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Subject: Betoptic S[®] (betaxolol) BPCA Drug Use Review

Drug Name(s): Betoptic S[®] (betaxolol)

Application Type/Number: NDA 19-845

Applicant/sponsor: Alcon

OSE RCM #: 2007-505

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EXECUTIVE SUMMARY

This review examines drug utilization patterns for betaxolol (ophthalmic formulation), a beta blocker, in the pediatric population, patients aged 0-17 and 18+ years, with a primary focus on patterns of use two years before and one year following the granting of Pediatric Exclusivity on February 28, 2007. Since approximately 76% of ophthalmic betaxolol bottles were sold to U.S. retail settings and about 24% were sold to non-retail [mainly long term care (~43%)] settings during the pre- and post-exclusivity periods, this review focuses on the outpatient setting. Outpatient proprietary drug use databases licensed by FDA were used to examine the patterns of use for ophthalmic betaxolol during the three 12-month periods from March 1, 2005 through February 29, 2008.

For each of the three 12-month periods from March 1, 2005 – February 29, 2008:

- Ophthalmic betaxolol represented approximately 6% of the total projected number of dispensed prescriptions for the selected ophthalmic agents.
- Ophthalmic betaxolol prescriptions in the pediatric population (ages 0-17 years) accounted for less than 1% (~ 2,500 TRx/12-month period of review) of total dispensed prescriptions.
- Similarly, less than 1% of the total projected patients who filled a prescription for ophthalmic betaxolol were pediatric patients.
- Ophthalmology was the top prescribing specialty for ophthalmic betaxolol.
- The top diagnosis code associated with the use of ophthalmic betaxolol for patients aged 0 to 17 years was “Glaucoma NOS” (ICD-9 365.9).
- Use of ophthalmic betaxolol in the pediatric and adult population has been declining over the three 12-month study periods examined.

1 INTRODUCTION

Using the currently available proprietary drug use databases licensed by the Agency, this review describes outpatient drug use patterns for ophthalmic betaxolol 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 February 28, 2007.

2 METHODS AND MATERIALS

IMS Health, IMS National Sales Perspectives™ data (see Appendix 2 for full database description) were used to determine the setting in which ophthalmic betaxolol was sold. Sales of this product by number of bottles (eaches) sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for three 12-month periods from March 1, 2005 through February 29, 2008 (data not provided).¹ During the three 12-month periods of this review, retail settings (chain stores, independent pharmacies, food stores with pharmacies, and mail service pharmacies) accounted for the majority of ophthalmic betaxolol sales at 76% and approximately 24% were sold to non-retail settings. Thus, the examination of ophthalmic betaxolol utilization patterns focused on the outpatient setting.

Outpatient use and patient demographics (stratified by ages 0-17 years and 18+ years for ophthalmic betaxolol) were measured from Verispan, LLC: Vector One®: National (VONA) and Total Patient Tracker (TPT) (Appendix 2). Indications for use were obtained from the Verispan’s Physician’s Drug and Diagnosis Audit (PDDA) (Appendix 2). From these data sources, estimates of the number of prescriptions dispensed, the number of patients who received a prescription for ophthalmic betaxolol, and the number of drug mentions by office-based physicians, were obtained from March 1, 2005 through February 29, 2008,

¹ IMS Health, IMS Nationals Sales Perspectives™, Data extracted 7-15-2008, Source file: 0807bet.DVR

inclusive. For comparative purposes, other select ophthalmic agents were also examined: including timolol, carteolol, dorzolamide/timolol, levobunolol, metipranolol, and brimonidine/timolol.

3 RESULTS

During the three 12-month periods from March 1, 2005 through February 29, 2008, dispensed prescriptions for ophthalmic betaxolol represented approximately 6% of the projected number of prescriptions dispensed for the selected ophthalmic agents in the United States. The projected number of ophthalmic betaxolol dispensed prescriptions decreased by close to 14% from the pre-exclusivity period (March 1, 2006 through February 28, 2007) to the post-exclusivity period (March 1, 2007 through February 29, 2008) (Appendix 1 Table 1).

