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Review, Drug Utilization Analysis
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CONTENTS

EXECUTIVE SUMMARY	2
1 Background.....	2
1.1 Introduction.....	2
1.2 Regulatory history.....	3
2 Methods and Materials	3
2.1 Introduction.....	3
2.2 Determining setting of care.....	3
2.3 Data sources used.....	3
3 Results	4
3.1 Dispensed Prescriptions for Antihypertensive / Angina Market.....	4
3.2 Dispensed Prescriptions for Metoprolol ER	4
3.3 Patient Demographics	4
3.4 Prescriber Specialty.....	5
3.5 Indication for use	5
4 Discussion.....	6
4.1 Epidemiology	6
4.2 Data Caveats and Limitations	6
5 Conclusions.....	7
APPENDICES	8

EXECUTIVE SUMMARY

This review is provided to provide context for the adverse event reporting required by the BPCA and describes the U.S. outpatient drug use patterns for Toprol XL[®] and generic metoprolol extended release (ER) in the pediatric and adult populations in the years prior to and following the granting of pediatric exclusivity for Toprol XL. Proprietary drug use databases licensed by FDA were used to conduct this analysis. This document will refer to the combined total use of Toprol XL and generic metoprolol ER as “metoprolol ER.”

The Verispan, LLC: Vector One[®]: National database was queried to obtain counts of retail pharmacy metoprolol ER prescriptions dispensed, as well as stratification of those prescriptions by patient age and prescriber specialty type. The number of prescriptions dispensed for all ages in the Anti-hypertensive/Angina has been increasing annually during this study period. Similar to the overall market data for all age groups, the number of dispensed prescriptions in the pediatric population (ages 0-16 years) has also been increasing annually.

The total number of metoprolol ER prescriptions dispensed by retail pharmacies increased by 8% from the pre-exclusivity period to the post-exclusivity period. A total of 38.9 million retail metoprolol ER prescriptions were dispensed during the post-exclusivity 12-month period of August 1, 2006 through July 31, 2007. Most patients (greater than 99%) who received a retail prescription for metoprolol ER were adults 17 years of age and older. Pediatric use revealed a slight decrease in the number of dispensed prescriptions for the overall pediatric population aged 0-16 years, but a larger decrease in the age 0-5 year subgroup and a slight increase in the older 6-16 year subgroup.

General practitioner, family medicine, osteopaths and internal medicine physicians were responsible for roughly 62% of dispensed prescriptions during the pre and post exclusivity years.

The Verispan, LLC: Total Patient Tracker (TPT) database was queried to obtain counts of patients who received at least one retail pharmacy prescription for metoprolol ER in each year of the study period. Most of these patients (99%) were adults 17 years of age and older. Patient-level data were similar to dispensed prescription data.

The Verispan, LLC: Physician Drug and Diagnosis Audit (PDDA) survey was queried to obtain counts of office-based physician visits for metoprolol ER, stratified by 4-digit diagnosis codes. Pediatric patients accounted for 0.04% of the of the surveyed office visits associated with metoprolol ER during the two pre-exclusivity 12-month periods (i.e., July 1, 2004 to June 30, 2006) and 0.3% of the office visits during the post-exclusivity year; the diagnoses associated with pediatric mentions were Tachycardia NOS,” “Hypertension, NOS,” “Atrial Fibrillation/Flutter,” and “Cardiac Dysrhythmias NOS.”

1 BACKGROUND

1.1 INTRODUCTION

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 reporting 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.

1.2 REGULATORY HISTORY

Toprol XL[®] (metoprolol succinate) is a beta₁-selective (cardiovascular) adrenoceptor blocking agent formulated as an extended release tablet for oral once-daily administration.

Toprol XL[®] was approved for marketing on January 10, 1992, under NDA 19-962, for the treatment for hypertension (either alone or in combination), and for the long term treatment of angina pectoris. At approval, the safety and effectiveness in pediatric patients had not been established and the product was labeled as such. In February, 2001, the indication for the treatment of congestive heart failure was added.

In response to a FDA Pediatric Written Request for studies of Toprol XL[®] in pediatric patients, Astra Zeneca conducted a study of 144 pediatric hypertensive patients ages 6-16 years of age. Pediatric Exclusivity was granted on July 27, 2006, with the following labeling changes approved on July 18, 2007. These changes include: a summary of the study results, a statement that the adverse event profile was similar to adults, that safety and effectiveness have not been established in patients < 6 years of age, and information on PK parameters, clinical studies, and pediatric dosing.

