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Subject: Timoptic[®] (timolol) BPCA Drug Use Review

Drug Name(s): Timoptic[®] (timolol)

Application Type/Number: NDA 18-086

Applicant/sponsor: Merck

OSE RCM #: 2007-506

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EXECUTIVE SUMMARY

This review examines drug utilization patterns for timolol (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. Approximately 99% of timolol sold is in ophthalmic formulations. Since approximately 58% of ophthalmic liquid timolol bottles were sold to U.S. retail settings and 69% of gel forming solution was sold to U.S. retail settings while about 18% and 11%, respectively were sold to non-retail 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 timolol 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 timolol represented approximately 52% of the total projected number of dispensed prescriptions for the selected ophthalmic agents.
- Ophthalmic timolol prescriptions in the pediatric population (ages 0-17 years) accounted for approximately 1.2% of total dispensed prescriptions.
- Similarly, approximately 1.8% of the total projected patients who filled a prescription for ophthalmic timolol were pediatric patients.
- Ophthalmology was the top prescribing specialty for ophthalmic timolol.
- The top diagnosis code associated with the use of ophthalmic timolol for patients aged 0 to 17 years was “vascular dis iris/ciliary” (ICD-9 364.4).
- Use of ophthalmic timolol in the adult population has been declining over the three 12-month study periods examined but use in the pediatric population has increased slightly.

1 INTRODUCTION

Using the currently available proprietary drug use databases licensed by the Agency, this review describes outpatient drug use patterns for ophthalmic timolol 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 timolol 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, and food stores with pharmacies) accounted for the majority of ophthalmic liquid timolol sales at 58% and with 69% of gel forming solution. Approximately 18% of liquid timolol and 11% of gel forming solution of timolol was sold to non-retail settings. Thus, the examination of ophthalmic timolol utilization patterns focused on the outpatient setting.

Outpatient use and patient demographics (stratified by ages 0-17 years and 18+ years for ophthalmic timolol) 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

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

number of patients who received a prescription for ophthalmic timolol, and the number of drug mentions by office-based physicians, were obtained from March 1, 2005 through February 29, 2008, inclusive. For comparative purposes, other select ophthalmic agents were also examined: including betaxolol, 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 timolol represented approximately 52% of the projected number of prescriptions dispensed for the selected ophthalmic agents in the United States. The projected number of ophthalmic timolol dispensed prescriptions decreased by close to 3% 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 timolol in the pediatric population (ages 0-17 years) accounted for approximately 1.2% of the total projected number of dispensed prescriptions for ophthalmic timolol (Appendix 1 Table 2). Of the 920,973 patients who filled a prescription for ophthalmic timolol in the outpatient retail pharmacy setting during the post-exclusivity period, approximately 2% of total projected patients were aged 0 to 17 years. The projected number of patients filling a prescription for ophthalmic timolol decreased by approximately 5.5% 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 timolol with approximately 71% of U.S. retail dispensed prescriptions followed by Unspecified, Optometrists, and General Practice/Family Medicine/Doctors of Osteopathy with 11%, 5% and 3%, respectively (Appendix 1 Table 4). Pediatricians accounted for less than 1% (around 10,000 TRx/12-month period of review) of overall dispensed prescriptions for ophthalmic timolol.

According to office-based physician practices in the U.S., “vascular dis iris/ciliary” (ICD-9 364.4) was the top diagnosis code associated with the use of ophthalmic timolol 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 timolol during the three 12-month study periods (Appendix 1 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 timolol 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

Dispensed prescriptions of ophthalmic timolol in the adult population have declined by approximately 3% between the pre-exclusivity and post exclusivity time period however; in the pediatric population it has increased slightly by about 10%.

CONCURRENCE

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APPENDICES

APPENDIX 1: Tables

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	
	Baseline		Pre-Exclusivity		Post-Exclusivity	
	Retail TRxs N	Share %	Retail TRxs N	Share %	Retail TRxs N	Share %
TOTAL MARKET	7,072,517	100.0%	6,864,090	100.0%	6,435,542	100.0%
Timolol	3,575,421	50.6%	3,571,152	52.0%	3,456,786	53.7%
dorzolamide hcl/timolol	2,530,560	35.8%	2,456,171	35.8%	2,227,857	34.6%
Betaxolol	463,264	6.6%	395,124	5.8%	339,818	5.3%
levobunolol hydrochloride	333,979	4.7%	300,365	4.4%	266,577	4.1%
Carteolol	114,974	1.6%	96,661	1.4%	82,708	1.3%
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 8/5/08. File: VONA 2007-506 Timolol BPCA TRx by comparators.xls