During the three 12-month periods from March 1, 2005 through February 29, 2008, dispensed prescriptions for ophthalmic betaxolol in the pediatric population (ages 0-17 years) accounted for less than 1% of the total projected number of dispensed prescriptions for ophthalmic betaxolol (Appendix 1 Table 2). Of the 78,814 patients who filled a prescription for ophthalmic betaxolol in the outpatient retail pharmacy setting during the post-exclusivity period, less than 1% of total projected patients were aged 0 to 17 years. The projected number of patients filling a prescription for ophthalmic betaxolol decreased by approximately 19% from the pre-exclusivity period (March 1, 2006 through February 28, 2007) to the post-exclusivity period (March 1, 2007 through February 29, 2008) (Appendix 1 Table 3).

During the three 12-month periods from March 1, 2005 through February 29, 2008, Ophthalmology was the top prescribing specialty for ophthalmic betaxolol with approximately 55% of U.S. retail dispensed prescriptions followed by General Practice/Family Medicine/Doctors of Osteopathy and Internal Medicine with 10% and 9%, respectively (Appendix 2 Table 4). Pediatricians accounted for less than 1% (over 2,700 TRx/12-month period of review) of overall dispensed prescriptions for ophthalmic betaxolol.

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 ophthalmic betaxolol for patients aged 0 to 17 years. Adults aged 18 years and older accounted for the majority (~98%) of office-based physician visits reportedly associated with the use of ophthalmic betaxolol during the three 12-month study periods (Appendix 2 Table 5).

4 LIMITATIONS

Findings from this consult should be interpreted in the context of the known limitations of the databases used. We estimated that ophthalmic betaxolol is distributed primarily in outpatient settings 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 non-retail 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’s Physician Drug & Diagnosis Audit (PDDA) data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the 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 interpreting projected annual uses or mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals.

5 CONCLUSIONS

Use of ophthalmic betaxolol in the pediatric and adult population has been declining over the three 12-month study periods examined.

CONCURRENCE

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APPENDICES

APPENDIX 1: Tables and Figures

Table 1. Total number of dispensed prescriptions through U.S. outpatient retail pharmacies for selected ophthalmic agents, March 1, 2005-February 29, 2008

| | March 2005-Feb 2006 | | March 2006-Feb 2007 | | March 2007 -Feb 2008 | |
|--------------------------------|---------------------|---------------|---------------------|---------------|----------------------|---------------|
| | Retail TRxs | Share | Retail TRxs | Share | Retail TRxs | Share |
| | N | % | N | % | N | % |
| TOTAL MARKET | 6,720,810 | 100.0% | 6,526,457 | 100.0% | 6,104,812 | 100.0% |
| timolol maleate | 3,223,714 | 48.0% | 3,233,519 | 49.5% | 3,126,056 | 51.2% |
| dorzolamide hcl/timolol | 2,530,560 | 37.7% | 2,456,171 | 37.6% | 2,227,857 | 36.5% |
| BETAXOLOL | 463,264 | 6.9% | 395,124 | 6.1% | 339,818 | 5.6% |
| levobunolol hydrochloride | 333,979 | 5.0% | 300,365 | 4.6% | 266,577 | 4.4% |
| carteolol hydrochloride | 114,974 | 1.7% | 96,661 | 1.5% | 82,708 | 1.4% |
| metipranolol hcl | 54,319 | 0.8% | 44,617 | 0.7% | 37,256 | 0.6% |
| brimonidine tartra/timolol mal | -- | -- | -- | -- | 24,540 | 0.4% |

Source: Verispan Vector One®: National, Data Extracted 7/3/08. File: VONA 2007-505 Betaxolol BPCA TRx by comparators.xls

