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: to09y05_mpr_wp27_v02

Request ID: to09y05_mpr_wp27_v02

Request Description: This request analyzed acute myocardial infarction (AMI) and stroke among members overall and among those with a pre-existing condition of one of the specified testosterone indications. This is report 2 of 2. Report 1 investigated new diagnoses for a testosterone-related indication and those who received a testosterone product in the following six months.

Modular Program Tool Used: Modular Program #6 (MP6)

Data Source: Data from January 1, 2007 through May 31, 2013 from 18 Data Partners contributing to the Mini-Sentinel Distributed Database (MSDD) were included in this report. This request was distributed to 18 Data Partners on March 28, 2014. Please see Appendix A for a list of dates of available data in the MSDD for each Data Partner.

Study Design: This request was designed to analyze AMI and stroke among members overall and those with a pre-existing condition of one of the specified testosterone indications. Results were stratified by age group, sex, and year.

Events of Interest: The events of interest in this request were AMI and stroke among members overall and those with a pre-existing condition of one of the specified testosterone indications. AMI and stroke were defined using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes. Please see Appendix B for a list of codes used to define the exposures in this request.

Cohort Eligibility Criteria: Patients were required to be continuously enrolled for 183 days in health plans with both drug and medical coverage, during which gaps in coverage of up to 45 days were allowed. Individuals were stratified into the following age groups: 0-39, 40-64, 65-74, and 75+ years. All eligible members with the events of interest were assessed; additionally, members with testosterone indications in the 183 days prior to index were assessed. These indications included: malignant neoplasm of pituitary gland, benign neoplasm of pituitary gland, other pituitary disorders, Klinefelter's syndrome, other testicular hypofunction, depressive disorder, muscular atrophy, malaise/fatigue, decreased libido, hypoactive sexual desire disorder, unspecified testicular dysfunction, and other testicular dysfunction. Testosterone-related indication diagnoses were defined using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes. Please see Appendix C for a list of diagnosis codes used to define the events of interest in this request.

Please see Appendix D for the specifications for parameters for the analyses in this request.

Limitations: Algorithms used to define exposures, outcomes, and inclusion criteria 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 Query Fulfillment Team (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 6*

Amount Supplied - number of units (pills, tablets, vials) dispensed in qualifying post-event treatment episodes.

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).

Claims - number of exposure event claims experienced by new patients.

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

Dispensings - number of dispensings in qualifying post-event treatment episodes.

Eligible Members - number of members eligible for an incident exposure/lookup period (defined by the 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.

Episode Duration - number of days in qualifying post-event treatment episodes.

Incidence Type (drug/exposure)- *Minimum Incidence type* will consider the first exposure/lookup period in the query period as long as it is the first exposure/lookup period 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 exposure/lookup period whereas *Multiple* will consider all qualifying exposures/lookup periods.

Incidence Type (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 exposures/lookup periods.

Inclusion/Exclusion Indicator - indicates whether condition(s) of interest are used for inclusion or exclusion criteria. A value of 1 instructs the program that members must have the condition of interest (inclusion criteria); a value of 0 instructs the program that members must not have the condition of interest (exclusion criteria).

Lookback Period Start and End - range of days relative to index that the program looks for inclusion/exclusion conditions of interest. For example, if the Inclusion/Exclusion Indicator =1, Lookback Period Start = -183 and Lookback Period End = 0, the cohort will only include members with the condition of interest present in the 183 days prior to and including the index date (the index date is day 0).

Lookup Period Duration - fixed period of time following an incident exposure that the MP6 program searches for events of interest.

Mean Post-event Treatment Intensity- mean number of days of post-event treatment during a valid lookup period divided by the mean lookup period duration.

Member-Years - sum of all days a member is eligible for an incident exposure/lookup period (i.e., days that the member meets all inclusion criteria such a incidence, pre-existing condition, and enrollment requirements) divided by 365.23.