Table 2. Total number of dispensed prescriptions for ophthalmic timolol 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 to
	Retail TRxs	Share	Retail TRxs	Share	Retail TRxs	Share	Exclusivity	Post-
	N	%	N	%	N	%	% change	% change
Timolol	3,575,347	100.0%	3,571,087	100.0%	3,456,809	100.0%	-3.32%	-3.20%
age 0-17	37,590	1.1%	42,301	1.2%	46,491	1.3%	23.68%	9.91%
age 18+	3,507,186	98.1%	3,511,550	98.3%	3,394,570	98.2%	-3.21%	-3.33%
age UNSPEC.	30,571	0.9%	17,236	0.5%	15,748	0.5%	-48.49%	-8.63%

Source: Verispan, Vector One®: National. Data Extracted 8/6/08. File: VONA 2007-506 Timolol BPCA TRx by Age.xls

Table 3. Projected Number of Patients Who Filled a Ophthalmic Timolol 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	
	Baseline		Pre-Exclusivity		Post-Exclusivity	
	Projected Patient Count	Share %	Projected Patient Count	Share %	Projected Patient Count	Share %
Timolol Total	989,875	100.00%	974,376	100.00%	920,973	100.00%
Age 0-17	15,853	1.60%	17,881	1.84%	19,100	2.07%
Age 18+	960,831	97.07%	948,937	97.39%	895,705	97.26%
Age Unspec.	61,887	6.25%	54,292	5.57%	52,829	5.74%

Source: Verispan, Vector One®: Total Patient Tracker, Data Extracted 8/6/08. File: TPT 2007-506 Timolol BPCA Patient Count by Age.xls

Table 4. Total number of ophthalmic timolol prescriptions dispensed from U.S. retail pharmacies by prescriber specialty (Top 20), MAT March 1, 2005-February 29, 2008

	March 2005-Feb 2006		March 2006-Feb 2007		March 2007 -Feb 2008	
	Baseline		Pre-Exclusivity		Post-Exclusivity	
	Retail TRxs N	Share %	Retail TRxs N	Share %	Retail TRxs N	Share %
TIMOLOL	3,662,078	100.0%	3,657,483	100.0%	3,536,050	100.0%
OPHTHALMOLOGY	2,558,133	69.9%	2,615,122	71.5%	2,542,543	71.9%
UNSPECIFIED	497,060	13.6%	370,450	10.1%	306,714	8.7%
OPTOMETRIST	146,899	4.0%	184,950	5.1%	219,538	6.2%
GP/FM/DO*	112,644	3.1%	120,100	3.3%	116,293	3.3%
INTERNAL MEDICINE	103,077	2.8%	105,517	2.9%	102,563	2.9%
HOSPITAL	100,898	2.8%	106,667	2.9%	96,157	2.7%
OTHER	22,767	0.6%	28,141	0.8%	31,578	0.9%
OTHER SPECIALTY	21,769	95.6%	26,864	95.5%	30,648	97.1%
OTOLOGY	297	1.3%	364	1.3%	199	0.6%
AEROSPACE MEDICINE	73	0.3%	152	0.5%	163	0.5%
MATERNAL AND FETAL MEDICINE	87	0.4%	156	0.6%	140	0.4%
ADDICTION MEDICINE	77	0.3%	91	0.3%	113	0.4%
NUCLEAR MEDICINE	62	0.3%	102	0.4%	73	0.2%
PSYCHOANALYSIS	23	0.1%	29	0.1%	56	0.2%
ADOLESCENT MEDICINE	42	0.2%	62	0.2%	54	0.2%
PUBLIC HEALTH	210	0.9%	198	0.7%	47	0.1%
MIDWIFE	11	0.0%	41	0.1%	37	0.1%
PAIN MEDICINE	39	0.2%	22	0.1%	34	0.1%
GENETICS	9	0.0%	8	0.0%	9	0.0%
LEGAL MEDICINE	46	0.2%	45	0.2%	5	0.0%
PHARMACOLOGY, CLINICAL	22	0.1%	7	0.0%	--	--
CARDIOVASCULAR DISEASES	14,551	0.4%	13,847	0.4%	12,643	0.4%
NEUROLOGY	10,663	0.3%	10,625	0.3%	10,534	0.3%
NEUROLOGY	10,463	98.1%	10,437	98.2%	10,376	98.5%
CHILD NEUROLOGY	200	1.9%	188	1.8%	158	1.5%
PEDIATRICS	10,092	0.3%	10,702	0.3%	10,317	0.3%
PEDIATRICS	5,272	52.2%	5,883	55.0%	5,867	56.9%
PEDIATRIC, OTHER	3,136	31.1%	3,229	30.2%	2,507	24.3%
PEDIATRICS, INTERNAL MEDICINE	1,034	10.2%	1,178	11.0%	1,367	13.2%
PEDIATRIC OTOLARYNGOLOGY	210	2.1%	188	1.8%	221	2.1%
PEDIATRIC PULMONOLOGY	62	0.6%	17	0.2%	81	0.8%
PEDIATRIC CARDIOLOGY	34	0.3%	21	0.2%	64	0.6%
PEDIATRIC SURGERY	165	1.6%	63	0.6%	45	0.4%
PEDIATRIC ENDOCRINOLOGY	51	0.5%	41	0.4%	44	0.4%
PEDIATRIC EMERGENCY MED.	11	0.1%	19	0.2%	33	0.3%
PEDIATRIC HEMATOLOGY	43	0.4%	37	0.3%	33	0.3%
PEDIATRIC RADIOLOGY	20	0.2%	12	0.1%	25	0.2%
PEDIATRIC NEPHROLOGY	9	0.1%	3	0.0%	16	0.2%
PEDIATRIC ALLERGY	45	0.4%	11	0.1%	14	0.1%
DENTISTS	7,663	0.2%	8,498	0.2%	8,700	0.2%
PSYCHIATRY	6,769	0.2%	6,936	0.2%	6,520	0.2%
PSYCHIATRY	5,560	82.1%	5,685	82.0%	5,539	85.0%
CHILD PSYCHIATRY	1,129	16.7%	1,169	16.9%	916	14.0%
PSYCHIATRY, GERIATRIC	80	1.2%	82	1.2%	65	1.0%
NURSE PRACTITIONER	4,879	0.1%	5,912	0.2%	6,193	0.2%
OB/GYN	5,860	0.2%	6,157	0.2%	6,175	0.2%
EMERGENCY MEDICINE	4,935	0.1%	5,726	0.2%	5,814	0.2%
GENERAL SURGERY	6,544	0.2%	6,115	0.2%	5,348	0.2%
ORTHOPEDIC SURGERY	4,672	0.1%	4,624	0.1%	4,455	0.1%
ORTHOPEDIC SURGERY	4,237	90.7%	4,207	91.0%	3,876	87.0%
ORTHOPEDIC SURGERY, OTHER	77	1.6%	133	2.9%	284	6.4%
ORTHO SURG, SPORTS MEDICINE	284	6.1%	226	4.9%	255	5.7%
ORTHO SURG, PED ORTHOPEDICS	74	1.6%	58	1.3%	40	0.9%
PHYSICIAN ASSISTANT	2,599	0.1%	3,653	0.1%	3,981	0.1%
AO SURG	3,877	0.1%	3,866	0.1%	3,444	0.1%
GERIATRICS	2,729	0.1%	3,105	0.1%	3,187	0.1%
All Others	34,767	0.9%	36,770	1.0%	33,353	0.9%

