Disclaimer

The following report(s) provides findings from an FDA-initiated query using its Mini-Sentinel pilot. While Mini-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 Mini-Sentinel, and seeking to better understand the capabilities of the Mini-Sentinel pilot.

Data obtained through Mini-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 the Mini-Sentinel pilot in the public domain as soon as possible. Any public health actions taken by FDA regarding products involved in Mini-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 msy4_mpr58, Report 2 of 2

Request ID: msy4_mpr58

Request Description: The goal of the query was to investigate angioedema among individuals with concomitant use of dipeptidyl peptidase IV (DPP IV) inhibitors and angiotensin converting enzyme (ACE) inhibitors in the Mini-Sentinel Distributed Database (MSDD). This is report 2 of 2. Report 1 examined angioedema among individuals with incident exposure to either DPP IV inhibitors or ACE inhibitors.

Sentinel Modular Program Tool Used: Modular Program #4 (MP4), version 5.0

Data Source: We included data from October 16, 2006 to December 31, 2012 from 18 Data Partners contributing to the MSDD. We distributed this request to Data Partners on December 20, 2013. See Appendix A for the dates of available data for each Data Partner.

Study Design: We designed this request to investigate angioedema following concomitant use of DPP IV Inhibitors and ACE Inhibitors. In total, eight scenarios were examined in one run of MP4 with differing order of exposure and event primary diagnosis (PDX) indicators: (1) the first two scenarios examine concomitant episodes where ACE Inhibitor is initiated before DPP IV Inhibitors, (2) the second two scenarios examine concomitant episodes where DPP IV Inhibitor is initiated before ACE Inhibitors, (3) the next two scenarios examine concomitant use where the order of initiation is not taken into account, and (4) the final two scenarios examine concomitant use where initiations of both exposures happens on the same day. Data were further stratified by sex, age group, and year.

Exposure of Interest: The exposures of interest were DPP IV Inhibitors and ACE Inhibitors. We defined exposures using National Drug Codes (NDCs). Please see Appendix B for a list of generic names of medical products used to define exposures in this request.

Outcome of Interest: The outcome of interest in this request was angioedema among concomitant users of DPP IV inhibitors and ACE inhibitors. We defined angioedema using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes. Please see Appendix C for a list of ICD-9-CM diagnosis codes used to define angioedema in this request.

Cohort Eligibility Criteria: We required members included in the cohort to be continuously enrolled in health plans with medical and drug coverage for at least 183 days prior to their first qualifying (index) DPP IV Inhibitor or ACE Inhibitor dispensing date, during which gaps in coverage of up to 45 days were allowed. We included individuals aged 20 years or older in the cohort.

Please see Appendices D and E for specifications of parameters used in the analyses for this request.

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

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

Mini-Sentinel

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Glossary of Terms in Modular Program 4*

Terms in Tables

Users - number of members with incident or prevalent exposure during the query period. For incidence, a 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.

Episodes - number of treatment episodes; length of episode is determined by days supplied in one dispensing (or consecutive dispensings bridged by the episode gap).

Dispensings - number of dispensings in qualifying treatment episodes.

Days Supplied - number of days supplied for all dispensings in qualifying treatment episodes.

Amount Supplied - number of units (pills, tablets, vials) dispensed.

Episode Duration - number of days in qualifying treatment episodes.

Days at Risk - number of days supplied plus any episode gaps and exposure extension periods.

Terms in Specifications

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

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

Age Groups - age group categories for reporting.

Event - outcome of interest.

Care Setting - type of medical encounter or facility where the event 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).

PDX Indicator - (Principal Diagnosis Indicator) diagnosis or condition established to be chiefly responsible for admission of the patient to the hospital. YES will only consider diagnoses flagged as Principal.

Incident with respect to - events that the event of interest is incident with respect to. For example, if an event is diabetes, we could examine diabetes incident with respect to itself (new diabetes patients who do not have a diabetes code in the prior washout period days). Instead, we could examine diabetes incident with respect to both diabetes and AMI (new diabetes patients who do not have a diabetes code or an AMI code in the prior washout period days).

Incident Only Care Setting - type of medical encounter or facility where the event in the "Incident w/ respect to:" column 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).

Incident Only PDX Indicator - event in the "Incident w/ respect to:" column established to be chiefly responsible for admission of the patient to the hospital. YES will only consider diagnoses flagged as Principal.

Washout Period (event) - 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 concomitant treatment episode.

