

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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SUBJECT: Serevent and Serevent[®] Diskus[®] (salmeterol); NDA 20-236/S035, 20-692
One Year Post-Pediatric Exclusivity Post-marketing Adverse Event Review:
Drug Utilization Data
Pediatric Exclusivity Grant Date: March 9, 2006

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

EXECUTIVE SUMMARY

This consult examines the drug utilization patterns for salmeterol (Serevent[®] Diskus[®]), a long acting inhaled beta agonist, and salmeterol combination products, two years before and one year following the granting of Pediatric Exclusivity on March 9, 2006, with a primary focus on the use in the pediatric population, ages 0 through 16 years. Outpatient drug utilization patterns for salmeterol and salmeterol/fluticasone were examined for the three 12-month periods from April 1, 2004 through March 31, 2007 using proprietary drug use databases licensed by FDA.

Examination of wholesale sales data indicated that salmeterol was primarily distributed to outpatient retail pharmacies. Salmeterol accounted for less than 5% of the yearly retail prescription volume of the inhaled beta agonists market and less than 2% of the asthma market. Over the 3 years of this analysis, the number of salmeterol prescriptions dispensed declined by 50% from the 12-month period April 2004 – March 2005 to the post-exclusivity year (April 2006 – March 2007). A 72% decline was found in the salmeterol prescriptions dispensed to pediatric patients age 0-16 years. General Practitioners, Internal Medicine, and pulmonary specialties were the three most frequent prescribers of salmeterol or salmeterol/fluticasone. The most common indication for use for a salmeterol containing product in both pediatric and adult patients was “Asthma NOS” (ICD-9 493.9).

These drug use data suggest that salmeterol account for only a small proportion of the asthma market. The small market for salmeterol could be explained by safety concerns raised following exacerbation of asthma episodes observed in the SMART safety study that led to the 2003 FDA safety alert issued to healthcare professionals on potential association between Serevent[®] and rare respiratory adverse events. In addition, the decline in the number of prescriptions dispensed for salmeterol from the pre- to the post-exclusivity periods is consistent with the timing of the FDA Public Health Advisory regarding long-acting beta 2-adrenergic agonists (LABA) issued in November 2005.

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 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.

Salmeterol xinafoate is a long-acting beta2-adrenergic agonist which is approved for long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma, who require regular treatment with inhaled, short-acting beta2-agonists. It should not be used in patients whose asthma can be managed by occasional use of inhaled, short-acting beta2-agonists. Salmeterol may be used alone or in combination with inhaled or systemic corticosteroid therapy. Salmeterol is also indicated for prevention of exercise-induced bronchospasm in patients 4 years of age and older.

Salmeterol xinafoate metered dose inhaler was first approved as Serevent[®] Inhalation on February 4, 1994 under NDA 20-236. On September 19, 1997, the dry powder inhaler, Serevent[®] Diskus[®] (salmeterol xinafoate inhalation powder), NDA 20-692, was approved, and by January 2003, the sponsor ceased the distribution of the metered dose inhaler. Although the marketing of the metered dose inhaler was discontinued, Pediatric Exclusivity was granted for Serevent[®] Inhalation, NDA 20-236, on March 9, 2006, based on four clinical studies which were conducted in children under the age of 5 years old using the metered dose inhaler. There were no label changes made as a result of these studies.

This review examines the drug utilization patterns for the currently available salmeterol (Serevent[®] Diskus[®]) and salmeterol combination products, two years before and one year following the granting of Pediatric, with a primary focus on the use in the pediatric population, ages 0 through 16 years.

METHODS

This review will focus on the currently available salmeterol dry powder inhalation product, Serevent[®] Diskus[®] (salmeterol xinafoate inhalation powder). All references to labeling will refer to the Diskus[®] product (unless otherwise stated) and all drug use data will be presented at the generic drug name level.