Minimum Lookup Period Duration - minimum number of enrollment days required after an incident exposure/lookup period start. For example, if the minimum duration =10, a member must have 10 or more days of continuous enrollment in drug and medical benefit coverage following the exposure/lookup period start in order for the lookup period to be included in output metrics.

New Patients - number of members with incident exposure/lookup period during the query period. A user may only be counted once in a query period.

New Patients with Post-Event Treatment - number of patients who have an incident claim for the post-event treatment of interest.

Post-event Treatment Intensity - sum of post-event treatment days across all members during a valid lookup period divided by the sum of all lookup period durations during the query period.

Principal Diagnosis - 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 evaluates exposures of interest.

Time-to-Event (tte)/Time-to-Treatment - number of days between the start of an event lookup period (index date) and the first treatment episode/procedure/diagnosis claim.

Washout Period (event/outcome) - number of days a user is required to have no evidence of a prior event (post-event treatment) and continuous drug and medical coverage prior to an incident exposure/lookup period.

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

*all terms may not be used in this report
**incident treatment episodes must be incident to both the exposure and the event

Table 1c. Summary of Acute Myocardial Infarction (AMI)/Stroke in the Mini-Sentinel Distributed Database (MSDD) between January 1, 2007 and May 31, 2013, by Pre-Existing Condition Criteria

	New Patients/ Lookup Periods*	Claims	Lookup Period Duration (Days)	Eligible Members	Member-Years	New Patients per 1,000 Eligible Members
Acute Myocardial Infarction						
With Pre-Existing Testosterone Conditions	121,578	376,310	17,139,506	17,624,390	13,088,568	7.09
No Pre-Existing Condition Criteria	574,475	1,914,278	86,706,518	86,810,801	197,260,771	6.63
Stroke						
With Pre-Existing Testosterone Conditions	256,596	892,533	38,830,988	17,531,122	12,862,594	6.61
No Pre-Existing Condition Criteria	949,451	3,608,712	148,062,048	86,776,774	196,443,215	6.41

* SING incidence type means the number of new patients = number of new lookup periods since this option only considers the first incident lookup period for each new patient

Table 2c. Summary of Acute Myocardial Infarction (AMI)/Stroke in the Mini-Sentinel Distributed Database (MSDD) between January 1, 2007 and May 31, 2013, by Pre-Existing Condition Criteria and Age Group

	New Patients/ Lookup Periods*	Claims	Lookup Period Duration (Days)	Eligible Members	Member-Years	New Patients per 1,000 Eligible Members
Acute Myocardial Infarction						
With Pre-Existing Testosterone Conditions						
0-39 years	2,428	4,683	382,418	6,523,504	3,933,029	0.37
40-64 years	38,985	112,620	5,990,757	8,557,059	6,494,488	4.56
65-74 years	27,972	93,753	4,031,337	1,752,483	1,339,195	15.96
75+ years	52,193	165,254	6,734,994	1,500,441	1,321,855	34.79
No Pre-Existing Condition Criteria						
0-39 years	17,556	43,507	2,829,556	50,952,951	101,599,284	0.34
40-64 years	235,055	763,485	37,521,515	32,117,303	74,307,403	7.32
65-74 years	130,375	467,200	19,975,981	5,586,167	12,408,748	23.34
75+ years	191,489	640,086	26,379,466	3,213,767	8,945,337	59.58
Stroke						
With Pre-Existing Testosterone Conditions						
0-39 years	10,299	28,220	1,639,414	6,518,083	3,922,490	1.58
40-64 years	78,052	250,033	12,248,507	8,521,395	6,427,990	9.16
65-74 years	55,918	207,400	8,586,516	1,725,325	1,290,369	32.41
75+ years	112,327	406,880	16,356,551	1,460,741	1,221,745	76.90
No Pre-Existing Condition Criteria						
0-39 years	58,592	167,678	9,436,420	50,949,951	101,526,188	1.15
40-64 years	330,520	1,222,425	52,793,839	32,100,184	74,122,841	10.30
65-74 years	210,599	853,170	33,364,477	5,567,189	12,236,529	37.83
75+ years	349,740	1,365,439	52,467,312	3,182,492	8,557,657	109.90

* SING incidence type means the number of new patients = number of new lookup periods since this option only considers the first incident lookup period for each new patient.

