inhibition of carbonic anhydrase and cause a diuretic effect for the following reasons:

1. Brinzolamide distributes almost entirely into RBCs due to the high affinity for carbonic anhydrase II, the most active isoenzyme of carbonic anhydrase, leading to saturation of this isoenzyme in RBCs at a brinzolamide concentration of 20 uM or 7.7 ug/mL.
2. Brinzolamide saturation of RBC carbonic anhydrase II (at a RBC concentration of 7.7 ug/mL) results in approximately 70-75% inhibition of carbonic anhydrase II activity, which is below the degree of inhibition expected to have a pharmacologic effect on renal function.

3. Maximal RBC concentrations of brinzolamide following ocular administration of a single drop of brinzolamide ophthalmic suspension, 3% in each eye three times daily for 15 days to healthy adults were 2.17 ug/mL. Plasma concentrations of brinzolamide were below the lower limit of quantitation (10 ng/mL) and well below the concentration resulting in brinzolamide saturation of the enzyme (7.7 ug/mL).

4. Following administration of brinzolamide ophthalmic suspension, 1% as a single drop in each eye three times daily for 12 months, RBC concentrations of brinzolamide were near or slightly above 20 uM by month 6 in the majority of patients. Plasma concentrations of brinzolamide were not assessed.

Interpretation:

Based on the limited data available, plasma concentrations of brinzolamide are anticipated to be below or near the lower limit of quantitation (10 ng/mL) following long-term administration of brinzolamide ophthalmic suspension, 1% three times daily and well below the concentration resulting in brinzolamide saturation of carbonic anhydrase. However, it is possible that the low plasma concentrations of brinzolamide may inhibit carbonic anhydrase II activity in the kidney to some degree if brinzolamide preferentially binds to carbonic anhydrase in the kidney rather than RBCs. Other patient factors such as impaired renal function may increase systemic concentrations of brinzolamide and increase the potential of inhibiting carbonic anhydrase causing a diuretic effect.

Aside from the potential for increased systemic concentrations in patients with impaired renal function, this review does not reveal any other new safety concerns for the use of brinzolamide in pediatric patients. We will continue routine monitoring of adverse events in pediatric patients.

Ronald Wassel, Pharm.D.
Safety Evaluator
Concur:

Melissa Truffa, R.Ph.
Team Leader

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ronald Wassel
9/10/2007 01:51:58 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
9/11/2007 05:39:28 PM
DRUG SAFETY OFFICE REVIEWER