Incidence Type (event/outcome)- *minimum incidence type* considers the first event in a valid concomitant episode as long as it is the first event in the user's entire available history. *Single and Multiple incidence types* will use the washout period to establish incidence; however, *Single* will only consider the first event in the query period whereas *Multiple* will consider all qualifying incident events. The program will always only consider one event per episode, but the *Multiple incidence type* will consider more than one event per user if a user has more than one incident episode.

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.

Exposure - exposure of interest (either primary or secondary).

Incident w/ respect to: - exposure that the exposure of interest is incident with respect to. For example, if an exposure is Drug X, we could examine Drug X incident with respect to itself (new Drug X users who do not have a Drug X dispensing in the prior washout period days). Instead, we could examine Drug X incident with respect to both Drug X and Drug Y (new Drug X users who do not have a Drug X or Drug Y dispensing in the prior washout period days).

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.

Incidence Type (drug/exposure)- *minimum incidence type* will consider the first treatment episode in the query period as long as it is the first treatment episode in the user's entire available history. *Single* and *Multiple incidence types* will use the washout period to establish incidence, however *Single* will only consider the first treatment episode whereas *Multiple* will consider all qualifying incident treatment episodes.

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

Minimum Episode Duration - specifies a minimum number of days in length of the episode for it to be considered.

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

Minimum Follow-up Period - number of days the member must be eligible for pharmacy and/or medical benefits after the exposure index date.

Episode Extension Period - number of days post treatment period in which the events are counted for a treatment episode.

Exposure Order Indicator - indicates whether the order of primary and secondary exposure is relevant when creating valid prevalent concomitant treatment episodes. A value of 'Y' instructs the program to always require primary exposure to be initiated before secondary exposure; a value of 'N' will not enforce an order restriction.

Event Washout Extension - indicates whether the event washout period should be extended to include all prior primary or secondary exposure days that were used to create the concomitant episode. This will be set to 'Y' if the requester wants washper days for the event of interest to include all days before the concomitant index date that are exposed to either the primary or secondary exposure used to define the concomitant exposure episode. For example, if a requester specifies a washper of 183 for the event and the event washout extension = 'Y', the program will look back whichever number of days is greater: 183 or the number of days before the concomitant index date that are exposed to the primary or secondary exposure used to define the concomitant exposure.

Number of concomitant episodes - indicates whether one or more than one valid incident concomitant episode should be included in output metrics. A value of 'ONE' will retain and report output metrics for only the first concomitant episode. A value of 'ALL' will retain and report output metrics for all valid concomitant episodes.

Minimum Follow-up Period - minimum number of days the member must be eligible for pharmacy and/or medical benefits after the concomitant episode index date.

Episode Extension Period - number of days post concomitant treatment period in which the events are counted for a treatment episode.

Minimum Episode Duration - specifies a minimum number of days in length of the concomitant episode for it to be considered.

*all terms may not be used in this report

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

Table 1. Summary of Angioedema following concomitant Angiotensin Converting Enzyme (ACE) Inhibitor and Dipeptidyl Peptidase IV (DPP IV) Inhibitor Exposure in the Mini-Sentinel Distributed Database (MSDD) between October 16, 2006 and December 31, 2012, by Order of Exposure and Diagnosis Position

Order of Exposure	Diagnosis Position	New Users	New Episodes	Episode Duration	Days at Risk	Years at Risk*	Episodes with Events	Episodes with Events per 10,000 Years at Risk*
ACE Inhibitors Initiated Before DPP IV Inhibitors								
ACE Inhibitor (Only) Initiation	Any	3,826,627	3,826,627	763,444,534	763,444,534	2,090,197	5,160	24.69
Followed by Concomitant DPP IV Inhibitor Initiation	Any	36,199	36,199	4,460,672	4,460,672	12,213	18	14.74
ACE Inhibitor (Only) Initiation	Primary	3,827,348	3,827,348	763,822,932	763,822,932	2,091,233	1,153	5.51
Followed by Concomitant DPP IV Inhibitor Initiation	Primary	36,204	36,204	4,461,698	4,461,698	12,215	5	4.09
DPP IV Inhibitors Initiated Before ACE Inhibitors								
DPP IV Inhibitor (Only) Initiation	Any	241,884	241,884	42,445,801	42,445,801	116,210	61	5.25
Followed by Concomitant ACE Inhibitor Initiation	Any	24,342	24,342	2,822,677	2,822,677	7,728	11	14.23
DPP IV Inhibitor (Only) Initiation	Primary	241,965	241,965	42,465,784	42,465,784	116,265	12	1.03
Followed by Concomitant ACE Inhibitor Initiation	Primary	24,346	24,346	2,823,141	2,823,141	7,729	3	3.88
Order of Initiation Not Considered								
Concomitant ACE Inhibitor/DPP IV Inhibitor Use	Any	51,794	51,794	6,477,572	6,477,572	17,735	25	14.10
Concomitant ACE Inhibitor/DPP IV Inhibitor Use	Primary	51,803	51,803	6,479,004	6,479,004	17,739	6	3.38
Initiation of ACE Inhibitors and DPP IV Inhibitors on Same Day								
Concomitant ACE Inhibitor/DPP IV Inhibitor Use	Any	11,133	11,133	1,112,661	1,112,661	3,046	6	19.70
Concomitant ACE Inhibitor/DPP IV Inhibitor Use	Primary	11,133	11,133	1,112,754	1,112,754	3,047	2	6.56

