Disclaimer

The following report(s) provides findings from an FDA-initiated query using Sentinel. While Sentinel queries may be undertaken to assess potential medical product safety risks, they may also be initiated for various other reasons. Some examples include determining a rate or count of an identified health outcome of interest, examining medical product use, exploring the feasibility of future, more detailed analyses within Sentinel, and seeking to better understand Sentinel capabilities.

Data obtained through Sentinel are intended to complement other types of evidence such as preclinical studies, clinical trials, postmarket studies, and adverse event reports, all of which are used by FDA to inform regulatory decisions regarding medical product safety. The information contained in this report is provided as part of FDA's commitment to place knowledge acquired from Sentinel in the public domain as soon as possible. Any public health actions taken by FDA regarding products involved in Sentinel queries will continue to be communicated through existing channels.

FDA wants to emphasize that the fact that FDA has initiated a query involving a medical product and is reporting findings related to that query does not mean that FDA is suggesting health care practitioners should change their prescribing practices for the medical product or that patients taking the medical product should stop using it. Patients who have questions about the use of an identified medical product should contact their health care practitioners.

The following report contains a description of the request, request specifications, and results from the modular program run(s).

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Overview for Request cder_mpl1r_wp028

Request ID: cder_mpl1r_wp028_nsdp_v02

Request Description: The goal of this request was to estimate the number of prevalent users and dispensings of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) among pediatric populations in the Sentinel Distributed Database (SDD).

Sentinel Modular Program Tool Used: Cohort Identification and Descriptive Analysis (CIDA) tool, version 2.2.3.

Data Source: Data from January 1, 2001 to December 31, 2012 from 15 Data Partners contributing to the SDD were included in this report. This request was distributed on July 1, 2016. See Appendix A for a list of the dates of available data for each Data Partner.

Study Design: This request was designed to calculate use of to ACE inhibitors and ARBs. The number of qualifying members with exposures, number of eligible members, and member-years were calculated overall and stratified by age group, sex, and year.

Exposures of Interest: The exposures of interest were ACE inhibitors as a group (benazepril, captopril, enalapril, lisinopril, ramipril, enalapril, fosinopril, perindopril, quinapril, trandolapril, moexipril), five individual ACE inhibitors (benazepril, captopril, enalapril, lisinopril, ramipril), and ARBs as a group (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, azilsartan). These were defined using generic and brand name drugs. See Appendix B for generic drug names used to define exposures in this request.

Cohort Eligibility Criteria: Members were required to be continuously enrolled in health plans with at least drug coverage for one day before their index dispensing date. Gaps between enrollment periods of up to 45 days were allowed. The following age groups were included in the cohort: 1-5 months, 6-11 months, 12-23 months, and 24-72 months.

Please see the Appendix C for the specifications of parameters used in the analyses for this request.

Limitations: Algorithms used to defines exposures and covariates are imperfect; thus, it is possible that there may be misclassification. Therefore, data should be interpreted with this limitation in mind.

Notes: Please contact the Sentinel Operations Center (info@sentinelsystem.org) for questions and to provide comments/suggestions for future enhancements to this document.

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Glossary of Terms for Analyses Using Cohort Identification and Descriptive Analysis (CIDA) Tool*

Amount Supplied - number of units (pills, tablets, vials) dispensed. Net amount per NDC per dispensing. This is equivalent to the "RxAmt" value in the Sentinel Common Data Model.

Blackout Period - number of days at the beginning of a treatment episode that events are to be ignored. If an event occurs during the blackout period, the episode is excluded.

Care Setting - type of medical encounter or facility where the exposure, event, or condition code was recorded. Possible care settings include: Inpatient Hospital Stay (IP), Non-Acute Institutional Stay (IS), Emergency Department (ED), Ambulatory Visit (AV), and Other Ambulatory Visit (OA). For laboratory results, possible care settings include: Emergency department (E), Home (H), Inpatient (I), Outpatient (O), or Unknown or Missing (U). Along with the Principal Diagnosis Indicator, forms the Care Setting/PDX parameter.