Table 3c. Summary of Acute Myocardial Infarction (AMI)/Stroke in the Mini-Sentinel Distributed Database (MSDD) between January 1, 2007 and May 31, 2013, by Pre-Existing Condition Criteria and Sex

	New Patients/ Lookup Periods*	Claims	Lookup Period Duration (Days)	Eligible Members	Member-Years	New Patients per 1,000 Eligible Members
Acute Myocardial Infarction						
With Pre-Existing Testosterone Conditions						
Female	59,392	181,773	8,346,221	10,843,189	8,207,660	5.48
Male	62,147	194,426	8,787,028	6,775,734	4,877,314	9.17
Unknown	39	111	6,257	5,467	3,594	7.13
No Pre-Existing Condition Criteria						
Female	230,282	737,177	34,179,966	44,149,747	101,564,275	5.22
Male	344,016	1,176,422	52,497,950	42,641,360	95,661,528	8.07
Unknown	177	679	28,602	19,694	34,968	8.99
Stroke						
With Pre-Existing Testosterone Conditions						
Female	147,979	506,169	22,574,451	10,795,401	8,067,643	13.71
Male	108,551	386,164	16,245,969	6,730,272	4,791,396	16.13
Unknown	66	200	10,568	5,449	3,555	12.11
No Pre-Existing Condition Criteria						
Female	499,875	1,838,174	78,092,581	44,131,144	100,987,194	11.33
Male	449,348	1,769,707	69,932,235	42,625,942	95,421,173	10.54
Unknown	228	831	37,232	19,688	34,848	11.58

* SING incidence type means the number of new patients = number of new lookup periods since this option only considers the first incident lookup period for each new patient

Table 4c. Summary of Acute Myocardial Infarction (AMI)/Stroke in the Mini-Sentinel Distributed Database (MSDD) between January 1, 2007 and May 31, 2013, by Pre-Existing Condition Criteria and Year

	New Patients/ Lookup Periods*	Claims	Lookup Period Duration (Days)	Eligible Members	Member-Years	New Patients per 1,000 Eligible Members
Acute Myocardial Infarction						
With Pre-Existing Testosterone Conditions						
2007	8,925	23,877	1,314,722	2,556,362	937,804	3.49
2008	17,440	51,953	2,530,854	5,003,540	1,746,263	3.49
2009	20,275	63,097	2,950,763	5,967,701	2,382,394	3.40
2010	20,853	65,112	3,013,702	5,898,264	2,362,632	3.54
2011	22,037	70,276	3,205,242	5,875,593	2,395,118	3.75
2012	23,555	76,949	3,387,250	5,821,848	2,397,923	4.05
2013	8,493	25,046	736,973	3,524,117	866,434	2.41
No Pre-Existing Condition Criteria						
2007	53,561	156,057	8,489,273	23,525,825	17,239,986	2.28
2008	92,050	294,269	14,291,521	44,772,546	28,414,909	2.06
2009	101,825	336,297	15,801,019	46,592,871	36,460,714	2.19
2010	97,530	334,863	15,027,240	44,773,536	35,191,367	2.18
2011	96,465	332,899	14,930,689	43,580,530	34,602,008	2.21
2012	98,081	347,011	14,876,823	42,456,659	33,397,282	2.31
2013	34,963	112,882	3,289,953	32,909,807	11,954,506	1.06
Stroke						
With Pre-Existing Testosterone Conditions						
2007	19,714	63,539	3,119,029	2,532,423	924,749	7.78
2008	37,948	125,832	5,937,433	4,958,285	1,718,053	7.65
2009	45,037	156,815	7,011,517	5,911,515	2,345,032	7.62
2010	45,068	159,949	6,975,282	5,835,366	2,321,865	7.72
2011	45,714	164,854	7,142,283	5,808,227	2,351,450	7.87
2012	46,765	172,111	7,161,993	5,749,067	2,351,399	8.13
2013	16,350	49,433	1,483,451	3,468,794	850,046	4.71