* Years at Risk stop accumulating when first event during episode is encountered

Table 2. Summary of Angioedema following concomitant Angiotensin Converting Enzyme (ACE) Inhibitor and Dipeptidyl Peptidase IV (DPP IV) Inhibitor Exposure in the Mini-Sentinel Distributed Database (MSDD) between October 16, 2006 and December 31, 2012, by Order of Exposure, Diagnosis Position, and Age Group

Age Group (year)	Diagnosis Position	New Users	New Episodes	Episode Duration	Days at Risk	Years at Risk*	Episodes with Events	Episodes with Events per 10,000 Years at Risk*
ACE Inhibitors Initiated Before DPP IV Inhibitors								
ACE Inhibitor (Only) Initiation	Any	3,826,627	3,826,627	763,444,534	763,444,534	2,090,197	5,160	24.69
Followed by Concomitant DPP IV Inhibitor Initiation	Any	36,199	36,199	4,460,672	4,460,672	12,213	18	14.74
20-44	Any	6,599	6,599	626,128	626,128	1,714	1	5.83
45-64	Any	21,199	21,199	2,689,437	2,689,437	7,363	11	14.94
65+	Any	8,401	8,401	1,145,107	1,145,107	3,135	6	19.14
ACE Inhibitor (Only) Initiation	Primary	3,827,348	3,827,348	763,822,932	763,822,932	2,091,233	1,153	5.51
Followed by Concomitant DPP IV Inhibitor Initiation	Primary	36,204	36,204	4,461,698	4,461,698	12,215	5	4.09
20-44	Primary	6,600	6,600	626,157	626,157	1,714	1	5.83
45-64	Primary	21,201	21,201	2,690,300	2,690,300	7,366	2	2.72
65+	Primary	8,403	8,403	1,145,241	1,145,241	3,135	2	6.38
DPP IV Inhibitors Initiated Before ACE Inhibitors								
DPP IV Inhibitor (Only) Initiation	Any	241,884	241,884	42,445,801	42,445,801	116,210	61	5.25
Followed by Concomitant ACE Inhibitor Initiation	Any	24,342	24,342	2,822,677	2,822,677	7,728	11	14.23
20-44	Any	4,350	4,350	373,564	373,564	1,023	1	9.78
45-64	Any	14,474	14,474	1,726,021	1,726,021	4,726	4	8.46
65+	Any	5,518	5,518	723,092	723,092	1,980	6	30.31
DPP IV Inhibitor (Only) Initiation	Primary	241,965	241,965	42,465,784	42,465,784	116,265	12	1.03
Followed by Concomitant ACE Inhibitor Initiation	Primary	24,346	24,346	2,823,141	2,823,141	7,729	3	3.88
20-44	Primary	4,350	4,350	373,564	373,564	1,023	1	9.78
45-64	Primary	14,477	14,477	1,726,262	1,726,262	4,726	1	2.12
65+	Primary	5,519	5,519	723,315	723,315	1,980	1	5.05
Order of Initiation Not Considered								
Concomitant ACE Inhibitor/DPP IV Inhibitor Use	Any	51,794	51,794	6,477,572	6,477,572	17,735	25	14.10
20-44	Any	8,457	8,457	806,602	806,602	2,208	3	13.58
45-64	Any	30,528	30,528	3,935,689	3,935,689	10,775	14	12.99
65+	Any	12,809	12,809	1,735,281	1,735,281	4,751	8	16.84
Concomitant ACE Inhibitor/DPP IV Inhibitor Use	Primary	51,803	51,803	6,479,004	6,479,004	17,739	6	3.38
20-44	Primary	8,458	8,458	806,666	806,666	2,209	1	4.53
45-64	Primary	30,533	30,533	3,936,779	3,936,779	10,778	3	2.78
65+	Primary	12,812	12,812	1,735,559	1,735,559	4,752	2	4.21