IMS Health, IMS National Sales Perspectives[™] data (see Appendix) were used to determine the setting in which salmeterol was sold. Sales of this product by number of inhalers or Diskus[®] packages sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for three 12-month periods from April 2004 through March 2007. From these data, it was clear that this product is distributed to outpatient settings of care (chain, independent, food store, and mail order pharmacies) which accounted for approximately 81% of the Serevent[®] Diskus[®] packages sold in each of the three 1-year periods in this analysis.¹ The combination product salmeterol/fluticasone (Advair[®] Diskus[®]) was also distributed into the retail channels accounting for roughly 84% of the product sales during each analysis year. Mail order pharmacies accounted for a substantial proportion of the overall distribution of these products; roughly 24% of Serevent[®] Diskus[®] and 17% of Advair[®] Diskus[®] were sold to mail order pharmacies (data not shown).

Because the bulk of drug product sales of salmeterol for this time period were into outpatient retail settings, we examined the utilization patterns for salmeterol, salmeterol/fluticasone, and other products contained in the asthma market focusing on the outpatient setting only.

Outpatient use and patient demographics were measured with two data sources from Verispan, LLC: Vector One[®]: National (VONA) and Total Patient Tracker (TPT). Nationally projected estimates of the number of prescriptions dispensed by retail pharmacies and the number of patients who received a dispensed Serevent[®] or Advair[®] retail prescription were obtained. Indications for use were obtained from the Physician's Drug and Diagnosis Audit (see Appendix). Due to the relatively low usage of salmeterol in pediatric patients, indication for use was obtained for salmeterol and salmeterol/fluticasone combined. Outpatient drug utilization patterns for salmeterol and salmeterol/fluticasone were examined for the three 12-month period from April 1, 2004 through March 31, 2007.

RESULTS

I. Dispensed Prescriptions

The total number of retail prescriptions dispensed in the asthma market rose approximately 7% from 114 million prescriptions in the 12-month period from April 2004 – March 2005 to 121 million prescriptions in the 12-month period ending March 2007 (**Table 1**). For the post-exclusivity period (April 2006 – March 2007) the most commonly dispensed classes of asthma medications were: inhaled beta agonists (ex. albuterol, salmeterol), leukotriene agonists (ex. montelukast, zafirlukast), inhaled beta agonists/steroid combinations (salmeterol/fluticasone), and inhaled steroids (ex. fluticasone). Within the asthma market, the inhaled beta agonists accounted for roughly 30% of the prescriptions dispensed during each of the 12-month period of this analysis, rising by 4.3% from 35 million prescriptions dispensed during April 2004 – March 2005 to 36 million in April 2006-March 2007. Inhaled beta agonists/steroid combination products (salmeterol/fluticasone) accounted for roughly 15% of the yearly dispensed prescription volume for the asthma market, which rose from 17 million prescriptions during April 2004 – March 2005 to 18 million prescriptions during April 2006 – March 2007, an increase of 9%. The “Other Beta Agonists” class (which contains the long acting formoterol) accounted for just 0.6% of the yearly retail prescription volume.

Within the inhaled beta agonist class, albuterol products are the most commonly dispensed, accounting for over 90% of the dispensing volume during each of the 12-month period. Over the 3 years of this analysis, the number of salmeterol prescriptions dispensed declined by 50% falling from 1.9 million prescriptions dispensed during April 2004 – March 2005 to 1.3 million prescriptions in the following 12-months April 2005 – March 2006, and finally to 976 thousand prescriptions dispensed in the post-exclusivity period, April 2006 – March 2007. In contrast, the number of prescriptions dispensed for salmeterol/fluticasone increased by 9% over the three 12-month periods examined with 16.8 million prescriptions dispensed in April 2004 – March 2005, 18.5 million prescriptions dispensed during April 2005 – March 2006 and 18.3 million prescriptions dispensed during April 2006 – March 2007. For both salmeterol and salmeterol/fluticasone combined, 19.8 million prescriptions were dispensed during the pre-exclusivity period April 2005 – March 2006 and 19.3 million prescriptions were dispensed in the post-exclusivity period April 2006 – March 2007; this represents a relative decline of 3%.