- **Ambulatory Visit (AV) -** includes visits at outpatient clinics, same-day surgeries, urgent care visits, and other same-day ambulatory hospital encounters, but excludes emergency department encounters.
- **Emergency Department (ED) -** includes ED encounters that become inpatient stays (in which case inpatient stays would be a separate encounter). Excludes urgent care visits.
- **Inpatient Hospital Stay (IP) -** includes all inpatient stays, same-day hospital discharges, hospital transfers, and acute hospital care where the discharge is after the admission date.
- **Non-Acute Institutional Stay (IS) -** includes hospice, skilled nursing facility (SNF), rehab center, nursing home, residential, overnight non-hospital dialysis and other non-hospital stays.
- **Other Ambulatory Visit (OA) -** includes other non overnight AV encounters such as hospice visits, home health visits, skilled nursing facility visits, other non-hospital visits, as well as telemedicine, telephone and email consultations.

Cohort Definition (drug/exposure) - indicates how the cohort will be defined: (1) 01: Cohort includes only the first valid treatment episode during the query period; (2) 02: Cohort includes all valid treatment episodes during the query period; (3) 03: Cohort includes all valid treatment episodes during the query period until an event occurs.

Days Supplied - number of days supplied for all dispensing's in qualifying treatment episodes.

Eligible Members - number of members eligible for an incident treatment episode (defined by the drug/exposure and event washout periods) with drug and medical coverage during the query period.

Enrollment Gap - number of days allowed between two consecutive enrollment periods without breaking a “continuously enrolled” sequence.

Episodes - treatment episodes; length of episode is determined by days supplied in one dispensing or consecutive dispensing's bridged by the episode gap.

Episode Gap - number of days allowed between two (or more) consecutive exposures (dispensing's/procedures) to be considered the same treatment episode.

Event Deduplication - specifies how events are counted by the MP algorithm: (0) 0: Counts all occurrences of an HOI during an exposure episode; (1) 1: de-duplicates occurrences of the same HOI code and code type on the same day; (2) 2: de-duplicates occurrences of the same HOI group on the same day (e.g., de-duplicates at the group level).

Exposure Extension Period - number of days post treatment period in which the outcomes/events are counted for a treatment episode. Extensions days are added after any episode gaps have been bridged.

Exposure Episode Length - number of days after exposure initiation that is considered "exposed time."

Lookback Period (pre-existing condition) - number of days wherein a member is required to have evidence of pre-existing condition (diagnosis/procedure/drug dispensing).

Maximum Episode Duration - truncates exposure episodes after a requester-specified number of exposed days. Applied after any gaps are bridged and extension days added to the length of the exposure episode.

Member-Years - sum of all days of enrollment with medical and drug coverage** in the query period preceded by an exposure washout period all divided by 365.25.

Minimum Days Supplied - specifies a minimum number of days in length of the days supplied for the episode to be considered.

Minimum Episode Duration - specifies a minimum number of days in length of the episode for it to be considered. Applied after any gaps are bridged and extension days added to the length of the exposure episode.

Principal Diagnosis (PDX) - diagnosis or condition established to be chiefly responsible for admission of the patient to the hospital. 'P' = principal diagnosis, 'S' = secondary diagnosis, 'X' = unspecified diagnosis, '.' = blank. Along with the Care Setting values, forms the Care setting/PDX parameter.

Query Period - period in which the modular program looks for exposures and outcomes of interest.

Treatment Episode Truncation Indicator - indicates whether observation of the incident query code during follow-up requires truncation of valid treatment episodes. A value of Y indicates that the treatment episodes should be truncated at the first occurrence of an incident query code. A value of N indicates that the treatment episodes should not be truncated at the occurrence of the incident query code.

Users - number of members with exposure during the query period. Member must have no evidence of exposure(s) of interest (defined by incidence criteria) in the prior washout period. A user may only be counted once in a query period.

Washout Period (drug/exposure) -** number of days a user is required to have no evidence of prior exposure (drug dispensing/procedure) and continuous drug and medical coverage prior to an incident treatment episode.

Washout Period (event/outcome) -** number of days a user is required to have no evidence of a prior event (procedure/diagnosis) and continuous drug and medical coverage prior to an incident treatment episode.