2 METHODS AND MATERIALS

2.1 INTRODUCTION

Using the currently available data resources, this review describes the outpatient drug use patterns for metoprolol ER in the pediatric and adult populations in the years prior to and following the granting of pediatric exclusivity for Toprol XL[®] on July 27, 2006. This document will refer to the combined total use Toprol XL[®] and generic metoprolol ER as “metoprolol ER.” Proprietary drug use databases licensed by FDA were used to conduct this analysis.

2.2 DETERMINING SETTING OF CARE

IMS Health, IMS National Sales Perspectives[™] data were used to determine the primary settings in which metoprolol ER (Toprol XL[®] and generic metoprolol ER) is sold. Cumulative sales of these products by number of oral dosage forms (i.e., “extended units” or EUs) sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for three 12-month periods from August 1, 2004 through July 31, 2007. A complete description of this IMS Health database is provided in Appendix One.

Using IMS Health, IMS National Sales Perspectives[™] data, we determined that retail pharmacies accounted for 69%, retail outpatient mail order pharmacies for 22-23% of the metoprolol ER tablets sold during the three 12-month study periods from August 2004 through July 2007. The remaining 8-9% of annual sales were to non-retail distribution channels which include hospitals, clinics, HMOs, educational facilities and prisons.

Because most metoprolol ER sold during this time period went to retail and mail order pharmacies (92% of sales on a tablet basis), we examined utilization patterns focusing on the outpatient setting. Sales data indicate that the Verispan database VONA is the most appropriate data source to measure the use of these products among the databases licensed by FDA.

2.3 DATA SOURCES USED

Outpatient use and patient demographics were measured with two data sources from Verispan, LLC: Vector One[®]: National (VONA), and Total Patient Tracker (TPT). From these sources, nationally projected estimates of the number of prescriptions dispensed by retail pharmacies and the number of patients who received a prescription dispensed by retail pharmacies for metoprolol ER were obtained. Indications for use were obtained from the Verispan, Physician Drug and Diagnosis Audit (PDDA). Outpatient drug utilization patterns were examined for three 12-month

periods from August 1, 2004 through July 31, 2007. Complete descriptions of the databases used are provided in Appendix One.

3 RESULTS

3.1 DISPENSED PRESCRIPTIONS FOR ANTIHYPERTENSIVE / ANGINA MARKET

The total number of prescriptions dispensed by retail pharmacies for all products within the Anti-hypertensive/Angina Market was obtained using Verispan, Vector One[®]: National (Appendix 1, Table 1). The overall number of prescriptions dispensed for this defined market of products has been increasing annually for each of the three 12-month period ending in July. The most commonly dispensed products during August 2006 through July 2007 were lisinopril and hydrochlorothiazide which accounted for roughly 10% and 8%, respectively, of the anti-hypertensive/angina market. Metoprolol ER was the fourth most commonly dispensed product within the defined market accounting for roughly 6% of overall dispensing. During the post-exclusivity year (August 2006 – July 2007), generic metoprolol ER became available and accounted for 14% of all metoprolol ER/Toprol XL prescriptions during the post-exclusivity year.

Similar to the overall market data for all age groups, the number of dispensed prescriptions in the pediatric population (ages 0-16 years) for the Anti-hypertensive/Angina market has been increasing annually for each of the three 12-month period ending in July. Among pediatric patients ages 0-16 years old, the most commonly dispensed product in the Anti-hypertensive/Angina Market were clonidine, accounting for 48% of retail prescriptions during the pre- (August 2005 – July 2006) and post-exclusivity (August 2006 – July 2007) years, followed by guanfacine (13% of prescriptions) and enalapril (roughly 7% of prescriptions) (Appendix 1, Table 2). Metoprolol ER was the 15th most commonly dispensed product and accounted for approximately 0.5% of retail prescriptions dispensed within the defined market. Compared to other beta-blockers during the post-exclusivity year, metoprolol ER (21,000 prescriptions) is the third most commonly used after atenolol (181,000 Prescriptions), and propranolol (154,000 prescriptions). The other beta-blockers each accounted for less than 0.25% of the overall number of pediatric beta-blocker prescriptions.