Table 1. Total Number of Prescriptions Dispensed (in Thousands) by Retail Pharmacies for the Asthma Market during April 2004 through March 2007 (mail order pharmacies not included)

	April 2004 - March 2005		April 2005 - March 2006		April 2006 - March 2007	
	TRxs* (%)		TRxs* (%)		TRxs* (%)	
TOTAL MARKET	113,519	(100)	117,068	(100)	121,336	(100)
28111 BETA AGON AEROSOL	34,973	(30.8)	35,714	(30.5)	36,492	(30.1)
albuterol	31,178	(89.2)	32,481	(91)	28,452	(78)
albuterol sulfate	1,058	(3)	1,240	(3.5)	5,473	(15)
levalbuterol tartrate	--	--	74	(0.2)	1,128	(3.1)
salmeterol xinafoate	1,948	(5.6)	1,333	(3.7)	976	(2.7)
pirbuterol acetate	675	(1.9)	488	(1.4)	382	(1.1)
metaproterenol sulfate	112	(0.3)	98	(0.3)	80	(0.2)
epinephrine	0	(0)	1	(0)	1	(0)
bitolterol mesylate	--	--	0	(0)	--	--
isoproterenol sulfate	0	(0)	--	--	--	--
28500 LEUKOTRIENE AGENTS	21,728	(19.1)	23,505	(20.1)	25,953	(21.4)
28430 BRONCHIAL COMBOS	16,757	(14.8)	18,481	(15.8)	18,274	(15.1)
salmeterol/fluticasone	16,757	(100)	18,481	(100)	18,274	(100)
28410 INHALED STER BRONCH	10,084	(8.9)	9,672	(8.3)	10,488	(8.6)
28112 BETA AGON NEB SOLN	9,604	(8.5)	9,723	(8.3)	9,683	(8)
28121 ANTICHOL BRONCH PLAIN	4,639	(4.1)	5,867	(5)	7,348	(6.1)
28122 ANTICHOL BRONCH COMBO	7,504	(6.6)	6,828	(5.8)	6,392	(5.3)
28131 XANTHINES	3,362	(3)	2,895	(2.5)	2,669	(2.2)
28114 BETA AGON ORAL LIQ	1,889	(1.7)	1,643	(1.4)	1,330	(1.1)
28118 BETA AGONISTS OTHER	678	(0.6)	660	(0.6)	715	(0.6)
formoterol fumarate	676	(99.8)	659	(99.8)	715	(99.9)
terbutaline sulfate	1	(0.2)	1	(0.2)	1	(0.1)
ephedrine sulfate	0	(0)	0	(0)	0	(0)
isoproterenol HCl	0	(0)	0	(0)	0	(0)
albuterol sulfate	0	(0)	0	(0)	--	--
All Others**	2,302	(2)	2,079	(1.8)	1,991	(1.6)

*a zero indicates less than 500 projected prescriptions, a – indicates no data

** All Others includes nasal anticholinergics, bronchial mucolytics, xanthine combos, oral/nasal/inhaled cromolyn, “others”

Verispan, LLC. Vector One® National (VONA) Data extracted 5-9-2007

Source File: 2007-745 VONA asthma market.qry

II. Patient Demographics

Salmeterol prescriptions were primarily dispensed to adult patients. Adults accounted for greater than 95% of the dispensed prescription volume during each year of this analysis (**Table 2**). Total salmeterol dispensing declined by 27% from the pre- (April 2005 – March 2006) to the post-exclusivity periods (April 2006 – March 2007), and dispensing among adult and pediatric age groups decreased by at least 26%. Salmeterol prescriptions dispensed to pediatric patients age 0-16 years of age decreased by 48% from 40 thousand prescriptions (3% of total salmeterol prescriptions) in the pre-exclusivity year to 21 thousand prescriptions (2.1% of total salmeterol prescriptions) during the post-exclusivity year. Prescriptions dispensed to 4-11 year olds declined by 51% (from 16,163 in the pre-exclusivity year to 7,877 prescriptions in the post-exclusivity year), while prescriptions dispensed to 12-16 year olds declined by 45% (23,773 prescriptions to 12,967 prescriptions). Finally, off-label use in patients age 0-3

years declined by 38% falling from 152 prescriptions in the pre-exclusivity year to 94 prescriptions in the post-exclusivity year.