Years at Risk - number of days supplied plus any episode gaps and exposure extension periods all divided by 365.25.

*all terms may not be used in this report

**incident treatment episodes must be incident to both the exposure and the event

Table 1. Prevalent Pediatric Angiotensin-Converting Enzyme (ACE) Inhibitor and Angiotensin Receptor Blocker (ARB) Use in the Sentinel Distributed Database (SDD) between January 1, 2001 and December 31, 2012, by Drug Product

	Users	Dispensings	Days Supplied	Amount Supplied (Tablets or Capsules)	Eligible Members	Member-Years	Users per 1,000 Eligible Members	Days Supplied per User	Dispensings per User	Days Supplied per Dispensing
All ACE Inhibitors[1]	7,380	69,555	2,098,997	25,901,777	11,960,963	21,062,248.1	0.62	284.42	9.42	30.18
Benazepril	72	354	10,152	14,328	11,960,963	21,062,248.1	0.01	141.00	4.92	28.68
Captopril	2,083	14,897	417,990	11,404,142	11,960,963	21,062,248.1	0.17	200.67	7.15	28.06
Enalapril	4,503	46,647	1,395,645	14,064,467	11,960,963	21,062,248.1	0.38	309.94	10.36	29.92
Lisinopril	1,125	7,044	255,162	333,425	11,960,963	21,062,248.1	0.09	226.81	6.26	36.22
Ramipril	80	245	8,222	69,497	11,960,963	21,062,248.1	0.01	102.78	3.06	33.56
All ARBs	388	2,603	80,698	329,114	11,960,963	21,062,248.1	0.03	207.98	6.71	31.00

[1]The "All ACE Inhibitors" includes mutual exclusivity of drugs while the individual drug groups do not. This means a patient with dispensings of more than one drug type could be seen in each drug type but only once in the "All" group. This means the sum of users for the drug types is higher than the number reported for users of All Ace Inhibitors

Table 2. Prevalent Pediatric Angiotensin-Converting Enzyme (ACE) Inhibitor and Angiotensin Receptor Blocker (ARB) Use in the Sentinel Distributed Database (SDD) between January 1, 2001 and December 31, 2012, by Drug Product and Age Group

Age Group	Users	Dispensings	Days Supplied	Amount Supplied (Tablets or Capsules)	Eligible Members	Member-Years	Users per 1,000 Eligible Members	Days Supplied per User	Dispensings per User	Days Supplied per Dispensing
All ACE Inhibitors[1]										
01-05 months	2,173	4,984	140,280	613,960	4,048,416	1,361,222.7	0.54	64.56	2.29	28.15
06-11 months	1,981	6,771	192,833	1,843,249	4,104,675	1,681,589.8	0.48	97.34	3.42	28.48
12-23 months	2,043	11,403	330,812	4,665,199	4,941,385	3,415,894.8	0.41	161.92	5.58	29.01
24-72 months	4,543	46,397	1,435,072	18,779,370	9,358,796	14,603,540.7	0.49	315.89	10.21	30.93
Benazepril										
01-05 months	7	11	320	321	4,048,416	1,361,222.7	0.00	45.71	1.57	29.09
06-11 months	4	5	134	164	4,104,675	1,681,589.8	0.00	33.50	1.25	26.80
12-23 months	9	14	365	386	4,941,385	3,415,894.8	0.00	40.56	1.56	26.07
24-72 months	56	324	9,333	13,457	9,358,796	14,603,540.7	0.01	166.66	5.79	28.81
Captopril										
01-05 months	1,025	2,361	64,052	494,293	4,048,416	1,361,222.7	0.25	62.49	2.30	27.13
06-11 months	752	2,414	64,705	1,181,259	4,104,675	1,681,589.8	0.18	86.04	3.21	26.80
12-23 months	612	3,245	88,712	2,902,885	4,941,385	3,415,894.8	0.12	144.95	5.30	27.34
24-72 months	760	6,877	200,521	6,825,704	9,358,796	14,603,540.7	0.08	263.84	9.05	29.16
Enalapril										
01-05 months	1,111	2,441	70,780	114,375	4,048,416	1,361,222.7	0.27	63.71	2.20	29.00
06-11 months	1,159	4,057	118,906	653,465	4,104,675	1,681,589.8	0.28	102.59	3.50	29.31
12-23 months	1,310	7,492	220,527	1,701,055	4,941,385	3,415,894.8	0.27	168.34	5.72	29.43
24-72 months	2,962	32,657	985,432	11,595,571	9,358,796	14,603,540.7	0.32	332.69	11.03	30.18
Lisinopril										
01-05 months	87	151	4,557	4,364	4,048,416	1,361,222.7	0.02	52.38	1.74	30.18
06-11 months	105	266	8,241	7,453	4,104,675	1,681,589.8	0.03	78.49	2.53	30.98
12-23 months	166	614	20,069	29,598	4,941,385	3,415,894.8	0.03	120.90	3.70	32.69
24-72 months	921	6,013	222,295	292,010	9,358,796	14,603,540.7	0.10	241.36	6.53	36.97