3.2 DISPENSED PRESCRIPTIONS FOR METOPROLOL ER

The total number of metoprolol ER prescriptions dispensed by retail pharmacies increased by approximately 8% from the pre-exclusivity period (August 2005 – July 2006) to the post-exclusivity period (August 2006 – July 2007) (Appendix 1, Table 3). A total of 35.9 million retail metoprolol ER prescriptions were dispensed during the pre-exclusivity 12-month period of August 1, 2005 through July 31, 2006. A total of 38.9 million retail metoprolol ER prescriptions were dispensed during the post-exclusivity 12-month period of August 1, 2006 through July 31, 2007.

3.3 PATIENT DEMOGRAPHICS

3.3.1 PRESCRIPTIONS DISPENSED

Verispan, LLC: Vector One[®], Prescription Services database was queried to obtain counts of metoprolol ER retail and mail order pharmacy prescriptions dispensed stratified by patient age.

Most patients (i.e., greater than 99%) who received retail prescriptions for metoprolol ER were adults over 16 years of age (Appendix 1, Table 4). A total of 22,032 retail metoprolol ER prescriptions were dispensed to children from 0 to 16 years of age during the pre-exclusivity 12-month period of August 1, 2005 through July 31, 2006. A total of 20,817 retail metoprolol ER prescriptions were dispensed to children from 0 to 16 years of age during the post-exclusivity 12-month period of August 1, 2006 through July 31, 2007. This represented a decrease of

approximately 5.5% between pre- and post-exclusivity time periods for the overall pediatric population.

Examination of the 0-5 year pediatric subgroup revealed that there was a dramatic decrease in the number of dispensed prescriptions for metoprolol ER during the entire study period. An estimated 8,800 prescriptions were dispensed during the 12 months period of August 2004 through July 2005, followed by 4,600 during the pre-exclusivity year of August 2005 – July 2006, and 2,000 prescriptions during the post exclusivity year of August 2006 – July 2007. Between the pre- and post-exclusivity periods, this represented a decrease of 56% in dispensed prescriptions among this age group.

In contrast, there was an 8% increase in the number of dispensed prescriptions among the 6-16 year age group from an estimated 17,400 prescriptions during the pre-exclusivity period to nearly 18,800 prescriptions during the post-exclusivity period.

3.3.2 PATIENT COUNTS FOR DISPENSED PRESCRIPTIONS

Verispan, LLC: Total Patient Tracker (TPT) was queried to obtain counts of patients who received at least one retail pharmacy prescription for metoprolol ER.

There were 6.8 million patients who received an outpatient prescription through retail pharmacies during the pre-exclusivity 12-month period of August 1, 2005 through July 31, 2006, and 6.9 million during the post-exclusivity 12-month period of August 1, 2006 through July 31, 2007; an increase of 1%. Most patients (i.e., greater than 99.7%) who received metoprolol ER via retail pharmacy prescriptions were adults 17 years of age and older. Analysis of patient-level data in the pediatric population revealed similar trends to dispensed prescription data. There was a slight decrease in use for the overall number of pediatric patients aged 0-16 years, but a larger decrease in the age 0-5 year subgroup and a slight increase in the older 6-16 year subgroup.

3.4 PRESCRIBER SPECIALTY

Verispan, LLC: Vector One[®]: National database was queried to obtain counts of retail pharmacy metoprolol ER prescriptions dispensed, stratified by prescriber medical specialty (Appendix 1, Table 5).

Most retail prescriptions for metoprolol ER were written by General Practice/Family Medicine/Doctors of Osteopathy physicians and cardiologists which each accounted for roughly 31% of prescriptions dispensed during each year of this analysis. These two medical specialties accounted for approximately 62% of the retail metoprolol ER prescriptions dispensed during the pre-exclusivity 12-month period of August 1, 2005 through July 31, 2006 and the post-exclusivity 12-month period of August 1, 2006 through July 31, 2007.

Pediatricians accounted for approximately 1% of metoprolol ER prescriptions for both pre- and post-exclusivity periods.

3.5 INDICATION FOR USE

Verispan, LLC: Physician Drug and Diagnosis Audit (PDDA) survey was queried to obtain counts of office-based physician visits for metoprolol ER, stratified by 4-digit diagnosis codes associated with the visits (Appendix 1, Table 6).