Prescriptions dispensed for salmeterol/fluticasone declined by 1% from 18.5 million prescriptions dispensed in the pre-exclusivity year to 18.3 million during the post-exclusivity year. Prescriptions for patients age 0-16 years declined by 21% over the same period from 2.5 million prescriptions dispensed to 2 million prescriptions dispensed. Dispensing to patients age 0-3 years increased by 59%, rising from 3,793 prescriptions dispensed in the pre-exclusivity year to 6,039 prescriptions dispensed in the post-exclusivity year. For patients age 4-11 years, salmeterol/fluticasone dispensing declined by 24% from 1.3 million prescriptions in the pre-exclusivity year to 976 thousand prescriptions in the post-exclusivity year.

Table 2. Total Number of Prescriptions Dispensed by Outpatient Retail Pharmacies for Salmeterol and Salmeterol/Fluticasone Stratified by Age during April 2004 through March 2007 (mail order pharmacies not included)

	April 2004 - March 2005		April 2005 - March 2006		April 2006 - March 2007	
	TRxs (%)		TRxs (%)		TRxs (%)	
Total	18,705,196	(100)	19,813,207	(100)	19,249,625	(100)
salmeterol/fluticasone	16,756,880	(89.6)	18,480,547	(93.3)	18,273,809	(94.9)
0-16	2,344,871	(14)	2,482,028	(13.4)	1,970,343	(10.8)
0-3	4,202	(0.2)	3,793	(0.2)	6,039	(0.3)
4-11	1,207,418	(51.5)	1,281,998	(51.7)	976,134	(49.5)
12-16	1,133,251	(48.3)	1,196,237	(48.2)	988,170	(50.2)
17+	14,263,067	(85.1)	15,841,158	(85.7)	16,241,263	(88.9)
UNSPEC.	148,942	(0.9)	157,361	(0.9)	62,203	(0.3)
salmeterol xinafoate	1,948,316	(10.4)	1,332,660	(6.7)	975,816	(5.1)
0-16	75,034	(3.9)	40,088	(3)	20,938	(2.1)
0-3	589	(0.8)	152	(0.4)	94	(0.4)
4-11	32,119	(42.8)	16,163	(40.3)	7,877	(37.6)
12-16	42,326	(56.4)	23,773	(59.3)	12,967	(61.9)
17+	1,851,468	(95)	1,278,667	(95.9)	950,949	(97.5)
UNSPEC.	21,814	(1.1)	13,905	(1)	3,929	(0.4)

*a zero indicates less than 500 projected prescriptions, a – indicates no data Verispan, LLC, Vector One® National (VONA) Data extracted 5-9-2007 Source File: 2007-745 VONA molecule-age.qry

The projected number of all unique patients receiving a prescription for salmeterol from a retail pharmacy decreased from 343,929 patients during the pre-exclusivity period to 236,395 patients during the post-exclusivity period (Table 3). This represents an approximate 31% decrease in the projected number of patients receiving a retail salmeterol prescription. The number of pediatric patients age 0-16 years declined by 49% from 16,840 (4.9% of total salmeterol patients) during the pre-exclusivity year to 8,658 patients (3.7% of total salmeterol patients) during the post-exclusivity year. Pediatric patients under 4 years of age accounted for less than 1% of pediatric patients receiving salmeterol during both the pre- and post-exclusivity years.

