

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

Request ID: msy4_mpr50_v2

Request Description: In this request we investigated switching between generic clonazepam and brand clonazepam (Klonopin).

Mini-Sentinel Modular Program Tool Used: Modular Program #3 (MP3), version 5.0

Data Source: We used data from January 1, 2004 - December 31, 2012 from 18 Data Partners contributing to the Mini-Sentinel Distributed Database (MSDD) in this report. We distributed this request to 18 Data Partners on August 2, 2013. Please see Appendix A for dates of available data for each Data Partner.

Study Design: We designed this request to investigate switching between generic clonazepam and brand clonazepam (Klonopin). This involved one run of MP3 with two different scenarios. The first scenario examined users of generic clonazepam with prior use of brand Klonopin in the past 183 days. In this scenario we captured outcomes of switch back to brand Klonopin within the generic treatment episode. The second scenario examined users of Klonopin with prior use of generic clonazepam in the past 183 days. In this scenario, we captured outcomes of switch back to generic use within the Klonopin treatment episode. We allowed a 10-day episode gap and applied a 30-day episode extension in identifying treatment episodes. We only captured the first valid treatment episode per patient for each scenario.

Cohort Eligibility Criteria: We required patients to be continuously enrolled in plans for at least six months (183 days) prior to their dispensing date, during which gaps in coverage of up to 45 days were allowed. We categorized results according to the following age groups: 0-21, 22-44, 45-64, and 65+ years.

Please see Appendix B for the 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.

Notes: Please contact the Sentinel Operations Center (info@sentinelssystem.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 Ambulatory Visit (OA).

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

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

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 episodes.

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 event per user if a user has more than one incident episode.

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 period.

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

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 - diagnosis or condition established to be chiefly responsible for admission of the patient to the hospital.

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. Summary of Clonazepam Use in the Mini-Sentinel Distributed Database (MSDD) between January 1, 2004 and December 31, 2012, by Scenario

	New Users	New Episodes	Dispensings	Total Days Supplied	Treatment Years	Eligible Members	Member-Years	New Users per 1,000 Eligible Members	Days Supplied per User	Dispensings per User	Days Supplied per Dispensing	Count of Switch-Backs	Switch-Backs per 1,000 Treatment-Years
Generic Users with Prior Brand Use													
	7,192	7,192	23,821	779,853	2,332	21,863	19,627	328.96	108.43	3.31	32.74	2,108	903.94
Brand Users with Prior Generic Use													
	7,564	7,564	17,915	582,288	1,684	1,686,560	1,857,568	4.48	76.98	2.37	32.50	3,457	2,052.37

Table 2. Summary of Clonazepam Use in the Mini-Sentinel Distributed Database (MSDD) between January 1, 2004 and December 31, 2012, by Scenario and Age Group

	New Users	New Episodes	Dispensings	Total Days Supplied	Treatment Years	Eligible Members	Member-Years	New Users per 1,000 Eligible Members	Days Supplied per User	Dispensings per User	Days Supplied per Dispensing	Count of Switch-Backs	Switch-Backs per 1,000 Treatment-Years
Generic Users with Prior Brand Use													
0 to 21 Years	464	464	1,339	43,306	129	1,673	970	277.35	93.33	2.89	32.34	108	835.97
22 to 44 Years	2,365	2,365	7,065	213,124	668	7,872	4,996	300.43	90.12	2.99	30.17	629	941.22
45 to 64 Years	3,700	3,700	13,117	440,393	1,293	11,108	11,443	333.09	119.03	3.55	33.57	1,162	898.41
65+ Years	663	663	2,300	83,030	241	2,141	2,217	309.67	125.23	3.47	36.10	209	866.68
Brand Users with Prior Generic Use													
0 to 21 Years	562	562	1,376	42,896	120	107,968	78,827	5.21	76.33	2.45	31.17	283	2,349.22
22 to 44 Years	3,008	3,008	6,529	191,660	566	739,244	636,909	4.07	63.72	2.17	29.36	1,442	2,546.82
45 to 64 Years	3,469	3,469	8,705	296,632	844	728,294	886,500	4.76	85.51	2.51	34.08	1,515	1,795.50
65+ Years	525	525	1,305	51,100	154	197,661	255,333	2.66	97.33	2.49	39.16	217	1,409.48

Table 3. Summary of Clonazepam Use in the Mini-Sentinel Distributed Database (MSDD) between January 1, 2004 and December 31, 2012, by Scenario and Sex

	New Users	New Episodes	Dispensings	Total Days Supplied	Treatment Years	Eligible Members	Member-Years	New Users per 1,000 Eligible Members	Days Supplied per User	Dispensings per User	Days Supplied per Dispensing	Count of Switch-Backs	Switch-Backs per 1,000 Treatment-Years
Generic Users with Prior Brand Use													
Female	4,736	4,736	15,549	507,078	1,515	14,755	13,518	320.98	107.07	3.28	32.61	1,410	930.77
Male	2,456	2,456	8,272	272,775	817	7,108	6,109	345.53	111.06	3.37	32.98	698	854.19
Unknown	0	0	0	0	0	0	0	---	---	---	---	0	---
Brand Users with Prior Generic Use													
Female	4,862	4,862	11,291	367,616	1,063	1,088,516	1,202,134	4.47	75.61	2.32	32.56	2,178	2,049.66
Male	2,702	2,702	6,624	214,672	622	597,997	655,391	4.52	79.45	2.45	32.41	1,279	2,057.01
Unknown	0	0	0	0	0	47	44	0.00	---	---	---	0	---