Table 2. Prevalent Pediatric Angiotensin-Converting Enzyme (ACE) Inhibitor and Angiotensin Receptor Blocker (ARB) Use in the Sentinel Distributed Database (SDD) between January 1, 2001 and December 31, 2012, by Drug Product and Age Group

Age Group	Users	Dispensings	Days Supplied	Amount Supplied (Tablets or Capsules)	Eligible Members	Member-Years	Users per 1,000 Eligible Members	Days Supplied per User	Dispensings per User	Days Supplied per Dispensing
Ramipril										
01-05 months	5	8	211	211	4,048,416	1,361,222.7	0.00	42.20	1.60	26.38
06-11 months	8	15	436	466	4,104,675	1,681,589.8	0.00	54.50	1.88	29.07
12-23 months	12	26	822	30,792	4,941,385	3,415,894.8	0.00	68.50	2.17	31.62
24-72 months	59	196	6,753	38,028	9,358,796	14,603,540.7	0.01	114.46	3.32	34.45
All ARBs										
01-05 months	27	70	2,313	2,308	4,048,416	1,361,222.7	0.01	85.67	2.59	33.04
06-11 months	43	104	3,319	3,788	4,104,675	1,681,589.8	0.01	77.19	2.42	31.91
12-23 months	57	251	7,333	12,468	4,941,385	3,415,894.8	0.01	128.65	4.40	29.22
24-72 months	325	2,178	67,733	310,550	9,358,796	14,603,540.7	0.03	208.41	6.70	31.10

[1]The "All ACE Inhibitors" includes mutual exclusivity of drugs while the individual drug groups do not. This means a patient with dispensings of more than one drug type could be seen in each drug type but only once in the "All" group. This means the sum of users for the drug types is higher than the number reported for users of All Ace Inhibitors

Table 3. Prevalent Pediatric Angiotensin-Converting Enzyme (ACE) Inhibitor and Angiotensin Receptor Blocker (ARB) Use in the Sentinel Distributed Database (SDD) between January 1, 2001 and December 31, 2012, by Drug Product and Sex