Table 3. Total Number of Patients Receiving Prescriptions Through Retail Pharmacies for Salmeterol by Patient Age, During April 2004 through March 2007* (mail order pharmacies not included)

	April 2004 - March 2005		April 2005 - March 2006		April 2006 - March 2007	
	Patients	(%)	Patients	(%)	Patients	(%)
Salmeterol	526,850	(100)	343,929	(100)	236,395	(100)
0-16	32,549	(6.2)	16,840	(4.9)	8,658	(3.7)
0-3	385	(1.2)	131	(0.8)	60	(0.7)
5 - 11	13,601	(41.8)	6,727	(39.9)	3,225	(37.3)
12 - 16	19,242	(59.1)	10,369	(61.6)	5,572	(64.4)
17+	488,079	(92.6)	323,205	(94)	226,739	(95.9)
Age Unknown	15,472	(2.9)	10,300	(3)	4,588	(1.9)

*Subtotals may not sum exactly, due to rounding error. 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 Total Patient Tracker

Files: 2007-745 TPT Serevent age 0-16.xls, 2007-745 TPT Serevent detail age.xls

While the number of pediatric patients who were dispensed salmeterol was relatively low, the number of patients who received a prescription for salmeterol or salmeterol/fluticasone was significantly higher. Overall, 6.3 million patients received a prescription for at least one of these products during the pre-exclusivity year and 5.8 million patients received a prescription in the post-exclusivity year (a 7% decrease) (Table 4). Pediatric patients age 0-16 years of age accounted for 16% of the patient count in the pre-exclusivity year (1 million patients) and 13.4% of the patient count in the post exclusivity year (779,000 patients), a decline of 22%.

Table 4. Total Number of Patients Receiving Prescriptions Through Retail Pharmacies for Salmeterol or Salmeterol/Fluticasone by Patient Age, During April 2004 through March 2007* (mail order pharmacies not included)

	April 2004 - March 2005		April 2005 - March 2006		April 2006 - March 2007	
	Patients	(%)	Patients	(%)	Patients	(%)
Salmeterol or Salmeterol/fluticasone	5,848,245	(100)	6,250,995	(100)	5,816,493	(100)
0-16	973,715	(16.6)	1,001,962	(16)	779,006	(13.4)
0-3	3,500	(0.4)	2,790	(0.3)	4,090	(0.5)
5 - 11	503,056	(51.7)	512,128	(51.1)	383,551	(49.2)
12 - 16	492,098	(50.5)	513,018	(51.2)	412,656	(53)
17+	4,841,426	(82.8)	5,214,735	(83.4)	5,034,059	(86.5)
Age Unknown	122,102	(2.1)	125,276	(2)	73,759	(1.3)

*Subtotals may not sum exactly, due to rounding error. 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 Total Patient Tracker

Files: 2007-745 TPT Serevent-Advair age 0-16.xls, 2007-745 TPT Serevent-Advair detail age.xls

III. Prescriber Specialty

General Practitioners, Internal Medicine, and Pulmonary specialties were the three most frequent prescribers of salmeterol or salmeterol/fluticasone during the post-exclusivity year accounting for roughly 32%, 27% and 16% of salmeterol and 32%, 23% and 12% of salmeterol/fluticasone prescriptions, respectively (**Table 5**). These proportions were similar for previous years. Pediatricians accounted for less than 9% of salmeterol/fluticasone and less than 3% of salmeterol prescriptions (data not shown) dispensed during each year analyzed.

