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Office of Surveillance and Epidemiology**

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Subject: Azopt[®] (brinzolamide) BPCA

Drug Name(s): Azopt[®] (brinzolamide)

Application Type/Number: NDA 20-816

Applicant/sponsor: Alcon Research, Ltd.

OSE RCM #: 2007-386

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EXECUTIVE SUMMARY

This consult examines the drug utilization patterns for Azopt® (brinzolamide), a carbonic anhydrase inhibitor, in the pediatric population, patients aged 0-16 years, with a primary focus on patterns of use two years before and one year following the granting of Pediatric Exclusivity on June 28, 2006. Outpatient proprietary drug use databases licensed by FDA were used to examine the patterns of use for Azopt® during the three 12-month periods from July 1, 2004 through June 30, 2007.

Azopt® (brinzolamide) represented approximately 14% of the selected market of carbonic anhydrase inhibitor ophthalmic solutions, while Cosopt® (dorzolamide and timolol) represented over 65% of sales. About 70% of Azopt® bottles were sold to U.S. retail pharmacy settings and 15% were sold to mail order pharmacies during the pre- and post-exclusivity periods. Azopt® is primarily used in adult patients. Less than 2% of the total Azopt® prescriptions were dispensed to patients aged 0-16 years. Ophthalmology was the most common prescribing specialty for Azopt® and the pediatric prescribing specialty accounted for less than 1% of prescribers during the three 12-month periods of this review. The most common diagnosis associated with a mention of Azopt® in the pediatric patients (aged 6-16 years) and adults (age 17 years and older) in office based physician-patient encounters was glaucoma.

Based on databases employed for this analysis, dispensed prescriptions for Azopt® in the pediatric population accounted for only a small proportion of the total dispensed prescriptions for that product during pre- and post-exclusivity periods. Childhood glaucoma is a rare condition and the small proportion of prescriptions dispensed for pediatric population is consistent with the low prevalence of this condition in the pediatric population.

1 INTRODUCTION

1.1 REGULATORY HISTORY

On January 4, 2002, Congress enacted the Best Pharmaceuticals for Children Act (BPCA) to improve the safety and efficacy of pharmaceuticals for children. Section 17 of that Act requires the review of adverse events associated with the use of a drug in children during the one year following the date on which the drug received marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric Advisory Committee on the drug utilization patterns and adverse events associated with the use of the drug soon after the one-year anniversary of granting exclusivity. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs.

Azopt® (brinzolamide), an ophthalmic carbonic anhydrase inhibitor, is available as a 1% ophthalmic suspension/drop (5ml, 10ml, 15ml) and was approved under NDA 20-816 on April 1, 1998. Azopt® is indicated for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. The recommended dose is 1 drop of Azopt® in the affected eye(s) three times daily.

In October of 1999, FDA issued a Pediatric Written Request for studies in pediatric patients with a clinical diagnosis of glaucoma or elevated intraocular pressure to evaluate the safety and clinical response on elevated intraocular pressure. Alcon Research, Ltd. conducted studies and gained approval for the use of Azopt® in pediatric patients for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma on September 28, 2006, under NDA 20-816/S-009. Pediatric Exclusivity was granted on June 28, 2006.

On September 28, 2006, NDA 20-816/S-009 provided for a change in the **PRECAUTIONS** section, **Pediatric Use** subsection of the labeling.

1.2 PRODUCT LABELING¹

INDICATIONS AND USAGE

AZOPT® (brinzolamide ophthalmic suspension) 1% is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

PRECAUTIONS

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

2 METHODS AND MATERIALS

2.1 INTRODUCTION

Using the currently available data resources, this review describes outpatient drug use patterns for Azopt® in the pediatric population as well as in the adult population and includes data for three 12-month periods starting two years before and one year following the granting of pediatric exclusivity on June 28, 2006. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

2.2 DETERMINING SETTINGS OF CARE

IMS Health, IMS National Sales Perspectives™ data (*see Appendix*) were used to determine the setting in which Azopt® was sold. Sales of this product by number of bottles of solution (eaches) sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for three 12-month periods from July 1, 2004-June 30, 2007 (*data not provided*).²

During the three 12-month periods of this review, retail settings (chain stores, independent stores, and food stores) plus mail order pharmacies accounted for the majority of Azopt® sales (~86 %). Chain, independent, and food stores with pharmacies accounted for approximately 71% of overall sales while mail order pharmacies accounted for approximately 14.5% of sales. Thus, the examination of Azopt® utilization patterns focused on the outpatient setting. It should be noted that Azopt® represented approximately 14% of the selected market of carbonic anhydrase inhibitor ophthalmic solutions, while Cosopt® (dorzolamide and timolol) represented over 65% of sales.