Table 4c. Summary of Acute Myocardial Infarction (AMI)/Stroke in the Mini-Sentinel Distributed Database (MSDD) between January 1, 2007 and May 31, 2013, by Pre-Existing Condition Criteria and Year

	New Patients/ Lookup Periods*	Claims	Lookup Period Duration (Days)	Eligible Members	Member-Years	New Patients per 1,000 Eligible Members
No Pre-Existing Condition Criteria						
2007	93,917	309,847	15,385,653	23,495,962	17,204,271	4.00
2008	161,350	571,452	25,972,040	44,709,149	28,327,960	3.61
2009	176,924	667,481	28,254,995	46,488,556	36,331,926	3.81
2010	160,126	629,054	25,375,793	44,634,396	35,039,259	3.59
2011	152,880	617,353	24,336,340	43,422,816	34,434,042	3.52
2012	151,349	629,172	23,659,449	42,282,928	33,216,518	3.58
2013	52,905	184,353	5,077,778	32,741,276	11,889,238	1.62

* SING incidence type means the number of new patients = number of new lookup periods since this option only considers the first incident lookup period for each new patient

Table 5. Summary of Testosterone Product Use after Acute Myocardial Infarction or Stroke (Post-Event Treatment) in the Mini-Sentinel Distributed Database (MSDD) between January 1, 2007 and May 31, 2013, by Testosterone Indication

Event	Patients with Post-Event Treatment	Percent of Patients with Post-Event Treatment	Post-Event Days Treated	Post-Event Treatment Intensity
All Testosterone Indications	239,938	1.7%	13,328,417	0.01
Malignant Neoplasm of Pituitary Gland	107	2.8%	6,225	0.01
Benign Neoplasm of Pituitary Gland	1,476	2.6%	90,052	0.01
Other Pituitary Disorders	5,290	16.5%	317,268	0.06
Klinefelter's Syndrome	431	18.8%	24,446	0.06
Other Testicular Hypofunction	153,817	31.6%	8,739,061	0.11
Depressive Disorder	14,494	0.3%	689,416	0.00
Muscular Atrophy	536	0.3%	23,455	0.00
Malaise/Fatigue	106,079	1.0%	5,726,685	0.00
Decreased Libido	25,489	10.1%	1,344,027	0.03
Hypoactive Sexual Desire Disorder	2,273	8.8%	114,521	0.03
Unspecified Testicular Dysfunction	1,401	13.5%	74,634	0.04
Other Testicular Dysfunction	4,447	16.5%	243,969	0.06

Appendix A. Dates of Available Data for Each Data Partner in the Mini-Sentinel Distributed Database (MSDD) as of Request Distribution Date (March 28, 2014)

DP ID	Start Date	End Date
DP001	1/1/2008	5/31/2013
DP002	1/1/2007	5/31/2013
DP003	1/1/2007	6/30/2012
DP004	1/1/2007	5/31/2013
DP005	1/1/2007	4/30/2012
DP006	6/1/2007	4/30/2013
DP007	1/1/2007	3/31/2013
DP008	1/1/2008	5/31/2013
DP009	1/1/2007	12/31/2012
DP010	1/1/2007	5/31/2013
DP011	1/1/2007	12/31/2012
DP012	1/1/2007	5/31/2013
DP013	1/1/2007	6/30/2012
DP014	1/1/2007	5/31/2013
DP015	1/1/2007	5/31/2013
DP016	1/1/2007	12/31/2011
DP017	1/1/2007	5/30/2013
DP018	1/1/2007	5/31/2013