Sex	Users	Dispensings	Days Supplied	Amount Supplied (Tablets or Capsules)	Eligible Members	Member-Years	Users per 1,000 Eligible Members	Days Supplied per User	Dispensings per User	Days Supplied per Dispensing
All ACE Inhibitors[1]										
Female	3,179	29,914	898,720	14,243,516	5,832,243	10,276,939.3	0.55	282.71	9.41	30.04
Male	4,201	39,641	1,200,277	11,658,261	6,127,970	10,784,554.8	0.69	285.71	9.44	30.28
Unknown	0	0	0	0	750	754.1	0.00	---	---	---
Benazepril										
Female	25	112	3,221	5,633	5,832,243	10,276,939.3	0.00	128.84	4.48	28.76
Male	47	242	6,931	8,695	6,127,970	10,784,554.8	0.01	147.47	5.15	28.64
Unknown	0	0	0	0	750	754.1	0.00	---	---	---
Captopril										
Female	919	6,466	182,125	8,341,402	5,832,243	10,276,939.3	0.16	198.18	7.04	28.17
Male	1,164	8,431	235,865	3,062,739	6,127,970	10,784,554.8	0.19	202.63	7.24	27.98
Unknown	0	0	0	0	750	754.1	0.00	---	---	---
Enalapril										
Female	1,988	20,029	597,290	5,703,540	5,832,243	10,276,939.3	0.34	300.45	10.07	29.82
Male	2,515	26,618	798,355	8,360,926	6,127,970	10,784,554.8	0.41	317.44	10.58	29.99
Unknown	0	0	0	0	750	754.1	0.00	---	---	---
Lisinopril										
Female	441	3,007	105,544	150,339	5,832,243	10,276,939.3	0.08	239.33	6.82	35.10
Male	684	4,037	149,618	183,086	6,127,970	10,784,554.8	0.11	218.74	5.90	37.06
Unknown	0	0	0	0	750	754.1	0.00	---	---	---
Ramipril										
Female	25	111	3,983	34,391	5,832,243	10,276,939.3	0.00	159.32	4.44	35.88
Male	55	134	4,239	35,106	6,127,970	10,784,554.8	0.01	77.07	2.44	31.63
Unknown	0	0	0	0	750	754.1	0.00	---	---	---
All ARBs										
Female	143	1,091	32,221	197,166	5,832,243	10,276,939.3	0.02	225.32	7.63	29.53
Male	245	1,512	48,477	131,949	6,127,970	10,784,554.8	0.04	197.87	6.17	32.06
Unknown	0	0	0	0	750	754.1	0.00	---	---	---

[1]The "All ACE Inhibitors" includes mutual exclusivity of drugs while the individual drug groups do not. This means a patient with dispensings of more than one drug type could be seen in each drug type but only once in the "All" group. This means the sum of users for the drug types is higher than the number reported for users of All Ace Inhibitors

Table 4. Prevalent Pediatric Angiotensin-Converting Enzyme (ACE) Inhibitor and Angiotensin Receptor Blocker (ARB) Use in the Sentinel Distributed Database (SDD) between January 1, 2001 and December 31, 2012, by Drug Product and Year

Year	Users	Dispensings	Days Supplied	Amount Supplied (Tablets or Capsules)	Eligible Members	Member-Years	Users per 1,000 Eligible Members	Days Supplied per User	Dispensings per User	Days Supplied per Dispensing
All ACE Inhibitors[1]										
2001	345	1,674	50,392	200,183	839,707	624,000.8	0.41	146.06	4.85	30.10
2002	379	2,040	63,348	221,911	839,238	624,600.0	0.45	167.15	5.38	31.05
2003	410	2,118	66,020	254,490	832,168	618,364.3	0.49	161.02	5.17	31.17
2004	480	2,626	82,164	3,680,450	871,241	649,509.6	0.55	171.18	5.47	31.29
2005	457	2,386	75,335	434,373	896,572	669,962.9	0.51	164.85	5.22	31.57
2006	935	4,783	146,150	439,294	2,148,482	1,518,029.9	0.44	156.31	5.12	30.56
2007	1,001	5,132	155,735	5,827,189	2,336,664	1,621,909.3	0.43	155.58	5.13	30.35
2008	2,123	11,273	339,449	4,052,463	4,631,454	3,229,872.5	0.46	159.89	5.31	30.11
2009	1,956	10,599	318,535	5,399,848	4,374,963	3,111,289.1	0.45	162.85	5.42	30.05
2010	1,854	10,159	302,866	3,339,250	4,079,003	2,913,575.4	0.45	163.36	5.48	29.81
2011	1,714	9,535	283,189	1,542,660	3,845,575	2,752,100.0	0.45	165.22	5.56	29.70
2012	1,438	7,230	215,814	509,664	3,832,707	2,729,034.3	0.38	150.08	5.03	29.85
Benazepril										
2001	16	66	1,968	2,222	839,707	624,000.8	0.02	123.00	4.13	29.82
2002	14	63	1,739	2,122	839,238	624,600.0	0.02	124.21	4.50	27.60
2003	12	41	1,103	1,510	832,168	618,364.3	0.01	91.92	3.42	26.90
2004	3	4	93	93	871,241	649,509.6	0.00	31.00	1.33	23.25
2005	2	2	60	90	896,572	669,962.9	0.00	30.00	1.00	30.00
2006	9	23	690	855	2,148,482	1,518,029.9	0.00	76.67	2.56	30.00
2007	10	14	420	555	2,336,664	1,621,909.3	0.00	42.00	1.40	30.00
2008	11	36	1,053	1,443	4,631,454	3,229,872.5	0.00	95.73	3.27	29.25
2009	8	26	758	946	4,374,963	3,111,289.1	0.00	94.75	3.25	29.15
2010	7	23	643	1,052	4,079,003	2,913,575.4	0.00	91.86	3.29	27.96
2011	4	31	895	1,780	3,845,575	2,752,100.0	0.00	223.75	7.75	28.87
2012	5	25	730	1,660	3,832,707	2,729,034.3	0.00	146.00	5.00	29.20

