



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

Date: January 30, 2008

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Subject: Pediatric Drug Use Update

Drug Name(s): Lotensin[®] (benazepril), Lotensin[®]HCT (benazepril/HCTZ), Lotrel[®]
(benazepril/amlodipine)

Application Type/Number: NDA 19-851, NDA 20-033, NDA 20-364

Submission Number:

Applicant/sponsor: Novartis

OSE RCM #: 2007-2126

1 INTRODUCTION

Outpatient drug use data for Lotensin[®] (benazepril) as well as all benazepril products was requested by Office of Pediatric Therapeutics and Pediatric and Maternal Health Staff to develop, with the Division of Cardiovascular and Renal Products, an overview of the pediatric safety issues concerning adverse events that are known to occur in adults. Lotensin[®] (benazepril) was approved for Pediatric Exclusivity on July 2, 2003. Since there were limited pediatric data in the initial 1-year post-exclusivity review period, August 2003 – July 2004, pediatric usage was re-examined for three additional years to determine whether any new or quantitative differences have evolved since then.

This review describes the projected number of dispensed prescriptions by age from August 2004 through July 2007 and the projected number of unique patients by age that filled a prescription from August 2004 through July 2007.

2 METHODS AND MATERIALS

2.1 DETERMINING SETTINGS OF CARE

The IMS Health, IMS National Sales Perspectives[™] was used to determine the various retail and non-retail channels of distribution for benazepril. The examination of wholesale sales data for September 2006 – August 2007 indicates that approximately 92% of benazepril tablets were distributed to outpatient retail pharmacy setting (72% of sales were to outpatient retail settings; approximately 20% mail order pharmacies; 8% to non-retail settings.¹ Thus, we examined outpatient utilization patterns.

2.2 DATA SOURCES

Proprietary drug use databases licensed by the Agency were used to conduct this analysis. Outpatient use and patient demographics were measured using Verispan, LLC: Vector One[®]: Prescription Services and Total Patient Tracker (TPT). From these two sources, nationally projected estimates of the number of prescriptions dispensed by retail pharmacies and the number of patients who received a dispensed prescription for ACE Inhibitors, Lotensin[®] (benazepril), and benazepril combination products were obtained. Indications for use were obtained from the Verispan, Physician Drug and Diagnosis Audit (PDDA) database. Complete descriptions of the databases used can be found in the Appendix.

2.3 DATA

2.3.1 Outpatient Prescription Data

Table 1 provides the projected number of prescriptions dispensed for ACE Inhibitors from U.S. retail pharmacies from August 2004 through July 2007. Mail order data are provided for August 2005 – July 2006, and August 2006 – July 2007 only.

¹ IMS Health, IMS National Sales Perspectives[™], September 2006 – August 2007, Extracted October 2007. Original File: 0710bena.dvr.

Table 1. Projected number of retail prescriptions for ACE Inhibitors dispensed from U.S. retail pharmacies, Moving Annual Totals August 2004 through July 2007

	August 2004 - July 2005				August 2005 - July 2006				August 2006 - July 2007			
	Total TRxs	Share	Retail TRxs	Share	Total TRxs	Retail TRxs	Share	Mail TRxs	Total TRxs	Retail TRxs	Share	Mail TRxs
	N	%	N	%	N	N	%	N	N	N	%	N
TOTAL MARKET			127,014,717	100.0%	146,735,775	132,314,824	100.0%	14,420,951	155,305,113	140,653,701	100.0%	14,651,412
31111 ACE INHIBITOR, SINGLE INGREDIENT			96,367,075	75.9%	109,966,866	99,112,985	74.9%	10,853,881	114,553,675	103,730,938	73.7%	10,822,737
All Others			89,833,840	93.2%	103,108,748	92,682,315	93.5%	10,426,433	107,521,332	97,120,629	93.6%	10,400,703
benazepril hydrochloride			6,533,235	6.8%	6,858,118	6,430,670	6.5%	427,448	7,032,343	6,610,309	6.4%	422,034
31112 ACE INHIB W/DIURETIC			16,627,455	13.1%	20,286,708	18,459,569	14.0%	1,827,139	22,945,758	20,992,483	14.9%	1,953,275
All Others			14,539,609	87.4%	18,146,723	16,502,079	89.4%	1,644,644	20,702,737	18,940,939	90.2%	1,761,798
benazepril hydrochloride/hctz			2,087,846	12.6%	2,139,985	1,957,490	10.6%	182,495	2,243,021	2,051,544	9.8%	191,477
31118 ACE INHIB, OTHER			14,020,187	11.0%	16,482,201	14,742,270	11.1%	1,739,931	17,805,680	15,930,280	11.3%	1,875,400
benazepril/amlodipine besylate			12,742,928	90.9%	14,949,766	13,373,404	90.7%	1,576,362	14,542,476	13,064,639	82.0%	1,477,837
All Others			1,277,259	9.1%	1,532,435	1,368,866	9.3%	163,569	3,263,204	2,865,641	18.0%	397,563

Verispan Vector One®: Prescription Services, Data extracted 12-2007.