Table 5. Total Number of Prescriptions Dispensed (Thousands) by Retail Pharmacies for Salmeterol and Salmeterol Fluticasone Stratified by Prescriber Specialty during April 2004 through March 2007 (mail order pharmacies not included)

	April 2004 - March 2005		April 2005 - March 2006		April 2006 - March 2007	
	TRxs (%)		TRxs (%)		TRxs (%)	
TOTAL MARKET	18,705	(100)	19,814	(100)	19,250	(100)
salmeterol/fluticasone	16,757	(89.6)	18,481	(93.3)	18,274	(94.9)
GP/FM/DO	4,744	(28.3)	5,489	(29.7)	5,765	(31.6)
Internal Medicine	3,526	(21)	4,041	(21.9)	4,248	(23.3)
Pulmonary	1,834	(10.9)	1,983	(10.7)	2,112	(11.6)
Pediatrics	1,388	(8.3)	1,566	(8.5)	1,351	(7.4)
Unspecified	2,000	(11.9)	1,765	(9.6)	1,127	(6.2)
Allergy/immunology	1,114	(6.7)	1,157	(6.3)	1,056	(5.8)
All Others	2,151	(12.8)	2,479	(13.4)	2,615	(14.3)
salmeterol xinafoate	1,948	(10.4)	1,333	(6.7)	976	(5.1)
GP/FM/DO	582	(29.9)	406	(30.4)	311	(31.9)
Internal Medicine	504	(25.9)	354	(26.6)	267	(27.4)
Pulmonary	273	(14)	197	(14.8)	156	(16)
All Others	590	(30.3)	376	(28.2)	242	(24.8)

*a zero indicates less than 500 projected prescriptions, a – indicates no data
 All Others includes all specialties with 5% or less of market share, based on Year 3 data
 Verispan, LLC. Vector One® National (VONA) Data extracted 5-9-2007
 Source File: 2007-745 VONA molecule-MD.qry

IV. Indication for Use

The most common indication for use for both pediatric and adult patients was “Asthma NOS” (ICD-9 493.9), which accounted for roughly 81% of the pediatric use and roughly 55% of the adult use. The second-most common indication for use in pediatrics was “bronchitis” (ICD-9 490.0), and for adults was “Chronic Airway Obstruction” (ICD-9 496.0).

Table 6. Indications for Use of Salmeterol and Salmeterol/Fluticasone Combined Mentioned During U.S. Office Based Physician Visits

Indications for Use	MAT/MAR/2005		MAT/MAR/2006		MAT/MAR/2007	
	Uses	Share	Uses	Share	Uses	Share
	(000)	%	(000)	%	(000)	%
Total Market Salmeterol and Salmeterol/Fluticasone Combined	14,741	100.0	14,683	100.0	11,725	100.0
0-16	1,897	12.9	2,151	14.7	1,293	11.0
493.9 Asthma Nos	1,549	81.7	1,728	80.3	1,062	82.1
490.0 Bronchitis Nos	71	3.8	77	3.6	87	6.7
All Others	276	14.6	346	16.1	144	11.2
17+	12,522	85.0	12,098	82.4	10,132	86.4
493.9 Asthma Nos	6,664	53.2	6,920	57.2	5,471	54.0
496.0 Chronic Airway Obstruct Nec	2,638	21.1	2,589	21.4	2,457	24.3
All Others	3,220	25.7	2,590	21.4	2,203	21.8
Unspecified	322	2.2	434	3.0	300	2.6
493.9 Asthma Nos	216	67.1	273	63	175	58.5
496.0 Chronic Airway Obstruct Nec	52	16.1	80	18.5	90	30.1
490.0 Bronchitis Nos	--	--	40	9.2	16	5.5
All Others	54	16.9	40	9.3	18	6.0

Source: Verispan Physician Drug and Diagnosis Audit File 2007-745 PDDA combined Age-Diag.xls

DISCUSSION

Based on the databases employed for this analysis, prescriptions dispensed for salmeterol accounted for only small proportion of the inhaled beta agonists class that dominated the asthma market. The small market for this product could be explained by safety concerns associated with the use of Serevent[®] raised in previous years. These concerns were raised following exacerbation of asthma episodes observed in SMART safety study and led to the 2003 FDA safety alert issued to healthcare professionals on potential association between Serevent[®] and rare respiratory adverse events.²