Table 2. Total number of dispensed prescriptions for betaxolol by patient age through U.S. outpatient retail pharmacies, March 1, 2005-February 29, 2008

| | March 2005-Feb 2006 | | March 2006-Feb 2007 | | March 2007-Feb 2008 | | Baseline to | Pre- |
|------------------|---------------------|---------------|---------------------|---------------|---------------------|---------------|----------------|----------------|
| | Baseline | | Pre-Exclusivity | | Post-Exclusivity | | Post- | Exclusivity |
| | Retail TRxs | Share | Retail TRxs | Share | Retail TRxs | Share | Exclusivity | to Post- |
| | N | % | N | % | N | % | % change | Exclusivity |
| BETAXOLOL | 463,244 | 100.0% | 395,135 | 100.0% | 339,760 | 100.0% | -26.66% | -14.01% |
| age 0-17 | 2,885 | 0.6% | 2,410 | 0.6% | 2,232 | 0.7% | -22.63% | -7.39% |
| age 18+ | 456,119 | 98.5% | 391,455 | 99.1% | 336,366 | 99.0% | -26.25% | -14.07% |
| age UNSPEC. | 4,240 | 0.9% | 1,270 | 0.3% | 1,162 | 0.3% | -72.59% | -8.50% |

Source: Verispan Vector One®: National, Data Extracted 7/3/08. File: VONA 2007-505 Betaxolol BPCA TRx by age.xls

Table 3. Projected Number of Patients Who Filled a Betaxolol Prescription at a U.S. Retail Pharmacy, March 1, 2005-Feb 29, 2008

| | March 2005-Feb 2006 | | March 2006-Feb 2007 | | March 2007 -Feb 2008 | |
|------------------------|-------------------------|----------------|-------------------------|----------------|-------------------------|----------------|
| | Projected Patient Count | Share % | Projected Patient Count | Share % | Projected Patient Count | Share % |
| Betaxolol Total | 115,815 | 100.00% | 96,883 | 100.00% | 78,814 | 100.00% |
| Age 0-17 | 962 | 0.83% | 778 | 0.80% | 638 | 0.81% |
| Age 18+ | 113,035 | 97.60% | 95,274 | 98.34% | 77,501 | 98.33% |
| Age Unspec. | 9,860 | 8.51% | 7,048 | 7.27% | 6,277 | 7.96% |

Verispan, Vector One®: Total Patient Tracker, Data Extracted 7/7/08. File: TPT 2007-505 Betaxolol Patient Count by Age.xls

Table 4. Total number of betaxolol prescriptions dispensed from U.S. retail pharmacies by prescriber specialty (Top 25), MAT March 1, 2005-February 29, 2008