2.3 DATA SOURCES USED

2.3.1 Outpatient data

Outpatient use and patient demographics were measured with three data sources from Verispan, LLC: Vector One®: National (VONA), Vector One®: Mail Order (VOMA), and Total Patient Tracker (TPT) (*see Appendix*). From these three sources, nationally projected estimates of the number of prescriptions dispensed by retail and mail order pharmacies and the number of patients who received a dispensed prescription for Azopt® were obtained. Data for three 12-month time periods, from July 1, 2004-June 30, 2007, were obtained for VONA and TPT, while data for VOMA, the mail order dispensed prescriptions portion, were retrieved for the 12-month period prior to and post granting of pediatric exclusivity (VOMA Data are available from January 2005 through present).

¹ PDR ® Electronic Library™, accessed August 2007.

² IMS Health, IMS Nationals Sales Perspectives™, Data extracted 8-15-2007, Source file: 0708brin.DVR

Indications for use were obtained from the Verispan, Physician Drug and Diagnosis Audit (PDDA) (*see Appendix*).

2.4 PRODUCTS INCLUDED

In addition to examining outpatient drug utilization patterns for Azopt[®], we examined outpatient prescription dispensing patterns for other carbonic anhydrase inhibitor ophthalmic solutions. These products were selected based on indication and dosage form. Comparator products analyzed include Trusopt[®] (dorzolamide) 2% ophthalmic solution, and Cosopt[®] (dorzolamide and timolol) 0.5% and 2% ophthalmic solution.

3 RESULTS

3.1 OUTPATIENT DATA

3.1.1 Dispensed Prescriptions

3.1.1.1 Ophthalmic Carbonic Anhydrase Inhibitor Prescriptions

For the two 12-month periods from July 1, 2005 through June 30, 2007, retail prescriptions represent over 90% of Azopt[®] use per period based on dispensed prescription data (*Table 1*). During the 12-month period prior to granting of exclusivity, the total number of Azopt[®] prescriptions account for almost 15% (602,000) of the carbonic anhydrase inhibitor ophthalmic solutions total prescription market and around 18% (695,000) during the 12-month period post-exclusivity (*Table 1*).

Table 1. Total Number of Dispensed Ophthalmic Carbonic Anhydrase Inhibitor Prescriptions (*In Thousands*) from Retail and Mail Order Pharmacies, July 1, 2004 through June 30, 2007

	7/2004-6/2005			7/2005-6/2006			7/2006-6/2007		
	Total Rxs (000)	Retail Rxs (000)	Mail* Rxs (000)	Total Rxs (000)	Retail Rxs (000)	Mail Rxs (000)	Total Rxs (000)	Retail Rxs (000)	Mail Rxs (000)
TOTAL MARKET	3,558	3,558	--	4,084	3,734	351	3,762	3,420	342
COSOPT (dorzolamide and timolol)	2,453	2,453		2,845	2,606	239	2,526	2,291	236
AZOPT (brinzolamide)	472	472	--	602	544	59	695	635	61
TRUSOPT (dorzolamide)	633	633		637	584	53	540	495	45

* Verispan, LLC: VOMA, data source for mail order dispensed prescriptions, provides data only from January 2005 to present.
 Verispan, LLC: Vector One[®]: Prescription Services (VONA+VOMA) Data extracted 9-4-2007.
 Source file: 2007-386 VONA 9-4-07 brinzolamide comparatorsTrx wmo.qry

3.1.2 Patient Demographics

3.1.2.1 Prescriptions by age

The majority of Azopt® prescriptions (~97%) were dispensed to adults aged 17 years or older; approaching 98% when including mail order prescriptions as seen in the 12-month periods pre- and post-exclusivity (**Table 2**). A total of 9,366 prescriptions were dispensed to patients aged 0-16 years during the 12-month pre-exclusivity period of July 1, 2005 through June 30, 2006. During this time, patients aged 6-16 years were the dominating pediatric age group with approximately 1% (6,730) of overall total dispensed prescriptions. A total of 11,513 prescriptions were dispensed to patients aged 0-16 years during the 12-month post-exclusivity period of July 1, 2006 through June 30, 2007. During this time, patients aged 6-16 years were the dominating pediatric age group with approximately 1% (8,785) of overall total dispensed prescriptions.