Table 2. Summary of Angioedema following concomitant Angiotensin Converting Enzyme (ACE) Inhibitor and Dipeptidyl Peptidase IV (DPP IV) Inhibitor Exposure in the Mini-Sentinel Distributed Database (MSDD) between October 16, 2006 and December 31, 2012, by Order of Exposure, Diagnosis Position, and Age Group

Age Group (year)	Diagnosis Position	New Users	New Episodes	Episode Duration	Days at Risk	Years at Risk*	Episodes with Events	Episodes with Events per 10,000 Years at Risk*
Initiation of ACE Inhibitors and DPP IV Inhibitors on Same Day								
Concomitant ACE Inhibitor/DPP IV Inhibitor Use	Any	11,133	11,133	1,112,661	1,112,661	3,046	6	19.70
20-44	Any	2,686	2,686	212,101	212,101	581	1	17.22
45-64	Any	6,621	6,621	676,052	676,052	1,851	1	5.40
65+	Any	1,826	1,826	224,508	224,508	615	4	65.08
Concomitant ACE Inhibitor/DPP IV Inhibitor Use	Primary	11,133	11,133	1,112,754	1,112,754	3,047	2	6.56
20-44	Primary	2,686	2,686	212,101	212,101	581	1	17.22
45-64	Primary	6,621	6,621	676,066	676,066	1,851	0	0.00
65+	Primary	1,826	1,826	224,587	224,587	615	1	16.26

* Years at Risk stop accumulating when first event during episode is encountered

Table 3. Summary of Angioedema following concomitant Angiotensin Converting Enzyme (ACE) Inhibitor and Dipeptidyl Peptidase IV (DPP IV) Inhibitor Exposure in the Mini-Sentinel Distributed Database (MSDD) between October 16, 2006 and December 31, 2012, by Order of Exposure, Diagnosis Position, and Sex

Sex	Diagnosis Position	New Users	New Episodes	Episode Duration	Days at Risk	Years at Risk*	Episodes with Events	Episodes with Events per 10,000 Years at Risk*
ACE Inhibitors Initiated Before DPP IV Inhibitors								
ACE Inhibitor (Only) Initiation	Any	3,826,627	3,826,627	763,444,534	763,444,534	2,090,197	5,160	24.69
Followed by Concomitant DPP IV Inhibitor Initiation	Any	36,199	36,199	4,460,672	4,460,672	12,213	18	14.74
Female	Any	14,577	14,577	1,684,841	1,684,841	4,613	4	8.67
Male	Any	21,620	21,620	2,775,651	2,775,651	7,599	14	18.42
Unknown	Any	2	2	180	180	0	0	0.00
ACE Inhibitor (Only) Initiation	Primary	3,827,348	3,827,348	763,822,932	763,822,932	2,091,233	1,153	5.51
Followed by Concomitant DPP IV Inhibitor Initiation	Primary	36,204	36,204	4,461,698	4,461,698	12,215	5	4.09
Female	Primary	14,578	14,578	1,685,100	1,685,100	4,614	1	2.17
Male	Primary	21,624	21,624	2,776,418	2,776,418	7,601	4	5.26
Unknown	Primary	2	2	180	180	0	0	0.00
DPP IV Inhibitors Initiated Before ACE Inhibitors								
DPP IV Inhibitor (Only) Initiation	Any	241,884	241,884	42,445,801	42,445,801	116,210	61	5.25
Followed by Concomitant ACE Inhibitor Initiation	Any	24,342	24,342	2,822,677	2,822,677	7,728	11	14.23
Female	Any	10,063	10,063	1,067,323	1,067,323	2,922	2	6.84
Male	Any	14,279	14,279	1,755,354	1,755,354	4,806	9	18.73
Unknown	Any	0	0	0	0	0	0	---
DPP IV Inhibitor (Only) Initiation	Primary	241,965	241,965	42,465,784	42,465,784	116,265	12	1.03
Followed by Concomitant ACE Inhibitor Initiation	Primary	24,346	24,346	2,823,141	2,823,141	7,729	3	3.88
Female	Primary	10,066	10,066	1,067,537	1,067,537	2,923	0	0.00
Male	Primary	14,280	14,280	1,755,604	1,755,604	4,807	3	6.24
Unknown	Primary	0	0	0	0	0	0	---
Order of Initiation Not Considered								
Concomitant ACE Inhibitor/DPP IV Inhibitor Use	Any	51,794	51,794	6,477,572	6,477,572	17,735	25	14.10
Female	Any	21,259	21,259	2,464,185	2,464,185	6,747	7	10.38
Male	Any	30,533	30,533	4,013,207	4,013,207	10,988	18	16.38
Unknown	Any	2	2	180	180	0	0	0.00
Concomitant ACE Inhibitor/DPP IV Inhibitor Use	Primary	51,803	51,803	6,479,004	6,479,004	17,739	6	3.38
Female	Primary	21,263	21,263	2,464,672	2,464,672	6,748	1	1.48
Male	Primary	30,538	30,538	4,014,152	4,014,152	10,990	5	4.55
Unknown	Primary	2	2	180	180	0	0	0.00