Adults aged 17 years and older accounted for the majority (i.e., 97% – 98%) of office-based physician visits during the three 12-month study periods with which metoprolol ER was associated. Pediatric patients accounted for less than 1% of the surveyed office visits associated with metoprolol ER for the pre- (August 2005 – July 2006) and post-exclusivity (August 2006 – July 2007) periods; pediatric patients were associated with the diagnoses of “Tachycardia NOS,” “Hypertension, NOS,” “Atrial Fibrillation/Flutter,” and Cardiac Dysrhythmias NOS.”

4 DISCUSSION

4.1 EPIDEMIOLOGY

There are several studies in the literature that describe the prevalence of hypertension in the pediatric population and most identify a positive relationship between overweight and hypertension. A recent school-based screening of 5,102 children examined blood pressure in a series of 1-3 measurements and found that the prevalence of elevated blood pressure after the first, second and third screenings was 19.4%, 9.5%, and 4.5%, respectively¹. The prevalence of hypertension increased progressively as the BMI increased from the 5th percentile (2%) to the 95th percentile (11%). To determine the frequency of undiagnosed hypertension, a subsequent study² utilized the medical records of children aged 3 to 18 who were observed at least 3 times for well-child care over a 7-year period. It revealed that of the 3.6% of children who had hypertension, only 26% had a diagnosis of elevated blood pressure or hypertension documented in the electronic medical record. It is generally believed that the obesity epidemic among children will lead to more diagnoses of pediatric/adolescent hypertension, and hence a growing use of antihypertensive agents among this age group.

4.2 DATA CAVEATS AND LIMITATIONS

This analysis of the outpatient use of metoprolol ER indicates that a minority of its use is in pediatric patients. The decrease in the number of prescriptions dispensed to patients 0-5 years of age from the pre- to post-exclusivity periods may be attributed to the decrease in off-label prescribing to these patients. However, the use in the age 6-16 year population may point to a different trend in the long run.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that the use of metoprolol ER was primarily in the 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 the number of tablets sold from the manufacturer to 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. The actual proportion of overall prescription dispensing by each pharmacy channel will differ based on the average prescription size dispensed.

The Verispan 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 the sampling and data collection methodologies, the small sample size can make these data unstable, particularly when use is not common in the pediatric population, as in the case of metoprolol ER. Verispan recommends trending PDDA data only when projected counts exceed 100,000 uses or visits per year.

While we conducted a comprehensive analysis of the use of this product in the outpatient settings, in which the majority of use occurred, use outside of the retail and mail order pharmacy settings was not captured in our analysis.

¹ Sorof JM, Lai D, Turner J, Poffenbarger T, Portman RJ. Overweight, ethnicity, and the prevalence of hypertension in school-aged children. *Pediatrics*. 2004;113(3 pt 1):475–482.

² Hansen ML, Gunn PW, Kaelber DC. Underdiagnosis of hypertension in children and adolescents. *JAMA*. 2007;298:874-879.

5 CONCLUSIONS

The clinical trial data submitted for Pediatric Exclusivity for Toprol XL[®] resulted in a labeling change providing information about safety and dosing in pediatric patients. Based on the databases licensed by FDA, a very small proportion of the total number of patients treated with metoprolol are pediatric patients (roughly 0.1% of overall use). Use in the overall pediatric population has declined slightly, mostly due to the large drop-off in use in the 0-5 year age group.

APPENDICES

APPENDIX ONE: Data Tables

Table 1. Projected Number of Retail Prescriptions Dispensed (in Thousands) through U.S. Retail Outpatient Pharmacies for the Antihypertensive/Angina Market, August 1, 2004 - July 31, 2007

