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 msy5_mpr12_v1

Request ID: msy5_mpr12_v1

Request Description: This report investigates exposure to rivaroxaban among all patients in the Mini-Sentinel Distributed Database (MSDD) and among patients with a pre-existing condition of atrial fibrillation or atrial flutter.

Modular Program Tool Used: Modular Program 3, version 6

Data Source: Data from July 1, 2011 to September 30, 2013 for 18 Data Partners contributing to the MSDD were included in this request (see Appendix A for a list of data availability dates). The request was distributed to Data Partners on November 22, 2013. The report includes information from 18 Data Partners.

Study Design: The request was designed to examine new rivaroxaban use among all patients and among patients with a pre-existing condition of atrial fibrillation or atrial flutter. In total, four scenarios differing by pre-existing condition criteria and episode gap were examined. Please see Appendix B for more details on each scenario.

Cohort Eligibility Criteria: A patient was considered a new user if he or she was not exposed to rivaroxaban in the previous 183 days (exposure washout period). Rivaroxaban incidence was assessed with respect to all anti-coagulants (including apixaban, dabigatran, rivaroxaban, and warfarin). For scenarios involving a pre-existing condition, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) for atrial fibrillation and atrial flutter were queried. Please see Appendix C for specific codes.

Exposure of Interest: The exposure of interest was incident rivaroxaban use, which was identified using National Drug Codes (NDCs).

Limitations: Algorithms used to define exposures and outcomes are imperfect; thus, it is possible that there may be misclassification.

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

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Glossary of Terms in Modular Program 3*

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

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

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 Days - irrespective of what query incidence type (WASHTYP) is specified, this is an optional parameter to further restrict the number of days of continuous enrollment prior to start of new incident treatment episode to reach a certain minimum. This parameter is used to ensure that appropriate enrollment requirements are met. Since at least washout period days of enrollment must be found prior to index date this minimum enrollment days requirement can only be binding if enrollment days > washout period days

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

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

Exposure Extension Period - number of days post treatment period in which the outcomes/events are counted for a 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

Incidence Type (event/outcome)- *Minimum incidence type* considers the first event in a valid episode as long as it is the first event in the user's entire available history. *Multiple incidence type* uses the washout period to establish incidence and considers all qualifying incident treatment episodes. The program will only consider one event per episode, but the *Multiple incidence type* will consider more than one

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

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

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

New Episodes - new treatment episodes; length of episode is determined by days supplied in one dispensing (or consecutive dispensings

New Users - number of members with incident 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.

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

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

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

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.

*all terms may not be used in this report

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

Table 1: Incident Rivaroxaban Use in the Mini-Sentinel Distributed Database (MSDD) between July 1, 2011 and September 30, 2013, by Pre-Existing Condition Criteria and Episode Gap

	New Users	New Episodes	Dispensings	Total Days Supplied	Years at Risk	Eligible Members	Member-Years	New Users / 1K Eligible Members	Days Supplied/ User	Dispensings / User	Days Supplied/ Dispensing
No Pre-Existing Condition of Atrial Fibrillation or Atrial Flutter											
3-Day Episode Gap	16,167	16,167	38,007	1,316,361	3,270.1	50,425,813	59,198,217	0.32	81.42	2.35	34.63
10-Day Episode Gap	16,167	16,167	46,239	1,592,937	3,997.3	50,425,813	59,198,217	0.32	98.53	2.86	34.45
Pre-Existing Condition of Atrial Fibrillation or Atrial Flutter											
3-Day Episode Gap	12,335	12,335	30,193	1,074,820	2,691.5	712,055	415,154	17.32	87.14	2.45	35.60
10-Day Episode Gap	12,335	12,335	37,207	1,312,486	3,318.7	712,055	415,154	17.32	106.40	3.02	35.28

Table 2: Incident Rivaroxaban Use in the Mini-Sentinel Distributed Database (MSDD) between July 1, 2011 and September 30, 2013, by Pre-Existing Condition Criteria, Episode Gap, and Age Group