Table 3. Summary of Angioedema following concomitant Angiotensin Converting Enzyme (ACE) Inhibitor and Dipeptidyl Peptidase IV (DPP IV) Inhibitor Exposure in the Mini-Sentinel Distributed Database (MSDD) between October 16, 2006 and December 31, 2012, by Order of Exposure, Diagnosis Position, and Sex

Sex	Diagnosis Position	New Users	New Episodes	Episode Duration	Days at Risk	Years at Risk*	Episodes with Events	Episodes with Events per 10,000 Years at Risk*
Initiation of ACE Inhibitors and DPP IV Inhibitors on Same Day								
Concomitant ACE Inhibitor/DPP IV Inhibitor Use	Any	11,133	11,133	1,112,661	1,112,661	3,046	6	19.70
Female	Any	4,316	4,316	399,059	399,059	1,093	0	0.00
Male	Any	6,817	6,817	713,602	713,602	1,954	6	30.71
Unknown	Any	0	0	0	0	0	0	---
Concomitant ACE Inhibitor/DPP IV Inhibitor Use	Primary	11,133	11,133	1,112,754	1,112,754	3,047	2	6.56
Female	Primary	4,316	4,316	399,059	399,059	1,093	0	0.00
Male	Primary	6,817	6,817	713,695	713,695	1,954	2	10.24
Unknown	Primary	0	0	0	0	0	0	---

* Years at Risk stop accumulating when first event during episode is encountered

Table 4. Summary of Angioedema following concomitant Angiotensin Converting Enzyme (ACE) Inhibitor and Dipeptidyl Peptidase IV (DPP IV) Inhibitor Exposure in the Mini-Sentinel Distributed Database (MSDD) between October 16, 2006 and December 31, 2012, by Order of Exposure, Diagnosis Position, and Year*