| | March 2005-Feb 2006 | | March 2006-Feb 2007 | | March 2007 -Feb 2008 | |
|------------------------------|---------------------|---------------|---------------------|---------------|----------------------|---------------|
| | Retail TRxs | Share | Retail TRxs | Share | Retail TRxs | Share |
| | N | % | N | % | N | % |
| BETAXOLOL | 589,712 | 100.0% | 512,923 | 100.0% | 444,347 | 100.0% |
| OPHTHALMOLOGY | 321,159 | 54.5% | 281,482 | 54.9% | 244,187 | 55.0% |
| GP/FM/DO* | 52,992 | 9.0% | 51,001 | 9.9% | 45,048 | 10.1% |
| INTERNAL MEDICINE | 51,756 | 8.8% | 48,716 | 9.5% | 42,062 | 9.5% |
| UNSPECIFIED | 76,452 | 13.0% | 45,116 | 8.8% | 33,556 | 7.6% |
| OPTOMETRIST | 22,576 | 3.8% | 25,334 | 4.9% | 25,731 | 5.8% |
| CARDIOVASCULAR DISEASES | 24,347 | 4.1% | 23,399 | 4.6% | 21,308 | 4.8% |
| HOSPITAL | 12,281 | 2.1% | 11,115 | 2.2% | 8,844 | 2.0% |
| NURSE PRACTITIONER | 2,068 | 0.4% | 2,535 | 0.5% | 2,755 | 0.6% |
| PEDIATRICS | 2,904 | 0.5% | 2,685 | 0.5% | 2,646 | 0.6% |
| PEDIATRICS | 1,251 | 43.1% | 1,188 | 44.2% | 1,127 | 42.6% |
| PEDIATRIC CARDIOLOGY | 697 | 24.0% | 758 | 28.2% | 769 | 29.1% |
| PEDIATRICS, INTERNAL MEDICIN | 474 | 16.3% | 408 | 15.2% | 472 | 17.8% |
| PEDIATRIC, OTHER | 349 | 12.0% | 254 | 9.5% | 187 | 7.1% |
| PEDIATRIC SURGERY | -- | -- | -- | -- | 68 | 2.6% |
| PEDIATRIC NEPHROLOGY | -- | -- | -- | -- | 12 | 0.5% |
| PEDIATRIC HEMATOLOGY | 17 | 0.6% | 39 | 1.5% | 8 | 0.3% |
| PEDIATRIC ALLERGY | 15 | 0.5% | -- | -- | 2 | 0.1% |
| PEDIATRIC ENDOCRINOLOGY | 25 | 0.9% | 22 | 0.8% | 1 | 0.0% |
| PEDIATRIC PULMONOLOGY | 70 | 2.4% | 16 | 0.6% | -- | -- |
| PEDIATRIC OTOLARYNGOLOGY | 6 | 0.2% | -- | -- | -- | -- |
| PSYCHIATRY | 1,820 | 0.3% | 1,923 | 0.4% | 1,727 | 0.4% |
| PSYCHIATRY | 1,442 | 79.2% | 1,483 | 77.1% | 1,301 | 75.3% |
| CHILD PSYCHIATRY | 376 | 20.7% | 440 | 22.9% | 400 | 23.2% |
| PSYCHIATRY, GERIATRIC | 2 | 0.1% | -- | -- | 26 | 1.5% |
| PHYSICAN ASSITANT | 1,644 | 0.3% | 1,870 | 0.4% | 1,652 | 0.4% |
| GENERAL SURGERY | 1,774 | 0.3% | 1,558 | 0.3% | 1,364 | 0.3% |
| OTHER SPECIALTY | 2,089 | 0.4% | 1,854 | 0.4% | 1,281 | 0.3% |
| PULMONARY DISEASES | 1,146 | 0.2% | 1,219 | 0.2% | 1,002 | 0.2% |
| OB/GYN | 1,518 | 0.3% | 1,481 | 0.3% | 967 | 0.2% |
| NEUROLOGY | 1,182 | 0.2% | 969 | 0.2% | 902 | 0.2% |
| NEUROLOGY | 1,175 | 99.4% | 965 | 99.6% | 902 | 100.0% |
| CHILD NEUROLOGY | 7 | 0.6% | 4 | 0.4% | -- | -- |
| NEPHROLOGY | 1,291 | 0.2% | 939 | 0.2% | 897 | 0.2% |
| EMERGENCY MEDICINE | 1,219 | 0.2% | 958 | 0.2% | 889 | 0.2% |
| DENTISTS | 855 | 0.1% | 964 | 0.2% | 797 | 0.2% |
| GERIATRICS | 680 | 0.1% | 640 | 0.1% | 722 | 0.2% |
| ORTHOPEDIC SURGERY | 783 | 0.1% | 718 | 0.1% | 694 | 0.2% |
| ORTHOPEDIC SURGERY | 747 | 95.4% | 690 | 96.1% | 689 | 99.3% |
| ORTHOPEDIC SURGERY, OTHER | 13 | 1.7% | 4 | 0.6% | 3 | 0.4% |
| ORTHO SURG, SPORTS MEDICINE | 19 | 2.4% | 12 | 1.7% | 2 | 0.3% |
| ORTHO SURG, PED ORTHOPEDICS | 4 | 0.5% | 12 | 1.7% | -- | -- |
| GASTROENTEROLOGY | 854 | 0.1% | 727 | 0.1% | 633 | 0.1% |
| ENDOCRINOLOGY | 741 | 0.1% | 664 | 0.1% | 556 | 0.1% |
| AO SURG | 814 | 0.1% | 699 | 0.1% | 529 | 0.1% |
| ONCOLOGY | 438 | 0.1% | 520 | 0.1% | 521 | 0.1% |
| All Others | 4,329 | 0.7% | 3,837 | 0.7% | 3,077 | 0.7% |