	New Users	New Episodes	Dispensings	Total Days Supplied	Years at Risk	Eligible Members	Member-Years	New Users / 1K Eligible Members	Days Supplied/ User	Dispensings / User	Days Supplied/ Dispensing
No Pre-Existing Condition of Atrial Fibrillation or Atrial Flutter											
3-Day Episode Gap											
0 to 40 Years	631	631	1,151	32,598	81.2	28,456,990	31,013,584	0.02	51.66	1.82	28.32
41 to 54 Years	2,394	2,394	5,156	158,773	400.0	11,915,179	13,356,600	0.20	66.32	2.15	30.79
55 to 64 Years	4,434	4,434	10,721	349,079	879.4	7,111,281	8,109,331	0.62	78.73	2.42	32.56
65 to 74 Years	4,096	4,096	9,634	351,310	865.0	3,474,619	4,011,702	1.18	85.77	2.35	36.47
75 to 84 Years	3,457	3,457	8,438	321,080	786.8	1,611,723	1,967,716	2.14	92.88	2.44	38.05
85+ Years	1,155	1,155	2,907	103,521	257.7	610,224	739,283	1.89	89.63	2.52	35.61
10-Day Episode Gap											
0 to 40 Years	631	631	1,314	37,703	94.2	28,456,990	31,013,584	0.02	59.75	2.08	28.69
41 to 54 Years	2,394	2,394	6,239	191,896	490.2	11,915,179	13,356,600	0.20	80.16	2.61	30.76
55 to 64 Years	4,434	4,434	13,340	431,739	1,100.6	7,111,281	8,109,331	0.62	97.37	3.01	32.36
65 to 74 Years	4,096	4,096	11,807	429,496	1,066.4	3,474,619	4,011,702	1.18	104.86	2.88	36.38
75 to 84 Years	3,457	3,457	10,040	378,225	935.1	1,611,723	1,967,716	2.14	109.41	2.90	37.67
85+ Years	1,155	1,155	3,499	123,878	310.8	610,224	739,283	1.89	107.25	3.03	35.40
Pre-Existing Condition of Atrial Fibrillation or Atrial Flutter											
3-Day Episode Gap											
0 to 40 Years	216	216	390	11,850	31.1	27,164	11,446	7.95	54.86	1.81	30.38
41 to 54 Years	1,445	1,445	3,218	103,345	265.3	78,227	37,380	18.47	71.52	2.23	32.11
55 to 64 Years	3,309	3,309	8,366	278,805	710.8	140,732	71,265	23.51	84.26	2.53	33.33
65 to 74 Years	3,427	3,427	8,294	306,188	757.9	183,687	99,997	18.66	89.35	2.42	36.92
75 to 84 Years	2,956	2,956	7,365	282,748	696.2	195,118	113,765	15.15	95.65	2.49	38.39
85+ Years	982	982	2,560	91,884	230.2	128,512	81,300	7.64	93.57	2.61	35.89
10-Day Episode Gap											
0 to 40 Years	216	216	446	13,650	35.7	27,164	11,446	7.95	63.19	2.06	30.61
41 to 54 Years	1,445	1,445	3,982	126,830	329.9	78,227	37,380	18.47	87.77	2.76	31.85
55 to 64 Years	3,309	3,309	10,611	349,735	901.5	140,732	71,265	23.51	105.69	3.21	32.96
65 to 74 Years	3,427	3,427	10,215	376,069	938.1	183,687	99,997	18.66	109.74	2.98	36.82
75 to 84 Years	2,956	2,956	8,824	334,711	832.0	195,118	113,765	15.15	113.23	2.99	37.93
85+ Years	982	982	3,129	111,491	281.6	128,512	81,300	7.64	113.53	3.19	35.63

Table 3: Incident Rivaroxaban Use in the Mini-Sentinel Distributed Database (MSDD) between July 1, 2011 and September 30, 2013, by Pre-Existing Condition Criteria, Episode Gap, and Sex