	Aug 2004 - Jul 2005		Aug 2005 - Jul 2006		Aug 2006 - Jul 2007	
	Retail TRxs	(%)	Retail TRxs	(%)	Retail TRxs	(%)
Total Market	546,118	(100)	568,289	(100)	594,507	(100)
Lisinopril	46,965	(8.6)	52,543	(9.2)	59,336	(10)
Hydrochlorothiazide (HCTZ)	42,158	(7.7)	44,263	(7.8)	45,607	(7.7)
Atenolol	42,691	(7.8)	42,825	(7.5)	42,710	(7.2)
Metoprolol ER	32,587	(6)	35,902	(6.3)	38,896	(6.5)
Toprol XL	32,587	(100)	35,902	(100)	33,619	(86.4)
Metoprolol Succinate	--	--	--	--	5,277	(13.6)
Furosemide	34,909	--	35,957	--	37,045	(6.2)
Amlodipine Besylate	32,242	(5.9)	33,296	(5.9)	33,433	(5.6)
Metoprolol Tartrate	21,656	(4)	23,867	(4.2)	26,577	(4.5)
HCTZ/Triamterene	24,069	(4.4)	23,323	(4.1)	22,309	(3.8)
Diltiazem HCl	17,324	(3.2)	17,319	(3)	17,428	(2.9)
Valsartan	12,406	(2.3)	13,455	(2.4)	14,853	(2.5)
Enalapril Maleate	12,846	(2.4)	12,864	(2.3)	13,087	(2.2)
Benazepril/Amlodipine	12,743	(2.3)	13,373	(2.4)	13,065	(2.2)
Valsartan/HCTZ	10,144	(1.9)	10,885	(1.9)	12,390	(2.1)
Lisinopril/HCTZ	10,289	(1.9)	9,864	(1.7)	11,733	(2)
Carvedilol	7,343	(1.3)	9,639	(1.7)	11,618	(2)
Clonidine HCl	9,681	(1.8)	10,309	(1.8)	10,819	(1.8)
Ramipril	11,311	(2.1)	11,201	(2)	10,665	(1.8)
Verapamil HCl	11,448	(2.1)	10,843	(1.9)	10,456	(1.8)
Nifedipine	9,162	(1.7)	9,196	(1.6)	9,631	(1.6)
Isosorbide Mononitrate	9,544	(1.7)	9,330	(1.6)	9,444	(1.6)
Losartan Potassium	8,363	(1.5)	8,384	(1.5)	8,582	(1.4)
Spironolactone	7,055	(1.3)	7,439	(1.3)	7,959	(1.3)
Quinapril HCl/Mag Carb	8,391	(1.5)	7,579	(1.3)	6,940	(1.2)
Benazepril HCl	6,533	(1.2)	6,431	(1.1)	6,610	(1.1)
Losartan Potassium/HCTZ	6,529	(1.2)	6,458	(1.1)	6,524	(1.1)
Olmesartan Medoxomil	4,396	(0.8)	5,293	(0.9)	5,979	(1)
All Others	93,334	(17.1)	96,452	(17)	100,813	(17)

Source: Verispan Vector One: National Data Extracted 9-2007

File: 2007-253 VONA Toprol Market by molecule-product.xls

*Total Others includes all molecules with less than 1% of Market Share during Aug 1 2006 - July 31, 2007

The Antihypertensive/Angina Market includes the following molecules: acebutolol, amiloride, amiloride/HCTZ, amlodipine, amlodipine/atorvastatin, amlodipine/benazepril, atenolol, benazepril, betaxolol, bisoprolol, bumetanide, candesartan, captopril, carvedilol, chlorothiazide, chlorthalidone/clonidine, clonidine, diltiazem, doxazosin mesylate, enalapril maleate, epienone, eprosartan, felodipine, fosinopril, furosemide, guanfacine, hydralazine, HCTZ/irbesartan, HCTZ/lisinopril, HCTZ/losartan, HCTZ/methyldopa, HCTZ/moexipril, HCTZ/olmesartan, HCTZ/telmisartan, HCTZ/timolol, HCTZ/triamterene, indapamide, irbesartan, isosorbide mononitrate, isradipine, labetalol, lisinopril, losartan, metolazone, metoprolol succinate, metoprolol tartrate, minoxidil, moexipril, nadolol, nicardipine, nifedipine, nisoldipine, nitroglycerin, nitroglycerin, olmesartan, penbutolol, perindopril, pindolol, prazosin, propranolol, quinapril, ramipril, spironolactone, telmisartan, terazosin, timolol, torsemide, trandolapril, trandolapril/verapamil, trandolopril, triamterene, valsartan, verapamil

Table 2. Projected Number of Pediatric (ages 0-16 years) Retail Prescriptions Dispensed (in Thousands) through U.S. Retail Outpatient Pharmacies for the Antihypertensive/Angina Market, August 1, 2004 - July 31, 2007