Table 4. Prevalent Pediatric Angiotensin-Converting Enzyme (ACE) Inhibitor and Angiotensin Receptor Blocker (ARB) Use in the Sentinel Distributed Database (SDD) between January 1, 2001 and December 31, 2012, by Drug Product and Year

Year	Users	Dispensings	Days Supplied	Amount Supplied (Tablets or Capsules)	Eligible Members	Member-Years	Users per 1,000 Eligible Members	Days Supplied per User	Dispensings per User	Days Supplied per Dispensing
Captopril										
2001	189	986	25,846	162,892	839,707	624,000.8	0.23	136.75	5.22	26.21
2002	195	1,080	29,171	167,389	839,238	624,600.0	0.23	149.59	5.54	27.01
2003	157	818	22,559	170,607	832,168	618,364.3	0.19	143.69	5.21	27.58
2004	150	718	21,873	845,336	871,241	649,509.6	0.17	145.82	4.79	30.46
2005	115	475	14,855	257,840	896,572	669,962.9	0.13	129.17	4.13	31.27
2006	230	1,080	30,516	171,710	2,148,482	1,518,029.9	0.11	132.68	4.70	28.26
2007	254	1,057	30,044	549,575	2,336,664	1,621,909.3	0.11	118.28	4.16	28.42
2008	532	2,323	67,119	2,215,883	4,631,454	3,229,872.5	0.11	126.16	4.37	28.89
2009	458	2,082	58,928	4,334,861	4,374,963	3,111,289.1	0.10	128.66	4.55	28.30
2010	379	1,789	49,104	1,998,988	4,079,003	2,913,575.4	0.09	129.56	4.72	27.45
2011	318	1,522	41,127	386,463	3,845,575	2,752,100.0	0.08	129.33	4.79	27.02
2012	245	967	26,848	142,596	3,832,707	2,729,034.3	0.06	109.58	3.95	27.76
Enalapril										
2001	67	348	10,359	22,826	839,707	624,000.8	0.08	154.61	5.19	29.77
2002	106	605	17,870	36,932	839,238	624,600.0	0.13	168.58	5.71	29.54
2003	188	1,007	29,357	69,840	832,168	618,364.3	0.23	156.15	5.36	29.15
2004	256	1,607	47,280	2,761,267	871,241	649,509.6	0.29	184.69	6.28	29.42
2005	280	1,647	48,539	163,968	896,572	669,962.9	0.31	173.35	5.88	29.47
2006	553	3,066	91,301	240,643	2,148,482	1,518,029.9	0.26	165.10	5.54	29.78
2007	620	3,421	101,405	5,237,995	2,336,664	1,621,909.3	0.27	163.56	5.52	29.64
2008	1,396	7,808	233,463	1,776,200	4,631,454	3,229,872.5	0.30	167.24	5.59	29.90
2009	1,287	7,473	225,356	1,019,339	4,374,963	3,111,289.1	0.29	175.10	5.81	30.16
2010	1,272	7,269	219,563	1,294,783	4,079,003	2,913,575.4	0.31	172.61	5.71	30.21
2011	1,201	6,921	207,060	1,105,452	3,845,575	2,752,100.0	0.31	172.41	5.76	29.92
2012	1,028	5,475	164,092	335,220	3,832,707	2,729,034.3	0.27	159.62	5.33	29.97