Table 2. Total Number of Azopt® Prescriptions Dispensed from U.S. Retail and Mail Order Pharmacies by age, July 1, 2004 through June 30, 2007

	7/2004-6/2005				7/2005-6/2006				7/2006-6/2007			
	Total Rxs	Retail Rxs	Share %	Mail* Rxs	Total Rxs	Share %	Retail Rxs	Mail Rxs	Total Rxs	Share %	Retail Rxs	Mail Rxs
AZOPT	471,879	471,879	100.0%		602,404	100.0%	543,575	58,829	695,402	100.0%	634,718	60,684
0-2 yrs	953	953	0.2%		855	0.1%	835	20	1,220	0.2%	1,204	16
3-5 yrs	2,531	2,531	0.5%	--	1,781	0.3%	1,749	32	1,508	0.2%	1,504	4
6-16 yrs	4,681	4,681	1.0%		6,730	1.1%	6,435	295	8,785	1.3%	8,649	136
17+ yrs	457,835	457,835	97.0%		588,015	97.6%	529,533	58,482	679,712	97.7%	619,184	60,528
Unspec	5,879	5,879	1.2%		5,023	0.8%	5,023	--	4,177	0.6%	4,177	--

* Verispan, LLC: VOMA, data source for mail order dispensed prescriptions, provides data only from January 2005 to present.

Verispan, LLC: Vector One®: Prescription Services (VONA+VOMA) Data extracted 9-4-2007. Source file: 2007-386 VONA 9-4-07 brinzolamideTrx age.qry

3.1.2.2 Patients by Age

According to Verispan, LLC: Vector One®: Total Patient Tracker (TPT), the majority of patients (~96%) who received at least one Azopt® prescription dispensed from a U.S. retail pharmacy were adults aged 17 years or older (**Table 3**). A total of 3,324 patients aged 0-16 received at least one Azopt® prescription during the 12-month pre-exclusivity period of July 1, 2005 through June 30, 2006. During this time period, the majority (68%) of pediatric use was among patients aged 6-16 years. A total of 4,467 patients aged 0-16 received at least one Azopt® prescription during the 12-month post-exclusivity period of July 1, 2006 through June 30, 2007, of which the majority (74%) use was in ages 6-16 years. Please note that patient counts for mail order prescriptions are not available.

Table 3. Total Number of Patients Receiving an Azopt® Prescription from U.S. Retail Pharmacies by age, July 1, 2004 through June 30, 2007

	7/2004-6/2005		7/2005-6/2006		7/2006-6/2007		TOTAL 7/2004-6/2007	
	Projected Patient Count	Total Patient Share						
TOTAL	122,477	100.0%	154,029	100.0%	173,802	100.0%	289,524	100.0%
0–16 yrs	2,903	2.4%	3,324	2.2%	4,467	2.6%	8,273	2.9%
0 – 2 yrs	369	0.3%	380	0.2%	638	0.4%	1,206	0.4%
3 – 5 yrs	959	0.8%	730	0.5%	645	0.4%	1,936	0.7%
6 – 16 yrs	1,641	1.3%	2,282	1.5%	3,304	1.9%	5,589	1.9%
17–85 yrs	117,142	95.6%	147,944	96.0%	167,482	96.4%	277,403	95.8%
Unknown age	9,140	7.5%	9,630	6.3%	10,585	6.1%	21,167	7.3%

*Subtotals may not sum exactly due to rounding. Because of patients aging during the study period (“the cohort effect”), patients may be counted more than once in the individual age categories. For this reason, summing across age bands is not advisable and will result in overestimates of patient counts.

Verispan, Total Patient Tracker, data extracted 8-24-07.

Source Files: 2007-386 TPT 8-24-07 brinzolamide 6-05to6-07disp.XLS and 2007-386 TPT 8-24-07 brinzolamide 6-05to6-07aggr.XLS

3.1.3 Prescriber Specialty (Top 5)

Ophthalmology was the most common prescribing specialty for Azopt® (**Table 4**). Pediatric prescribing specialty accounted for 0.3% of prescribers who dispensed prescriptions for Azopt® during the study period of this review; there were no prescriptions dispensed by mail order (data not shown).

Table 4. Total Number of Azopt Prescriptions Dispensed (*In Thousands*) from U.S. Retail and Mail Order Pharmacies by Prescriber Specialty (Top 5), July 1, 2004 through June 30, 2007

	7/2004-6/2005				7/2005-6/2006				7/2006-6/2007			
	Total Rxs (000)	Retail Rxs (000)	Share %	Mail* Rxs (000)	Total Rxs (000)	Share %	Retail Rxs (000)	Mail Rxs (000)	Total Rxs (000)	Share %	Retail Rxs (000)	Mail Rxs (000)
AZOPT TOTAL	472	472	100.0%	--	602	100.0%	544	59	695	100.0%	635	61
OPHTH	331	331	70.2%	--	438	72.8%	391	48	513	73.8%	465	48
UNSPEC	79	79	16.8%	--	82	13.6%	75	7	72	10.3%	65	7
OPT	18	18	3.8%	--	27	4.5%	26	2	41	5.9%	39	3
HOSP	12	12	2.6%	--	15	2.5%	15	0	19	2.7%	19	0
GP/FM/DO[†]	8	8	1.7%	--	11	1.8%	10	0	14	2.0%	13	1
All Others	25	25	4.7%	--	30	4.6%	28	1	37	5.3%	35	1

* Verispan, LLC: VOMA, data source for mail order dispensed prescriptions, provides data only from January 2005 to present.