	Aug 2004 - Jul 2005		Aug 2005 - Jul 2006		Aug 2006 - Jul 2007	
	Retail TRxs	(%)	Retail TRxs	(%)	Retail TRxs	(%)
0-16	3,526	(100)	3,696	(100)	3,874	(100)
Clonidine hcl	1,653	(46.9)	1,786	(48.3)	1,840	(47.5)
Guanfacine hcl	453	(12.8)	469	(12.7)	510	(13.2)
Enalapril maleate	235	(6.7)	262	(7.1)	291	(7.5)
Atenolol	158	(4.5)	170	(4.6)	181	(4.7)
furosemide	128	(3.6)	142	(3.8)	156	(4)
Propranolol	166	(4.7)	155	(4.2)	154	(4)
Amlodipine besylate	111	(3.1)	128	(3.5)	151	(3.9)
Spirololactone	83	(2.4)	87	(2.3)	93	(2.4)
Lisinopril	79	(2.2)	85	(2.3)	93	(2.4)
benazepril hydrochloride	37	(1)	47	(1.3)	53	(1.4)
hydrochlorothiazide	47	(1.3)	43	(1.2)	41	(1.1)
Diltiazem hydrochloride	35	(1)	34	(0.9)	36	(0.9)
Captopril	39	(1.1)	37	(1)	35	(0.9)
Verapamil hcl	27	(0.8)	24	(0.7)	22	(0.6)
Metoprolol succinate	28	(0.8)	22	(0.6)	21	(0.5)
All Others	248	(7)	206	(5.6)	198	(5.1)

Source: Verispan Vector One: National, extracted 9/2007 File: 2007-253 VONA Toprol Market by Age0-16.qry

Table 3. Projected Number of Retail Prescriptions Dispensed through U.S. Outpatient Pharmacies for Metoprolol ER by Patient Age, August 1, 2004 - July 31, 2007

	Aug 2004 - Jul 2005		Aug 2005 - Jul 2006		Aug 2006 - Jul 2007	
	Retail TRxs	(%)	Retail TRxs	(%)	Retail TRxs	(%)
metoprolol succinate	32,587,156	(100)	35,901,774	(100)	38,895,565	(100)
0-16	27,579	(0.1)	22,032	(0.1)	20,817	(0.1)
0-5	8,831	(32)	4,610	(20.9)	2,026	(9.7)
6-16	18,748	(68)	17,422	(79.1)	18,791	(90.3)
17+	32,398,740	(99.4)	35,762,761	(99.6)	38,802,706	(99.8)
UNSPEC.	160,837	(0.5)	116,981	(0.3)	72,042	(0.2)

Source: Verispan Vector One: National Data Extracted 9-2007 File: 2007-253 VONA Toprol by age

Table 4. Projected Number of Patients Receiving a Metoprolol ER Prescription through U.S. Retail Outpatient Pharmacies by Patient Age, August 1, 2004 - July 31, 2007

	Aug 2004 - Jul 2005		Aug 2005 - Jul 2006		Aug 2006 - Jul 2007	
	Projected Patients	(%)	Projected Patients	(%)	Projected Patients	(%)
Grand Total	5,935,219	(100)	6,795,543	(100)	6,894,588	(100)
0 - 16	9,306	(0.2)	8,003	(0.1)	7,122	(0.1)
0 - 5	3,001	(32.3)	2,008	(25.1)	943	(13.2)
6 - 16	6,382	(68.6)	6,077	(75.9)	6,218	(87.3)
17+	5,877,178	(99)	6,739,157	(99.2)	6,859,971	(99.5)
UNKNOWN	200,746	(3.4)	194,397	(2.9)	190,708	(2.8)

Source: Verispan Total Patient Tracker, Data Extracted 9-2007

File: TPT Metoprolol 0-5 6-16 17+.xls, TPT Metoprolol 0-16.xls

*Values may not sum exactly due to patient aging during study period

Table 5: Projected number of Retail Prescriptions Dispensed (in Thousands) through U.S. Retail Outpatient Pharmacies for Metoprolol ER by Physician Specialty, August 1, 2004 - July 31, 2007