Year	Diagnosis Position	New Users	New Episodes	Episode Duration	Days at Risk	Years at Risk**	Episodes with Events	Episodes with Events per 10,000 Years at Risk**
ACE Inhibitors Initiated Before DPP IV Inhibitors								
ACE Inhibitor (Only) Initiation	Any	3,826,627	3,826,627	763,444,534	763,444,534	2,090,197	5,160	24.69
Followed by Concomitant DPP IV Inhibitor Initiation	Any	36,199	36,199	4,460,672	4,460,672	12,213	18	14.74
2006	Any	67	67	6,769	6,769	19	0	0.00
2007	Any	1,617	1,617	264,351	264,351	724	0	0.00
2008	Any	3,861	3,861	543,327	543,327	1,488	0	0.00
2009	Any	5,520	5,520	734,099	734,099	2,010	3	14.93
2010	Any	6,427	6,427	866,657	866,657	2,373	5	21.07
2011	Any	8,994	8,994	1,097,824	1,097,824	3,006	7	23.29
2012	Any	9,713	9,713	947,645	947,645	2,595	3	11.56
ACE Inhibitor (Only) Initiation	Primary	3,827,348	3,827,348	763,822,932	763,822,932	2,091,233	1,153	5.51
Followed by Concomitant DPP IV Inhibitor Initiation	Primary	36,204	36,204	4,461,698	4,461,698	12,215	5	4.09
2006	Primary	67	67	6,769	6,769	19	0	0.00
2007	Primary	1,617	1,617	264,351	264,351	724	0	0.00
2008	Primary	3,861	3,861	543,327	543,327	1,488	0	0.00
2009	Primary	5,520	5,520	734,113	734,113	2,010	2	9.95
2010	Primary	6,427	6,427	867,031	867,031	2,374	1	4.21
2011	Primary	8,998	8,998	1,098,383	1,098,383	3,007	2	6.65
2012	Primary	9,714	9,714	947,724	947,724	2,595	0	0.00
DPP IV Inhibitors Initiated Before ACE Inhibitors								
DPP IV Inhibitor (Only) Initiation	Any	241,884	241,884	42,445,801	42,445,801	116,210	61	5.25
Followed by Concomitant ACE Inhibitor Initiation	Any	24,342	24,342	2,822,677	2,822,677	7,728	11	14.23
2006	Any	40	40	4,458	4,458	12	0	0.00
2007	Any	962	962	152,134	152,134	417	0	0.00
2008	Any	2,715	2,715	359,934	359,934	985	0	0.00
2009	Any	4,260	4,260	547,257	547,257	1,498	3	20.02
2010	Any	4,317	4,317	535,654	535,654	1,467	2	13.64
2011	Any	5,374	5,374	596,595	596,595	1,633	3	18.37
2012	Any	6,674	6,674	626,645	626,645	1,716	3	17.49
DPP IV Inhibitor (Only) Initiation	Primary	241,965	241,965	42,465,784	42,465,784	116,265	12	1.03
Followed by Concomitant ACE Inhibitor Initiation	Primary	24,346	24,346	2,823,141	2,823,141	7,729	3	3.88
2006	Primary	40	40	4,458	4,458	12	0	0.00
2007	Primary	962	962	152,134	152,134	417	0	0.00
2008	Primary	2,715	2,715	359,934	359,934	985	0	0.00
2009	Primary	4,261	4,261	547,297	547,297	1,498	2	13.35
2010	Primary	4,320	4,320	535,858	535,858	1,467	1	6.82
2011	Primary	5,374	5,374	596,737	596,737	1,634	0	0.00
2012	Primary	6,674	6,674	626,723	626,723	1,716	0	0.00

Table 4. Summary of Angioedema following concomitant Angiotensin Converting Enzyme (ACE) Inhibitor and Dipeptidyl Peptidase IV (DPP IV) Inhibitor Exposure in the Mini-Sentinel Distributed Database (MSDD) between October 16, 2006 and December 31, 2012, by Order of Exposure, Diagnosis Position, and Year*

Year	Diagnosis Position	New Users	New Episodes	Episode Duration	Days at Risk	Years at Risk**	Episodes with Events	Episodes with Events per 10,000 Years at Risk**
Order of Initiation Not Considered								
Concomitant ACE Inhibitor/DPP IV Inhibitor Use	Any	51,794	51,794	6,477,572	6,477,572	17,735	25	14.10
2006	Any	79	79	8,234	8,234	23	0	0.00
2007	Any	2,209	2,209	354,782	354,782	971	0	0.00
2008	Any	5,383	5,383	777,633	777,633	2,129	0	0.00
2009	Any	8,318	8,318	1,129,593	1,129,593	3,093	3	9.70
2010	Any	9,276	9,276	1,288,905	1,288,905	3,529	7	19.84
2011	Any	12,425	12,425	1,532,158	1,532,158	4,195	10	23.84
2012	Any	14,104	14,104	1,386,267	1,386,267	3,795	5	13.17
Concomitant ACE Inhibitor/DPP IV Inhibitor Use	Primary	51,803	51,803	6,479,004	6,479,004	17,739	6	3.38
2006	Primary	79	79	8,234	8,234	23	0	0.00
2007	Primary	2,209	2,209	354,782	354,782	971	0	0.00
2008	Primary	5,383	5,383	777,633	777,633	2,129	0	0.00
2009	Primary	8,319	8,319	1,129,633	1,129,633	3,093	2	6.47
2010	Primary	9,279	9,279	1,289,480	1,289,480	3,530	2	5.67
2011	Primary	12,429	12,429	1,532,845	1,532,845	4,197	2	4.77
2012	Primary	14,105	14,105	1,386,397	1,386,397	3,796	0	0.00
Initiation of ACE Inhibitors and DPP IV Inhibitors on Same Day								
Concomitant ACE Inhibitor/DPP IV Inhibitor Use	Any	11,133	11,133	1,112,661	1,112,661	3,046	6	19.70
2006	Any	28	28	2,993	2,993	8	0	0.00
2007	Any	412	412	67,799	67,799	186	0	0.00
2008	Any	1,364	1,364	150,070	150,070	411	0	0.00
2009	Any	1,927	1,927	210,294	210,294	576	3	52.11
2010	Any	1,978	1,978	192,029	192,029	526	1	19.02
2011	Any	2,492	2,492	238,201	238,201	652	1	15.33
2012	Any	2,932	2,932	251,275	251,275	688	1	14.54
Concomitant ACE Inhibitor/DPP IV Inhibitor Use	Primary	11,133	11,133	1,112,754	1,112,754	3,047	2	6.56
2006	Primary	28	28	2,993	2,993	8	0	0.00
2007	Primary	412	412	67,799	67,799	186	0	0.00
2008	Primary	1,364	1,364	150,070	150,070	411	0	0.00
2009	Primary	1,927	1,927	210,308	210,308	576	2	34.73
2010	Primary	1,978	1,978	192,053	192,053	526	0	0.00
2011	Primary	2,492	2,492	238,229	238,229	652	0	0.00
2012	Primary	2,932	2,932	251,302	251,302	688	0	0.00