Source: Verispan, Vector One®: National, Data Extracted 8/5/08. File: VONA 2007-506 Timolol BPCA TRx by prescribing specialty.xls

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

Table 5. Diagnosis associated with the use* of ophthalmic timolol 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		Pre-Exclusivity		Post-Exclusivity	
	Uses (000)	Share %	Uses (000)	Share %	Uses (000)	Share %
Timolol	2,562	100.0%	2,465	100.0%	2,112	100.0%
0-17	3	0.1%	11	0.5%	5	0.2%
3644 VASCULR DIS IRIS/CILIARY	--	--	--	--	5	100.0%
3651 OPEN-ANGLE GLAUCOMA	--	--	6	51.3%	--	--
3659 GLAUCOMA NOS	3	100.0%	6	48.7%	--	--
18+	2,472	96.5%	2,423	98.3%	2,064	97.8%
3659 GLAUCOMA NOS	1,801	72.9%	1,736	71.7%	1,394	67.5%
3651 OPEN-ANGLE GLAUCOMA	376	15.2%	327	13.5%	429	20.8%
3650 BORDERLINE GLAUCOMA	117	4.7%	166	6.9%	161	7.8%
V670 SURGERY FOLLOW-UP	19	0.8%	34	1.4%	21	1.0%
3656 GLAUC W OCULAR DIS NEC	7	0.3%	--	--	10	0.5%
3625 DEGENERATION OF MACULA	6	0.3%	29	1.2%	8	0.4%
3669 CATARACT NOS	25	1.0%	11	0.5%	6	0.3%
3688 VISUAL DISTURBANCES NEC	--	--	--	--	6	0.3%
3619 RETINAL DETACHMENT NOS	6	0.3%	--	--	5	0.3%
3655 GLAUCOMA W LENS DISORDER	--	--	--	--	4	0.2%
All Others	115	4.7%	118	4.9%	21	1.0%
UNSPEC.	87	3.4%	31	1.2%	42	2.0%
3659 GLAUCOMA NOS	61	69.3%	23	74.5%	25	59.9%
3651 OPEN-ANGLE GLAUCOMA	7	8.4%	8	25.5%	11	26.9%
3652 PRIM ANGL-CLOSURE GLAUC	--	--	--	--	6	13.2%
3793 OTHER LENS DISORDERS	3	3.5%	--	--	--	--
3669 CATARACT NOS	5	6.1%	--	--	--	--
V670 SURGERY FOLLOW-UP	11	12.6%	--	--	--	--

Source: Verispan Physician Drug and Diagnosis Audit. Extracted 8/6/08. File: PDDA 2007-506 Timool 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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