	New Users	New Episodes	Dispensings	Total Days Supplied	Years at Risk	Eligible Members	Member-Years	New Users / 1K Eligible Members	Days Supplied/ User	Dispensings / User	Supplied/ Dispensing
No Pre-Existing Condition of Atrial Fibrillation or Atrial Flutter											
3-Day Episode Gap											
Female	6,103	6,103	14,805	514,916	1,275.5	25,771,755	30,410,614	0.24	84.37	2.43	34.78
Male	10,064	10,064	23,202	801,445	1,994.6	24,651,564	28,785,000	0.41	79.63	2.31	34.54
Unknown	0	0	0	0	0.0	2,494	2,603	0.00	---	---	---
10-Day Episode Gap											
Female	6,103	6,103	17,727	614,674	1,536.0	25,771,755	30,410,614	0.24	100.72	2.90	34.67
Male	10,064	10,064	28,512	978,263	2,461.3	24,651,564	28,785,000	0.41	97.20	2.83	34.31
Unknown	0	0	0	0	0.0	2,494	2,603	0.00	---	---	---
Pre-Existing Condition of Atrial Fibrillation or Atrial Flutter											
3-Day Episode Gap											
Female	4,449	4,449	11,492	412,569	1,031.4	313,594	184,624	14.19	92.73	2.58	35.90
Male	7,886	7,886	18,701	662,251	1,660.1	398,448	230,523	19.79	83.98	2.37	35.41
Unknown	0	0	0	0	0.0	13	6	0.00	---	---	---
10-Day Episode Gap											
Female	4,449	4,449	13,946	497,937	1,254.7	313,594	184,624	14.19	111.92	3.13	35.70
Male	7,886	7,886	23,261	814,549	2,064.1	398,448	230,523	19.79	103.29	2.95	35.02
Unknown	0	0	0	0	0.0	13	6	0.00	---	---	---

Table 4: Incident Rivaroxaban Use in the Mini-Sentinel Distributed Database (MSDD) between July 1, 2011 and September 30, 2013, by Pre-Existing Condition Criteria, Episode Gap, and Year

	New Users	New Episodes	Dispensings	Total Days Supplied	Years at Risk	Eligible Members	Member-Years	New Users / 1K Eligible Members	Days Supplied/ User	Dispensings / User	Days Supplied/ Dispensing
No Pre-Existing Condition of Atrial Fibrillation or Atrial Flutter											
3-Day Episode Gap											
2011	153	153	428	15,316	41.0	39,522,999	17,795,839	0.00	100.10	2.80	35.79
2012	9,376	9,376	25,262	899,004	2,315.3	42,323,259	33,206,959	0.22	95.88	2.69	35.59
2013	6,638	6,638	12,317	402,041	913.8	20,553,086	8,195,419	0.32	60.57	1.86	32.64
10-Day Episode Gap											
2011	153	153	627	22,673	60.8	39,522,999	17,795,839	0.00	148.19	4.10	36.16
2012	9,376	9,376	31,829	1,121,458	2,911.0	42,323,259	33,206,959	0.22	119.61	3.39	35.23
2013	6,638	6,638	13,783	448,806	1,025.4	20,553,086	8,195,419	0.32	67.61	2.08	32.56
Pre-Existing Condition of Atrial Fibrillation or Atrial Flutter											
3-Day Episode Gap											
2011	134	134	392	13,694	36.7	395,870	119,768	0.34	102.19	2.93	34.93
2012	8,068	8,068	22,132	794,652	2,052.7	530,093	235,107	15.22	98.49	2.74	35.91
2013	4,133	4,133	7,669	266,474	602.1	255,943	60,278	16.15	64.47	1.86	34.75
10-Day Episode Gap											
2011	134	134	582	20,781	55.7	395,870	119,768	0.34	155.08	4.34	35.71
2012	8,068	8,068	28,038	995,484	2,591.1	530,093	235,107	15.22	123.39	3.48	35.50
2013	4,133	4,133	8,587	296,221	671.9	255,943	60,278	16.15	71.67	2.08	34.50