Source File: 2007-2126 benazepril age 12-13-07.qry

Table 2 provides the projected number of prescriptions for benazepril and benazepril combination products dispensed to pediatric patients aged 0-16 years from August 2004 through July 2007. Mail order data are provided for August 2005 – July 2006, and August 2006 – July 2007 only.

Table 2. Projected number of retail prescriptions, by age, for benazepril and benazepril combination products dispensed from U.S. retail pharmacies, Moving Annual Totals August 2004 through July 2007

	August 2004 - July 2005				August 2005 - July 2006				August 2006 - July 2007			
	Total TRxs	Share	Retail TRxs	Share	Total TRxs	Retail TRxs	Share	Mail TRxs	Total TRxs	Retail TRxs	Share	Mail TRxs
	N	%	N	%	N	N	%	N	N	N	%	N
TOTAL MARKET			21,363,901	100.0%	23,946,902	21,761,607	100.0%	2,185,295	23,817,742	21,726,580	100.0%	2,091,162
benazepril/amlodipine besylate			12,742,876	59.6%	14,949,682	13,373,391	61.5%	1,576,291	14,542,468	13,064,661	60.1%	1,477,807
0-16			6,770	0.1%	5,865	5,736	0.0%	129	4,015	3,923	0.0%	92
17+			12,662,862	99.4%	14,892,578	13,316,529	99.6%	1,576,049	14,513,286	13,035,682	99.8%	1,477,604
UNSPEC.			73,244	0.6%	51,239	51,126	0.4%	113	25,167	25,056	0.2%	111
benazepril			6,533,215	30.6%	6,857,163	6,430,656	29.6%	426,507	7,032,258	6,610,291	30.4%	421,967
0-16			36,757	0.6%	47,372	46,901	0.7%	471	53,149	52,931	0.8%	218
17+			6,439,315	98.6%	6,764,974	6,338,987	98.6%	425,987	6,953,095	6,531,404	98.8%	421,691
UNSPEC.			57,143	0.9%	44,817	44,768	0.7%	49	26,014	25,956	0.4%	58
benazepril/hctz			2,087,810	9.8%	2,140,057	1,957,560	9.0%	182,497	2,243,016	2,051,628	9.4%	191,388
0-16			1,114	0.1%	852	822	0.0%	30	841	801	0.0%	40
17+			2,077,460	99.5%	2,132,604	1,950,154	99.6%	182,450	2,238,052	2,046,723	98.8%	191,329
UNSPEC.			9,236	0.4%	6,601	6,584	0.3%	17	4,123	4,104	0.2%	19

Verispan Vector One®: National, Data extracted 12-2007.

Source File: 2007-2126 benazepril age 12-13-07.qry

Table 3 provides number of prescriptions for benazepril and benazepril combination products, by physician specialty, dispensed from U.S. retail pharmacies from August 2004 through July 2007. Mail order data are provided for August 2005 – July 2006, and August 2006 – July 2007 only.

Table 3: Total number of prescriptions dispensed for benazepril and benazepril combination products by top 10 prescriber specialties, Moving Annual Total August 2004 through July 2007

	August 2004 - July 2005				August 2005 - July 2006				August 2006 - July 2007			
	Total TRxs	Share	Retail TRxs	Share	Total TRxs	Retail TRxs	Share	Mail TRxs	Total TRxs	Retail TRxs	Share	Mail TRxs
	N	%	N	%	N	N	%	N	N	N	%	N
TOTAL MARKET			21,363,983	100.0%	23,947,288	21,761,445	100.0%	2,185,843	23,817,706	21,726,415	100.0%	2,091,291
GP/FM/DO			9,041,095	42.3%	10,410,483	9,488,650	43.6%	921,833	10,493,052	9,627,303	44.3%	865,749
IM			7,058,192	33.0%	7,991,418	7,211,029	33.1%	780,389	7,872,500	7,135,096	32.8%	737,404
CARD			1,225,061	5.7%	1,453,677	1,300,924	6.0%	152,753	1,497,692	1,350,337	6.2%	147,355
UNSPEC			1,636,497	7.7%	1,289,985	1,160,852	5.3%	129,133	965,182	826,922	3.8%	138,260
NP			320,620	1.5%	430,393	401,611	1.8%	28,782	530,204	494,395	2.3%	35,809
PA			259,677	1.2%	331,243	309,660	1.4%	21,583	390,783	365,353	1.7%	25,430
PED			212,770	1.0%	248,627	230,939	1.1%	17,688	276,298	257,404	1.2%	18,894
NEPH			209,522	1.0%	239,354	220,190	1.0%	19,164	257,897	239,212	1.1%	18,685
HOSP			189,830	0.9%	187,208	183,870	0.8%	3,338	173,798	170,490	0.8%	3,308
EM			129,013	0.6%	157,411	147,344	0.7%	10,067	158,884	149,182	0.7%	9,702
All Others			1,081,706	5.1%	1,207,489	1,106,376	5.1%	101,113	1,201,416	1,110,721	5.1%	90,695

Verispan Vector One®: National, Data extracted 12-2007.