[†]GP/FM/DO = General Practice, Family Medicine, Doctors of Osteopathy

Source: Verispan, LLC: Vector One®: Prescription Services. File: 2007-386 VONA 9-5-07 brinzolamide specialty wmo.qry

3.1.4 Indication for Use (Top 5)

According to office-based physician practices in the U.S., “glaucoma NOS” (ICD-9 365.9) was the top diagnosis code associated with the use of Azopt[®] for all ages (data not provided).³ Adults aged 17 years and older accounted for the majority (~98%) of office-based physician visits reportedly associated with the use of Azopt[®] during the three 12-month study periods. There were no pediatric visits recorded in this survey from July 1, 2004 – June 30, 2005. Pediatric patients, aged 6-16 only, accounted for the only surveyed office visits associated with Azopt[®] pediatric use for the 12-month period prior to exclusivity (July 1, 2005 to June 30, 2006). There were no pediatric visits recorded in this survey for the post-exclusivity period (i.e., July 1, 2006 – June 30, 2007). There were no recorded visits for patients younger than 6 years of age for any of the three 12-month periods.

4 DISCUSSION

Based on the databases employed for this analysis, Azopt[®] represented approximately 14% of the selected market of carbonic anhydrase inhibitor ophthalmic solutions and prescriptions dispensed for Azopt[®] in the pediatric population accounted for only small proportion of the total prescriptions for that product during the pre- and post-exclusivity periods. Childhood glaucoma is a rare condition and occurs in one out of every 10,000 births in the United States.⁴ Childhood glaucoma is diagnosed, in most cases, by the age of six months, with 80% being diagnosed by the first year of life. The small proportion of prescriptions dispensed for the pediatric population is consistent with the low prevalence of glaucoma in the pediatric population.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that brinzolamide is distributed primarily in outpatient setting based on the IMS Health, IMS National Sales Perspectives[™]. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail and mail order channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

Verispan, LLC: Physician Drug and Diagnosis Audit (PDDA) data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to sampling and data collection methodologies, the small sample size can make these data unstable, particularly if use is not common in the pediatric population. Verispan recommends caution when interpreting projected annual uses or mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals and trending variability. The low use of this product in the pediatric population was consistent across all the databases used.

5 CONCLUSION

Outpatient prescription data indicate that use of Azopt[®] in the pediatric population is low. In the most recent 12-months of this analysis, Ophthalmology was the most common prescribing specialty for Azopt[®]. Prescriptions by pediatricians accounted for less than 1% of all dispensed prescriptions for Azopt[®] during each year of this analysis. According to office-based physician practices in the U.S., “glaucoma” was the top diagnosis code associated with the use of Azopt[®] for all ages.

³ Source: Verispan, LLC: Physician Drug and Diagnosis Audit (PDDA). File: 2007-386 PDDA 9-5-07 brinzolamide age 4ddx.qry

⁴ http://www.glaucoma.org/learn/does_your_child.php

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APPENDICES

APPENDIX 1: Database Descriptions

IMS Health, IMS National Sales Perspective, Retail, Non-Retail or Combined

The IMS Health, IMS National Sales Perspective measures the volume of drug products (both prescription and over-the-counter) and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. IMS National Sales Perspectives™ measures the volume of drug products moving from manufacturer into retail and non-retail settings in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections.

Verispan, LLC: Vector One®: National (VONA)

Verispan's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 1.5 billion prescription claims per year, representing over 100 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

Verispan, LLC: Vector One®: Mail Order (VOMA)

Verispan's VOMA measures mail order dispensing of prescriptions or the frequency with which drugs move out of mail order pharmacies into the hands of consumers via formal prescriptions. Information on the number of prescriptions, extended units, patient age and gender, acquisition cost, prescription size and prescriptions per physician is available.

The Vector One® Mail Order data are collected directly from contracted mail order pharmacies which provide data for every prescription dispensed. Verispan's Mail Order sample contains approximately 25% of all mail order prescriptions dispensed in the U.S. Data are received from approximately 140 mail order stores out of a 250 store universe, and are obtained from both Medco and non-Medco sources.

Verispan captures roughly 5 million raw scripts which are projected to a national total of mail order activity of 20 million prescriptions.

Verispan, LLC: Vector One®: Total Patient Tracker (TPT)

Verispan's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 1.5 billion prescription claims per year, representing over 100 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Verispan, LLC: Physician Drug & Diagnosis Audit (PDDA)

Verispan's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Verispan uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

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