Appendix A: Dates of Available Data for Each Data Partner as of Request Send Date (November 22, 2013)

Data Partner ID	Start Date	End Date
DP0001	7/1/2011	5/31/2013
DP0002	7/1/2011	6/30/2012
DP0003	7/1/2011	6/30/2013
DP0004	7/1/2011	12/31/2012
DP0005	7/1/2011	3/31/2013
DP0006	7/1/2011	9/30/2013
DP0007	7/1/2011	12/31/2012
DP0008	7/1/2011	6/30/2012
DP0009	7/1/2011	12/31/2012
DP0010	7/1/2011	5/31/2013
DP0011	7/1/2011	1/31/2013
DP0012	7/1/2011	5/30/2013
DP0013	7/1/2011	4/30/2012
DP0014	7/1/2011	12/31/2012
DP0015	7/1/2011	12/31/2012
DP0016	7/1/2011	9/30/2013
DP0017	7/1/2011	12/31/2011
DP0018	7/1/2011	5/30/2013

Appendix B: Modular Program Specifications for Query MSY5_MPR12_v1

Modular Program #3 was used to examine new rivaroxaban use among all members and among those with a pre-existing condition of atrial fibrillation/flutter (See Appendix C for a list of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes. In total, four different scenarios were examined in this request with differing pre-existing condition criteria and episode gaps. See below for a description of each of these scenarios.

Coverage Requirement	Drug and Medical
Query Period	July 1, 2011 to September 30, 2013
Enrollment Gap	45 Days
Enrollment Days	183
Age Stratifications	0-40, 41-54, 55-64, 65-74, 75-84, and 85+

	Drug/Exposure								Pre-Existing Condition					Event/Outcome
Scenario	**Incident exposure**	**Incident w/ respect to:**	**Ep. Gap**	**Ep. Ext. Period**	**Min. Ep. Duration**	**Min. Days Supplied**	**Washout (days)**	**Incidence Type*** **	**Pre-Existing Condition**	**Include/ Exclude**	**Lookback Start**	**Lookback End**	**Care Setting PDX**	**Event/ Outcome**
1	Rivaroxaban*	All Anti-Coagulants**	3	2	0	0	183	SING	None	N/A	N/A	N/A	N/A	Dummy
2	Rivaroxaban*	All Anti-Coagulants**	3	2	0	0	183	SING	Atrial Fibrillation/Flutter	1	-183	0	Any	Dummy
3	Rivaroxaban*	All Anti-Coagulants**	10	2	0	0	183	SING	None	N/A	N/A	N/A	N/A	Dummy
4	Rivaroxaban*	All Anti-Coagulants**	10	2	0	0	183	SING	Atrial Fibrillation/Flutter	1	-183	0	Any	Dummy

National Drug Codes (NDCs) checked against First Data Bank's "National Drug Data File (NDDF®) Plus"
International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) diagnosis and procedure codes checked against "Ingenix 2012 ICD-9-CM Data File" provided by OptumInsight
Healthcare Common Procedure Coding System (HCPCS) codes checked against "Optum 2012 HCPCS Level II Data File" provided by OptumInsight
Current Procedural Terminology, Fourth Revision (CPT-4) codes checked against "Optum 2012 Current Procedure Codes & Relative Values Data File" provided by OptumInsight

*10MG-dose NDCs were excluded.

**All anti-coagulants include apixaban, dabigatran, rivaroxaban, and warfarin.

***Single washout type for the exposure will only consider the first incident episode for each user during the query period that satisfies the Washout Period criteria (183). There can be at most one episode per user.

Appendix C: Atrial Fibrillation or Atrial Flutter International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Diagnosis Codes Queried in this Request

Code	Description
427.31	Atrial Fibrillation
427.32	Atrial Flutter