Source File: 2007-2126 benazepril MD 12-13-07.qry

2.3.1.1 Patient Data

Table 4 provides the projected number of patients by age that received a prescription dispensed from U.S. retail pharmacies for benazepril and benazepril combination products from August 2004 through July 2007. Mail order data are not provided for patient counts.

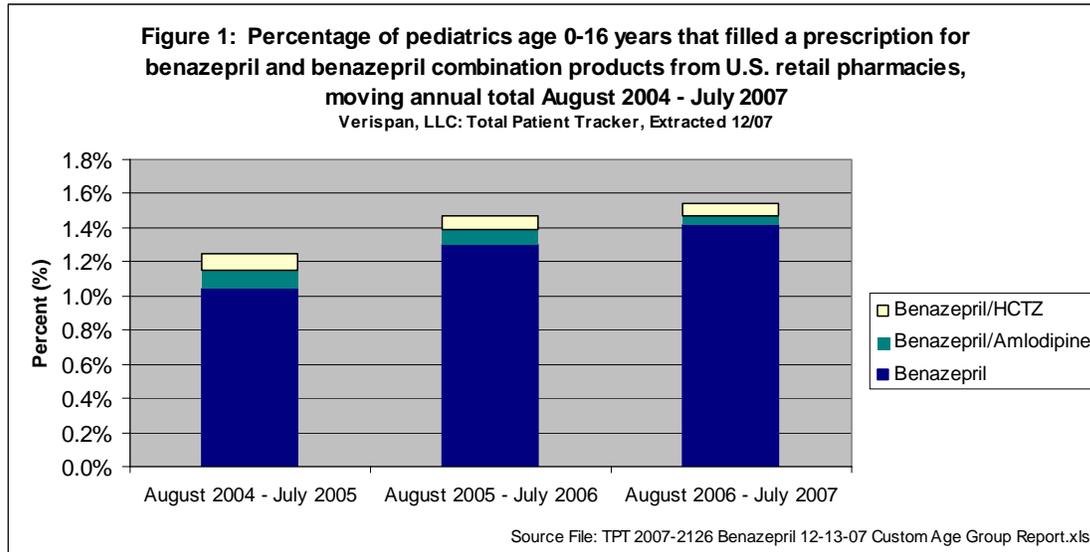
Table 4: Total number of patients*, by age, receiving a prescription for benazepril and benazepril combination products, from outpatient retail pharmacies, Moving Annual Total August 2004 through July 2007 (mail order pharmacies not included)

	August 2004 - July 2005		August 2005 - July 2006		August 2006 - July 2007	
	Projected Patient Count	Total Patient Share	Projected Patient Count	Total Patient Share	Projected Patient Count	Total Patient Share
	N	%	N	%	N	%
Grand Total	3,462,181	100.00%	3,815,201	100.00%	3,872,640	100.00%
Benazepril	1,042,277	100.00%	1,122,754	100.00%	1,186,914	100.00%
0 - 16	10,896	1.05%	14,646	1.30%	16,798	1.42%
17+	1,021,038	97.96%	1,099,415	97.92%	1,166,120	98.25%
unknown age	39,747	3.81%	36,640	3.26%	30,678	2.58%
Lotrel	2,204,160	63.66%	2,457,305	64.41%	2,448,377	63.22%
0 - 16	2,301	0.10%	2,086	0.08%	1,318	0.05%
17+	2,184,552	99.11%	2,439,920	99.29%	2,439,208	99.63%
unknown age	64,003	2.90%	56,534	2.30%	49,921	2.04%
Benazepril/HCTZ	312,272	100.00%	354,496	100.00%	367,187	100.00%
0 - 16	319	0.10%	279	0.08%	251	0.07%
17+	310,091	99.30%	352,371	99.40%	365,818	99.63%
unknown age	7,190	2.30%	6,720	1.90%	6,073	1.65%

*Subtotals may not sum exactly, due to rounding. Due to aging of patients 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.