*Year refers to start of concomitant treatment episode.

** Years at Risk stop accumulating when first event during episode is encountered

Appendix A. Dates of Available Data for Each Data Partner (DP) in the Mini-Sentinel Distributed Database (MSDD) as of Request Distribution Date (December 20, 2013)

DPID	DP Start Date	DP End Date
DP001	1/2/2008	12/31/2012
DP002	10/16/2006	12/31/2012
DP003	10/16/2006	6/30/2012
DP004	10/16/2006	12/31/2012
DP005	10/16/2006	4/30/2012
DP006	6/2/2007	12/31/2012
DP007	10/16/2006	12/31/2012
DP008	1/2/2008	12/31/2012
DP009	10/16/2006	12/31/2012
DP010	10/16/2006	12/31/2012
DP011	10/16/2006	12/31/2012
DP012	10/16/2006	12/31/2012
DP013	10/16/2006	6/30/2012
DP014	10/16/2006	12/31/2012
DP015	10/16/2006	12/31/2012
DP016	10/16/2006	12/31/2011
DP017	10/16/2006	12/31/2012
DP018	10/16/2006	12/31/2012

Appendix B. List of Generic Names of Medical Products Used to Define Exposures in this Request

Generic Name
Amlodipine besylate/benazepril
Benazepril HCl
Benazepril/hydrochlorothiazide
Captopril
Captopril/hydrochlorothiazide
Enalapril mal/diltiazem mal
Enalapril maleate
Enalapril maleate/felodipine
Enalapril/hydrochlorothiazide
Fosinopril sodium
Fosinopril/hydrochlorothiazide
Lisinopril
Lisinopril/dietary sup.cmb10
Lisinopril/hydrochlorothiazide
Moexipril HCl
Moexipril/hydrochlorothiazide
Perindopril erbumine
Quinapril HCl
Quinapril/hydrochlorothiazide
Ramipril
Trandolapril
Trandolapril/verapamil HCl
Alogliptin benz/metformin HCl
Alogliptin benz/pioglitzone
Alogliptin benzoate
Linagliptin
Linagliptin/metformin HCl
Saxagliptin HCl
Saxagliptin HCl/metformin HCl
Sitagliptin phos/metformin HCl
Sitagliptin phosphate
Sitagliptin/simvastatin

Appendix C. List of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Codes Used to Define Outcomes in this Request

Code	Description	Code Type
995.1	Angioneurotic edema, not elsewhere classified	ICD-9-CM

Appendix D. Specifications of Event and Primary Exposure Parameters Used in this Request

This request utilized the Mini-Sentinel Modular Program #4 (MP4) to examine angioedema individuals with concomitant use of dipeptidyl peptidase IV (DPP IV) inhibitors and angiotensin converting enzyme (ACE) inhibitors in the Mini-Sentinel Distributed Database (MSDD). In total, eight different scenarios will be examined in this report. See below for a description of each of these scenarios.