Table 4. Summary of Clonazepam Use in the Mini-Sentinel Distributed Database (MSDD) between January 1, 2004 and December 31, 2012, by Scenario and Year

	New Users	New Episodes	Dispensings	Total Days Supplied	Treatment Years	Eligible Members	Member-Years	New Users per 1,000 Eligible Members	Days Supplied per User	Dispensings per User	Days Supplied per Dispensing	Count of Switch-Backs	Switch-Backs per 1,000 Treatment-Years
Generic Users with Prior Brand Use													
2004	539	539	2,465	70,943	197	2,900	1,199	185.86	131.62	4.57	28.78	205	1,040.45
2005	644	644	2,087	59,844	174	2,596	1,137	248.07	92.93	3.24	28.67	165	950.96
2006	495	495	1,897	69,707	211	4,015	1,429	123.29	140.82	3.83	36.75	109	516.45
2007	660	660	2,578	85,006	252	4,252	2,226	155.22	128.80	3.91	32.97	204	810.38
2008	1,139	1,139	3,775	127,606	384	7,534	3,293	151.18	112.03	3.31	33.80	313	814.80
2009	1,230	1,230	3,693	125,996	381	7,108	3,790	173.04	102.44	3.00	34.12	363	953.12
2010	915	915	2,681	89,389	275	5,566	3,035	164.39	97.69	2.93	33.34	278	1,010.13
2011	1,183	1,183	3,965	128,419	383	4,244	2,153	278.75	108.55	3.35	32.39	370	965.64
2012	387	387	680	22,943	75	2,709	1,365	142.86	59.28	1.76	33.74	101	1,340.88
Brand Users with Prior Generic Use													
2004	993	993	3,128	86,868	203	108,050	64,168	9.19	87.48	3.15	27.77	624	3,079.07
2005	535	535	1,047	29,336	65	114,744	68,863	4.66	54.83	1.96	28.02	370	5,701.01
2006	471	471	1,089	39,979	111	196,036	89,048	2.40	84.88	2.31	36.71	206	1,862.14
2007	773	773	1,764	57,931	174	261,529	133,502	2.96	74.94	2.28	32.84	314	1,808.80
2008	1,035	1,035	2,156	73,454	231	509,676	241,484	2.03	70.97	2.08	34.07	412	1,783.33
2009	1,480	1,480	4,041	136,670	406	588,337	324,987	2.52	92.34	2.73	33.82	640	1,577.08
2010	966	966	2,108	73,283	229	582,314	325,420	1.66	75.86	2.18	34.76	377	1,643.82
2011	758	758	1,642	53,098	165	586,499	330,038	1.29	70.05	2.17	32.34	309	1,868.55
2012	553	553	940	31,669	101	538,507	280,059	1.03	57.27	1.70	33.69	205	2,028.51

Appendix A. Dates of Available Data for Each Data Partner (DP) as of Request Distribution Date (August 2, 2013)

DP ID	Start Date*	End Date*
DP001	1/1/2004	12/31/2012
DP002	1/1/2004	6/30/2012
DP003	1/31/2004	12/31/2012
DP004	1/1/2004	12/31/2012
DP005	1/1/2004	12/31/2012
DP006	1/1/2004	12/31/2012
DP007	1/1/2004	12/31/2011
DP008	1/1/2004	6/30/2012
DP009	1/1/2004	9/30/2012
DP010	1/1/2004	12/31/2012
DP011	6/2/2007	10/31/2012
DP012	1/2/2008	11/30/2012
DP013	1/1/2004	4/30/2012
DP014	1/2/2008	9/30/2012
DP015	1/2/2005	9/30/2012
DP016	1/1/2004	12/31/2012
DP017	1/1/2004	12/31/2011
DP018	1/2/2006	12/30/2012

*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. Specifications Defining Parameters for this Request

Modular Program #3 (version 5.0) was used to investigate switching between generic clonazepam and brand klonopin in the Mini-Sentinel Distributed Database (MSDD). The first scenario outlined below examines generic users with a pre-existing condition of brand use in the prior 183 days who switch back to brand use within their generic treatment episode. The second scenario examines brand users with a pre-existing condition of generic use in the prior 183 days who switch back to generic use within their brand treatment episode.

Enrollment Gap: 45 days
Query Period: January 1, 2004 to December 31, 2012
Age Groupings: 0-<22, 22-<45, 45-<65, 65+ years

Scenario	Drug/Exposure							Pre-Existing Condition				Event/Outcome				
	Incident exposure	Incident with respect to:	Episode Gap	Exposure extension period	Minimum episode duration	Minimum days supplied	Washout (days)	Incidence Type*	Pre-Existing Condition	Lookback Start	Lookback End	Event/Outcome	Incident with respect to:	Washout (days)	Washout Type**	Blackout Period
1	Generic Clonazepam	Generic Clonazepam	10	30	0	0	183	Single (SING)	Brand Klonopin	-183	-1	Brand Klonopin	Brand Klonopin	0	Multiple (MULT)	0
2	Brand Klonopin	Brand Klonopin	10	30	0	0	183	SING	Generic Clonazepam	-183	-1	Generic Clonazepam	Generic Clonazepam	0	MULT	0

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

*Single incidence 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 days). There can be at most one episode per user.

**Multiple washout type for the event will only consider the first event for each episode that satisfies the Washout Period criteria of 183 days. There can be at most one event per episode and consequently, one event per user.