Source: Verispan, LLC: Total Patient Tracker, August 2004 - July 2007, Extracted December 07. File: TPT 2007-2126 Benazepril 12-13-07 Custom Age Group Report.xls

Figure 1 provides the percentage of pediatric patients, aged 0-16 years, who have received a prescription for benazepril and benazepril combination products from August 2004 through July 2007.



3 RESULTS

- There was an overall increase in the number of retail prescriptions dispensed for the single ingredient and combination ACE Inhibitor class from an estimated 127 million prescriptions during August 2004 – July 2005, to 140 million prescriptions during August 2006 – July 2007. This represented a 11% increase in prescriptions dispensed.
- The number of retail prescriptions dispensed for single ingredient benazepril products only slightly increased from approximately 6.5 million prescriptions from August 2004 – July 2005 to 6.6 million prescriptions from August 2006 – July 2007.
- The total number of retail prescriptions dispensed for the combination benazepril products remained steady at 2.1 million for benazepril/HCTZ products and increased approximately 1% from 12.7 million to 13.1 million for the benazepril/amlodipine products in the same time period, August 2004 – July 2005 to August 2006 – July 2007.
- Of all the benazepril-containing products, the combination benazepril/amlodipine products held the majority of the market with 60%, followed by the single ingredient benazepril products (30%) and the combination benazepril/HCTZ products (9%) for the period of August 2006 – July 2007.
- Less than 1% of prescriptions dispensed for benazepril and benazepril combination products were for pediatric patients aged 0-16 years from August 2004 – July 2007.
- The majority of prescriptions dispensed from U.S. retail pharmacies for benazepril and benazepril combination products were prescribed by the general practice² (average 43%) and internal medicine specialties (average 33%) from August 2004 – July 2007. Pediatricians averaged approximately 1% of prescriptions during the same time period.

² Includes General Practice, Family Medicine, and Osteopathic Medicine.

- The percentage of pediatric patients aged 0-16 years that received a prescription for single ingredient benazepril products were slightly greater than 1% for each of the three 12-month periods examined during August 2004 – July 2007.
- The percentage of pediatric patients that received a prescription for a benazepril combination product are similar to prescription data, with less than 1% of pediatric patients receiving a prescription August 2004 – July 2007.
- No mention of single ingredient benazepril or benazepril/hydrochlorothiazide in association with a pediatric patients was recorded during the entire period, August 2004 – July 2007; however, the diagnosis “essential hypertension” (ICD-9 401.9) was associated with a mention of benazepril/amlodipine with pediatric patients noted during the 12-month period of August 2005 – July 2006 for (data not shown)³.
- The diagnosis associated with the use of benazepril single ingredient and combination products in adults was “essential hypertension” (3-digit ICD-9 code 409).

4 DISCUSSION

Findings from this review should be interpreted in the context of the known limitations of the databases used. While we conducted a comprehensive analysis of the use of this product in the outpatient setting, in which the majority of use occurred, a significant proportion (an average 20%) of wholesale sales of benazepril products were to mail order pharmacies.⁴ Verispan’s mail order data begins January 2005, and mail order data from that date onward was included in this analysis.

5 CONCLUSIONS

Similar to the previous BPCA drug utilization review completed on October 7, 2004, less than 1% of dispensed prescription for benazepril and benazepril combination products were for pediatric patients.⁵ Overall, there was a 11% increase in prescriptions dispensed for the single ingredient and combination ACE Inhibitor class from August 2004 – July 2005 to August 2006 – July 2007. The majority of prescriptions dispensed from U.S. retail pharmacies for benazepril and benazepril combination products were prescribed by the general practice⁶ and internal medicine specialties from August 2004 – July 2007. The percentage of pediatric patients that received a prescription for a benazepril combination product was less than 1% from August 2004 – July 2007. On average, pediatric patients aged 0-16 years represented slightly greater than 1% of patients that received a prescription for single ingredient benazepril products. Less than 1% of prescriptions dispensed for benazepril and benazepril combination products were for pediatric patients aged 0-16 years from August 2004 – July 2007. There were no mentions of single

³ Source File: PDDA 2007-2198 colazal diag 10-19-07.xls

⁴ Data not included. IMS HEALTH, IMS National Sales Perspective™, September 2006 – August 2007. Data extracted 10-4-2007. Source File: NSPC 2007-2126 benazepril 10-24-07 0710bena.xls.

⁵ Governale, L. Benazepril BPCA Drug Utilization Review 10-7-04

⁶ Includes General Practice, Family Medicine, and Osteopathic Medicine.

ingredient benazepril or benazepril/hydrochlorothiazide in association with pediatric patients; however, there were mentions of benazepril/amlopidine associated with pediatric patients noted during the 12-month period of August 2005 – July 2006 for the diagnosis “essential hypertension” (ICD-9 401.9).

6 APPENDIX

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 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.

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