Query Period: October 16, 2006 to December 31, 2012
Enrollment Gap: 45 days
Age Groups: 20-44, 45-64, 65+ years
Coverage Requirement: Medical and Drug Coverage
Enrollment Requirement: 183 days

	Event									Primary Exposure								
Scenario	Event	Care Setting	Primary Diagnosis (PDX) Indicator	Incident with Respect to:	Incident Only Care Setting	Incident Only PDX Indicator	Washout (days)	Washout Type[1]	Blackout Period (days)	Primary Exposure	Incident with Respect to:	Washout (days)	Incidence Type[1]	Episode Gap (days)	Minimum Episode Duration (days)	Minimum Days Supplied (days)	Minimum Follow-up Period (days)	Episode Extension Period (days)
1	Angioedema	Inpatient (IP), Emergency Department (ED)	NO	Angioedema	IP ED	NO	183	MULT	0	ACE Inhibitors	DPP IV Inhibitors and ACE Inhibitors	183	SING	10	0	0	0	0
2	Angioedema	IP ED	YES	Angioedema	IP ED	YES	183	MULT	0	ACE Inhibitors	DPP IV Inhibitors and ACE Inhibitors	183	SING	10	0	0	0	0
3	Angioedema	IP ED	NO	Angioedema	IP ED	NO	183	MULT	0	DPP IV Inhibitors	DPP IV Inhibitors and ACE Inhibitors	183	SING	10	0	0	0	0
4	Angioedema	IP ED	YES	Angioedema	IP ED	YES	183	MULT	0	DPP IV Inhibitors	DPP IV Inhibitors and ACE Inhibitors	183	SING	10	0	0	0	0
5	Angioedema	IP ED	NO	Angioedema	IP ED	NO	183	MULT	0	DPP IV Inhibitors	DPP IV Inhibitors	183	SING	10	0	0	0	0
6	Angioedema	IP ED	YES	Angioedema	IP ED	YES	183	MULT	0	DPP IV Inhibitors	DPP IV Inhibitors	183	SING	10	0	0	0	0
7	Angioedema	IP ED	NO	Angioedema	IP ED	NO	183	MULT	0	DPP IV Inhibitors	DPP IV Inhibitors	183	SING	10	0	0	0	0
8	Angioedema	IP ED	YES	Angioedema	IP ED	YES	183	MULT	0	DPP IV Inhibitors	DPP IV Inhibitors	183	SING	10	0	0	0	0

Appendix E. Specifications of Secondary and Concomitant Exposure Parameters Used in this Request

This request utilized the Mini-Sentinel Modular Program #4 (MP4) to examine angioedema individuals with concomitant use of dipeptidyl peptidase IV (DPP IV) inhibitors and angiotensin converting enzyme (ACE) inhibitors in the Mini-Sentinel Distributed Database (MSDD). In total, eight different scenarios will be examined in this report. See below for a description of each of these scenarios.

Query Period: October 16, 2006 to December 31, 2012
Enrollment Gap: 45 days
Age Groups: 20-44, 45-64, 65+ years
Coverage Requirement: Medical and Drug Coverage
Enrollment Requirement: 183 days

	Secondary Exposure									Concomitant Exposure						
Scenario	Secondary Exposure	Incident with Respect to:	Washout (days)	Incidence Type[1]	Episode Gap (days)	Minimum Episode Duration (days)	Minimum Days Supplied (days)	Minimum Follow-up Period (days)	Episode Extension Period (days)	Exposure Order Indicator	Event Washout Extension	Number of Concomitant Episodes	Minimum Follow-up Period (days)	Episode Extension Period (days)	Minimum Episode Duration (days)	Both Exposures Start on Same Day for Concomitant Exposure
1	DPP IV Inhibitors	DPP IV Inhibitors	183	SING	10	0	0	0	0	Y	N	1	0	0	0	N
2	DPP IV Inhibitors	DPP IV Inhibitors	183	SING	10	0	0	0	0	Y	N	1	0	0	0	N
3	ACE Inhibitors	ACE Inhibitors	183	SING	10	0	0	0	0	Y	N	1	0	0	0	N
4	ACE Inhibitors	ACE Inhibitors	183	SING	10	0	0	0	0	Y	N	1	0	0	0	N
5	ACE Inhibitors	ACE Inhibitors	183	SING	10	0	0	0	0	N	N	1	0	0	0	N
6	ACE Inhibitors	ACE Inhibitors	183	SING	10	0	0	0	0	N	N	1	0	0	0	N
7	ACE Inhibitors	ACE Inhibitors	183	SING	10	0	0	0	0	N	N	1	0	0	0	Y
8	ACE Inhibitors	ACE Inhibitors	183	SING	10	0	0	0	0	N	N	1	0	0	0	Y