Although salmeterol market was small, we found that the number of prescriptions dispensed for salmeterol declined by almost one third from the pre- to the post-exclusivity periods. This decline in salmeterol product is consistent with the timing of the FDA Public Health Advisory regarding long-acting beta 2-adrenergic agonists (LABA) issued in November 2005, during the pre-exclusivity year. FDA requested manufacturers of Advair Diskus[®], Foradil[®] Aerolizer[®], and Serevent[®] Diskus[®] to update their existing product labels with new warnings to alert healthcare professionals and patients that these medicines may increase the risk of severe asthma episodes, and asthma-related death.³ The FDA's public health advisory was issued to emphasize recommendations about use of a LABA that should not be the first medicine used to treat asthma. The public advisory followed by a new boxed warning in the labeling and Medication Guides for patients for these products.

While the majority of salmeterol prescriptions were dispensed to adults, the most prominent decline occurred in prescriptions dispensed to the pediatric patients age 0-16 years. It is noteworthy that similar trends were seen in the counts of patients receiving a prescription for salmeterol containing products dispensed through retail pharmacies. The reason for this decline is unclear, yet it should be noted that the NHLBI/NAEPP guidelines for children and adults recommend inhaled corticosteroids as the first step in control therapy, with LABAs as an option if low- to medium-dose inhaled corticosteroids do not adequately control the patient's asthma.⁴

Findings from this consult should be interpreted in the context of the known limitations of the databases used. We estimated that salmeterol products are distributed primarily in outpatient settings based on the IMS Health, IMS National Sales Perspectives™. During the post-exclusivity period, 66% of salmeterol/fluticasone and 58% of salmeterol sales were into retail pharmacies of the type sampled by Verispan. Mail order pharmacies accounted for 17% of salmeterol/fluticasone sales and 23% of salmeterol sales. 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.

While we conducted a comprehensive analysis of the use of this product in the outpatient settings, in which the majority of use occurred, a substantial proportion of wholesale sales of salmeterol products were to mail order pharmacies, a distribution channel not currently captured by Verispan's retail prescription audits.

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 and trending variability.

CONCLUSION

In summary, over the 3 years of this analysis, the number of salmeterol prescriptions dispensed declined by 50%. There was a 6% decrease in the number of prescriptions dispensed for salmeterol containing products and a 7% decrease in the number of patients receiving a prescription for salmeterol containing products (Serevent Discus® or Advair®) from the pre- to the post-exclusivity time periods. The number of pediatric patients age 0-16 years of age receiving a prescription for a salmeterol containing product declined by 22% over the same period.

General Practitioners, Internal Medicine, and Pulmonary specialties were the three most frequent prescribers of salmeterol or salmeterol/fluticasone during the post-exclusivity year accounting for roughly 32%, 27% and 16% of salmeterol and 32%, 23% and 12% of salmeterol/fluticasone prescriptions, respectively. The most common indication for use for a salmeterol containing product in both pediatric and adult patients was "Asthma NOS" (ICD-9 493.9), which accounted for approximately 81% of pediatric use and 55% of adult use.

REFERNCES

¹ IMS Health, IMS Nationals Sales Perspectives™, Data extracted 5-8-2007, File: 0705sal1.dvr

² 2003 Safety Alert - Serevent (salmeterol xinafoate) MedWatch- The FDA Safety Information and Adverse Event Reporting Program. Available at:

<http://www.fda.gov/medwatch/SAFETY/2003/serevent.htm>

³ FDA Public Health Advisory: Serevent Diskus (salmeterol xinafoate inhalation powder), Advair Diskus (fluticasone propionate & salmeterol inhalation powder), Foradil Aerolizer (formoterol fumarate inhalation powder), November 2005. Available at: <http://www.fda.gov/cder/drug/advisory/LABA.htm>

⁴ NAEP Expert Panel Report. Guidelines for the Diagnosis and Management of Asthma—Update on Selected Topics 2002. National Institute of Health, NHLBI.

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 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 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.

IMS Health: NSP Retail, Non-Retail or Combined (National Sales Perspectives)

The IMS Health 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.

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