Table 4. Prevalent Pediatric Angiotensin-Converting Enzyme (ACE) Inhibitor and Angiotensin Receptor Blocker (ARB) Use in the Sentinel Distributed Database (SDD) between January 1, 2001 and December 31, 2012, by Drug Product and Year

Year	Users	Dispensings	Days Supplied	Amount Supplied (Tablets or Capsules)	Eligible Members	Member-Years	Users per 1,000 Eligible Members	Days Supplied per User	Dispensings per User	Days Supplied per Dispensing
Lisinopril										
2001	52	160	8,811	7,633	839,707	624,000.8	0.06	169.44	3.08	55.07
2002	54	180	11,271	10,292	839,238	624,600.0	0.06	208.72	3.33	62.62
2003	62	194	11,351	10,545	832,168	618,364.3	0.07	183.08	3.13	58.51
2004	69	226	10,809	11,575	871,241	649,509.6	0.08	156.65	3.28	47.83
2005	66	230	10,941	10,955	896,572	669,962.9	0.07	165.77	3.48	47.57
2006	147	541	20,885	22,846	2,148,482	1,518,029.9	0.07	142.07	3.68	38.60
2007	146	600	22,126	37,323	2,336,664	1,621,909.3	0.06	151.55	4.11	36.88
2008	238	1,051	35,504	56,313	4,631,454	3,229,872.5	0.05	149.18	4.42	33.78
2009	246	982	32,279	43,203	4,374,963	3,111,289.1	0.06	131.22	3.99	32.87
2010	258	1,070	33,330	44,156	4,079,003	2,913,575.4	0.06	129.19	4.15	31.15
2011	231	1,055	33,943	48,711	3,845,575	2,752,100.0	0.06	146.94	4.57	32.17
2012	189	755	23,912	29,874	3,832,707	2,729,034.3	0.05	126.52	3.99	31.67
Ramipril										
2001	9	14	404	404	839,707	624,000.8	0.01	44.89	1.56	28.86
2002	6	10	294	510	839,238	624,600.0	0.01	49.00	1.67	29.40
2003	7	12	360	390	832,168	618,364.3	0.01	51.43	1.71	30.00
2004	20	52	1,539	61,598	871,241	649,509.6	0.02	76.95	2.60	29.60
2005	6	26	780	1,080	896,572	669,962.9	0.01	130.00	4.33	30.00
2006	14	39	1,438	1,816	2,148,482	1,518,029.9	0.01	102.71	2.79	36.87
2007	9	24	971	1,001	2,336,664	1,621,909.3	0.00	107.89	2.67	40.46
2008	10	31	1,350	1,380	4,631,454	3,229,872.5	0.00	135.00	3.10	43.55
2009	10	17	524	539	4,374,963	3,111,289.1	0.00	52.40	1.70	30.82
2010	3	6	166	211	4,079,003	2,913,575.4	0.00	55.33	2.00	27.67
2011	3	6	164	254	3,845,575	2,752,100.0	0.00	54.67	2.00	27.33
2012	2	8	232	314	3,832,707	2,729,034.3	0.00	116.00	4.00	29.00

Table 4. Prevalent Pediatric Angiotensin-Converting Enzyme (ACE) Inhibitor and Angiotensin Receptor Blocker (ARB) Use in the Sentinel Distributed Database (SDD) between January 1, 2001 and December 31, 2012, by Drug Product and Year