Source: Verispan Vector One®: National, Data Extracted 7/3/08. File: VONA 2007-505 Betaxolol BPCA TRx by Prescribing Specialty.xls

*GP/FM/DO = General Practice, Family Medicine, Doctors of Osteopathy

Table 5. Diagnosis associated with the use* of betaxolol by patient age as reported by office-based physician practices, March 1, 2005-Feb 29, 2008

| | March 2005-FEB 2006 | | March 2006-FEB 2007 | | March 2007-FEB 2008 | |
|--------------------------------------|---------------------|---------------|---------------------|---------------|---------------------|---------------|
| | Baseline | | Baseline | | Baseline | |
| | Uses (000) | Share % | Uses (000) | Share % | Uses (000) | Share % |
| Betaxolol | 286 | 100.0% | 224 | 100.0% | 141 | 100.0% |
| 0-17 | -- | -- | 4 | 1.7% | -- | -- |
| 3659 GLAUCOMA NOS | -- | -- | 4 | 100.0% | -- | -- |
| 18+ | 278 | 97.0% | 220 | 98.3% | 138 | 98.2% |
| 3659 GLAUCOMA NOS | 231 | 83.1% | 163 | 73.9% | 111 | 80.1% |
| V670 SURGERY FOLLOW-UP | 10 | 3.4% | 20 | 9.2% | 8 | 5.9% |
| 2500 DIABETES MELLITUS UNCOMI | -- | -- | -- | -- | 6 | 4.3% |
| 3651 OPEN-ANGLE GLAUCOMA | 28 | 9.9% | 27 | 12.0% | 5 | 3.7% |
| 3644 VASCULR DIS IRIS/CILIARY | -- | -- | -- | -- | 3 | 2.3% |
| 3669 CATARACT NOS | -- | -- | -- | -- | 3 | 1.9% |
| 3623 RETINAL VASC OCCLUSION | 3 | 1.2% | -- | -- | 3 | 1.9% |
| 3650 BORDERLINE GLAUCOMA | -- | -- | 4 | 1.9% | -- | -- |
| 3793 OTHER LENS DISORDERS | -- | -- | 3 | 1.4% | -- | -- |
| 3619 RETINAL DETACHMENT NOS | 6 | 2.3% | -- | -- | -- | -- |
| 3665 AFTER-CATARACT | -- | -- | 3 | 1.5% | -- | -- |
| UNSPEC. | 9 | 3.0% | -- | -- | 3 | 1.8% |
| 3659 GLAUCOMA NOS | 3 | 39.8% | -- | -- | 3 | 100.0% |
| 3651 OPEN-ANGLE GLAUCOMA | 5 | 60.2% | -- | -- | -- | -- |

Source: Verispan Physician Drug and Diagnosis Audit. Extracted 7/7/08. File: PDDA 2007-505 Betaxolol BPCA Diagnosis by Age.xls

*Use-projected uses for a product linked to a diagnosis. The projected number of times a product has been reported for a treatment of a particular disease. --means no data

APPENDIX 2: Database Descriptions

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 2.0 billion prescription claims per year, representing over 160 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®: 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 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

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.

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ 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. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. 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.

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