	Aug 2004 - Jul 2005		Aug 2005 - Jul 2006		Aug 2006 - Jul 2007	
	Retail TRxs	(%)	Retail TRxs	(%)	Retail TRxs	(%)
Total	32,587	(100)	35,902	(100)	38,896	(100)
GP/FM/DO	9,783	(30)	11,218	(31.3)	12,472	(32.1)
Internal Med	9,731	(29.9)	10,909	(30.4)	11,897	(30.6)
Cardiology	6,748	(20.7)	7,340	(20.4)	8,015	(20.6)
Unspecified	2,548	(7.8)	2,049	(5.7)	1,517	(3.9)
Nurse Pract.	521	(1.6)	685	(1.9)	883	(2.3)
Hospitalist	484	(1.5)	551	(1.5)	569	(1.5)
NEPH	351	(1.1)	398	(1.1)	446	(1.2)
Physician Assistant	346	(1.1)	447	(1.3)	574	(1.5)
Pediatrician	264	(0.8)	305	(0.9)	360	(0.9)
PUD	189	(0.6)	208	(0.6)	223	(0.6)
All Others	1,621	(5)	1,791	(5)	1,940	(5)

Source: Verispan Vector One: National, Data Extracted 9-2007 File: 2007-253 VONA Toprol by MD

Table 6. Diagnoses Associated with a Mention of Metoprolol ER During Office Based Physician Visits (in thousands), August 2004 - July 2007

	Aug 2004 - Jul 2005		Aug 2005 - Jul 2006		Aug 2006 - Jul 2007	
	Uses	(%)	Uses	(%)	Uses	(%)
Metoprolol Succinate	17,816	(100)	18,693	(100)	18,147	(100)
0-16	--	--	8	(0)	58	(0.3)
7850 Tachycardia Nos	--	--	8	(100)	19	(33.3)
4019 Hypertension Nos	--	--	--	--	16	(26.9)
4273 Atrial Fibrill/Flutter	--	--	--	--	16	(26.9)
4278 Cardiac Dysrhythmias Nec	--	--	--	--	7	(12.9)
17+	17,490	(98.2)	18,095	(96.8)	17,565	(96.8)
4019 Hypertension Nos	8,976	(51.3)	9,299	(51.4)	8,507	(48.4)
4140 Coronary Atherosclerosis	1,844	(10.5)	1,956	(10.8)	1,896	(10.8)
4139 Angina Pectoris Nec/Nos	1,177	(6.7)	905	(5)	1,494	(8.5)
4273 Atrial Fibrill/Flutter	1,562	(8.9)	1,204	(6.7)	1,347	(7.7)
4280 Congestive Heart Failure	896	(5.1)	574	(3.2)	540	(3.1)
7851 Palpitations	188	(1.1)	296	(1.6)	311	(1.8)
7865 Chest Pain	252	(1.4)	285	(1.6)	280	(1.6)
V458 Oth Postsurgical Status	89	(0.5)	257	(1.4)	262	(1.5)
4240 Mitral Valve Disorder	111	(0.6)	65	(0.4)	185	(1.1)
4278 Cardiac Dysrhythmias Nec	98	(0.6)	150	(0.8)	178	(1)
All Others	2,296	(13.1)	3,103	(17.2)	2,566	(14.6)
Unspecified	326	(1.8)	590	(3.2)	523	(2.9)
4019 Hypertension Nos	203	(62.2)	286	(48.5)	300	(57.3)
4140 Coronary Atherosclerosis	20	(6.1)	101	(17.2)	64	(12.2)
7851 Palpitations	8	(2.5)	--	--	39	(7.4)
4139 Angina Pectoris Nec/Nos	--	--	28	(4.7)	19	(3.7)
4279 Cardiac Dysrhythmia Nos	--	--	--	--	16	(3)
V458 Oth Postsurgical Status	--	--	51	(8.7)	12	(2.3)
4148 Chr Ischemic Hrt Dis Nec	--	--	--	--	12	(2.3)
V670 Surgery Follow-Up	--	--	--	--	12	(2.3)
4299 Heart Disease Nos	--	--	13	(2.2)	11	(2.1)
4120 Old Myocardial Infarct	--	--	10	(1.7)	9	(1.6)
All Others	95	(29.2)	100	(17)	31	(5.9)

Source: Verispan Physician Drug and Diagnosis Audit, Data Extracted 9-2007 File: 2007-253 PDDA Toprol indications.xls

APPENDIX TWO: 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 billion prescription claims, representing over 160 million unique patients.

Prescriptions are captured from a sample of approximately 54,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent approximately 50% 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 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. The IMS Health, 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.

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/s/

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DRUG SAFETY OFFICE REVIEWER

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