Year	Users	Dispensings	Days Supplied	Amount Supplied (Tablets or Capsules)	Eligible Members	Member-Years	Users per 1,000 Eligible Members	Days Supplied per User	Dispensings per User	Days Supplied per Dispensing
All ARBs										
2001	15	31	793	984	839,707	624,000.8	0.02	52.87	2.07	25.58
2002	9	36	1,108	1,594	839,238	624,600.0	0.01	123.11	4.00	30.78
2003	13	41	1,161	1,697	832,168	618,364.3	0.02	89.31	3.15	28.32
2004	14	43	1,243	1,091	871,241	649,509.6	0.02	88.79	3.07	28.91
2005	13	28	759	1,953	896,572	669,962.9	0.01	58.38	2.15	27.11
2006	45	195	6,076	11,296	2,148,482	1,518,029.9	0.02	135.02	4.33	31.16
2007	51	244	7,529	23,309	2,336,664	1,621,909.3	0.02	147.63	4.78	30.86
2008	94	475	14,812	43,090	4,631,454	3,229,872.5	0.02	157.57	5.05	31.18
2009	90	342	11,026	33,905	4,374,963	3,111,289.1	0.02	122.51	3.80	32.24
2010	76	336	10,621	29,941	4,079,003	2,913,575.4	0.02	139.75	4.42	31.61
2011	78	417	12,663	146,416	3,845,575	2,752,100.0	0.02	162.35	5.35	30.37
2012	83	415	12,907	33,837	3,832,707	2,729,034.3	0.02	155.51	5.00	31.10

[1]The "All ACE Inhibitors" includes mutual exclusivity of drugs while the individual drug groups do not. This means a patient with dispensings of more than one drug type could be seen in each drug type but only once in the "All" group. This means the sum of users for the drug types is higher than the number reported for users of All Ace Inhibitors

Appendix A. Dates of Available Data in the Sentinel Distributed Database (SDD) as of Request Distribution Date (July 1, 2016)

DP ID	Start Date[1]	End Date[1]
DP0001	1/2/2005	12/31/2012
DP0002	1/2/2000	12/31/2012
DP0003	1/31/2000	12/31/2012
DP0004	1/2/2000	12/31/2012
DP0005	1/2/2000	12/31/2012
DP0006	1/2/2008	12/31/2012
DP0007	1/1/2008	12/31/2012
DP0008	1/31/2000	12/31/2012
DP0009	6/2/2007	12/31/2012
DP0010	1/2/2000	12/31/2012
DP0011	1/2/2000	12/31/2012
DP0012	1/2/2000	12/31/2012
DP0013	1/1/2006	12/31/2012
DP0014	1/2/2008	12/31/2012
DP0015	1/31/2004	12/31/2012

[1]The start and end dates are based on the minimum and maximum dates within each DP. The month with the maximum date must have at least 80% of the number of records in the previous month.

Appendix B. Generic Drug Names Used to Define Exposures in this Request

Generic Name
azilsartan medoxomil
benazepril HCl
candesartan cilexetil
captopril
enalapril maleate
eprosarten mesylate
fosinopril sodium
irbesartan
lisinopril
losartan potassium
moexipril HCl
olmesartan medoxomil
perindopril erbumine
quinapril HCl
ramipril
telmisartan
trandolapril
valsartan

Appendix C. Specifications for Parameters for this Request

The Cohort Identification and Descriptive Analysis (CIDA) tool, version 2.2.3, was used to investigate use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) among pediatric patients in the Sentinel Distributed Database (SDD).

Enrollment Gap: 45 days
Age Groups: 1-5 months, 6-11 months, 12-23 months, 24-72 months
Query Period: January 1, 2001 - December 31, 2012
Pre-Exposure Enrollment Requirement: 1 day
Coverage Requirement: At least drug coverage

	Drug/Exposure		
Scenario	**Prevalent Exposure**	**Washout (days)**	**Cohort Definition**
1	All ACE inhibitors (benazepril, captopril, enalapril, lisinopril, ramipril, enalapril, fosinopril, perindopril, quinapril, trandolapril, moexipril)	0	Include all valid prevalent dispensings during the query period
2	benazepril	0	Include all valid prevalent dispensings during the query period
3	captopril	0	Include all valid prevalent dispensings during the query period
4	enalapril	0	Include all valid prevalent dispensings during the query period
5	lisinopril	0	Include all valid prevalent dispensings during the query period
6	ramipril	0	Include all valid prevalent dispensings during the query period
7	All ARBs (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, azilsartan)	0	Include all valid prevalent dispensings during the query period

National drug codes (NDCs) checked against First Data Bank's "National Drug Data File (NDDF®) Plus"