Appendix E. List of International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) Diagnosis Codes used to Define Events of Interest in this Request

Code	Description	Code Type
AMI		
410.*0	Acute myocardial infarction, episode of care unspecified	ICD-9-CM
410.*1	Acute myocardial infarction, initial episode of care	ICD-9-CM
Stroke		
430*	Subarachnoid hemorrhage	ICD-9-CM
431*	Intracerebral hemorrhage	ICD-9-CM
433.*1	Occlusion and stenosis of cerebral arteries with cerebral infarction	ICD-9-CM
434.*1	Occlusion of cerebral arteries with cerebral infarction	ICD-9-CM
436*	Acute but ill-defined cerebrovascular disease	ICD-9-CM

signifies "starts with." For example, 194.3 will consider 194.3, 194.30, 194.31, 194.32, and so on.

Appendix C. List of International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) Diagnosis Codes used to Define Pre-existing Conditions in this Request

Diagnosis Code	Description	Code Type
194.3*	Malignant neoplasm of pituitary gland and craniopharyngeal duct	ICD-9-CM
227.3*	Benign neoplasm of pituitary gland and craniopharyngeal duct	ICD-9-CM
253.4*	Other anterior pituitary disorders	ICD-9-CM
758.7*	Klinefelter's syndrome	ICD-9-CM
257.2*	Other testicular hypofunction	ICD-9-CM
311*	Depressive disorder, not elsewhere classified	ICD-9-CM
728.2*	Muscular wasting and disuse atrophy, not elsewhere classified	ICD-9-CM
780.79	Other malaise and fatigue	ICD-9-CM
799.81	Decreased libido	ICD-9-CM
302.71	Hypoactive sexual desire disorder	ICD-9-CM
257.8*	Other testicular dysfunction	ICD-9-CM
257.9*	Unspecified testicular dysfunction	ICD-9-CM

signifies "starts with." For example, 194.3 will consider 194.3, 194.30, 194.31, 194.32, and so on.

Appendix D. Specifications for Parameters for this Request

Modular Program #6 (MP6) was used to investigate the number of individuals with incident and prevalent diagnosis for a testosterone-related indication and the number of those individuals who received a testosterone product in the following 6 months (scenarios 1-13). It also investigated acute myocardial infarction (AMI) and stroke among members overall and those with a pre-existing condition of one of the specified testosterone indications (scenarios 14-17). In total, 17 different scenarios are examined in this report with differing exposures of interest and pre-existing condition criteria. See below for a description of each of these scenarios.

Coverage Requirement	Drug and Medical Coverage
Query Period	January 1, 2007 to May 31, 2013
Enrollment Gap	45 Days
Enrollment Days	183
Age Stratifications	0-39, 40-64, 65-74, 75+ years
Minimum Lookup	0 Days

	Exposure Criteria (Event file in MP6)						Exclusion/Inclusion Criteria						Outcome (Post-event treatment file in MP6)					
Scenario	Incident exposure	Incident with respect to:	Incidence Type	Washout Period (days)	Lookup Period Duration (Days)	Care Setting	Condition	Exclude/ Include	Lookback Period Start	Lookback Period End	Care Setting	Principal Diagnosis	Event/ Outcome	Incident with respect to:	Incidence Type	Washout Period (days)	Care Setting	Principal Diagnosis
1	AMI	AMI	SING	183	183	IP	All testosterone indications	Include	-183	-1	Any	Any	None	n/a	n/a	n/a	n/a	n/a
2	AMI	AMI	SING	183	183	IP	None	n/a	n/a	n/a	n/a	n/a	None	n/a	n/a	n/a	n/a	n/a
3	Stroke	Stroke	SING	183	183	IP	All testosterone indications	Include	-183	-1	Any	Any	None	n/a	n/a	n/a	n/a	n/a
4	Stroke	Stroke	SING	183	183	IP	None	n/a	n/a	n/a	n/a	n/a	None	n/a	n/a	n/a	n/a	n/a

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