

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_mpr27_v1

Request Description: This report investigates exposure to generic and brand name clonazepam, and examines counts of newly exposed members, dispensings, days supplied, events, days at risk, and denominator data.

Sentinel Modular Program Tool Used: Modular Program #3 (MP3)

Data Source: Data from January 1, 2004 - December 31, 2012 from 18 Data Partners contributing to the Mini-Sentinel Distributed Database (MSDD) were included in this report. This request was distributed to Data Partners on April 12, 2013. See Appendix A for a list of the dates of available data for each Data Partner.

Study Design: This request was designed to provide counts of new clonazepam users, dispensings, total days supplied, eligible members, and member-days for patients. Two exposures were examined: (1) all generic and brand National Drug Codes (NDCs) for clonazepam, and (2) clonazepam NDCs with brand name Klonopin. Two scenarios were examined for each exposure: (1) a user was considered new if he/she was not exposed to the exposure itself in the prior 183 days, and (2) a user was considered new if he/she was not exposed to any clonazepam in the prior 183 days.

Cohort Eligibility Criteria: Patients were required 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. Members were excluded if they had any oral bisphosphonate use in the six months (183 days) prior to exposure initiation. The following age groups were included in the cohort: 0-21, 22-44, 45-65, and 65+ years. See Appendix C for the specifications for this request.

Limitations: Algorithms to define exposures are imperfect and, therefore, they may be misclassified.

Notes: Please contact the Sentinel Operations Center Query Fulfillment Team (qf@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.

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 consecutive dispensings bridged by the episode gap).

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. 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.

Washout Type (drug/exposure)- *Minimum washout 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 washout 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.

Washout Type (event/outcome)- *Minimum washout 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 washout 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 washout type* will consider more than one event per user if a user has more than one incident 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 Incident Clonazepam Use in the Mini-Sentinel Distributed Database (MSDD) between January 1, 2004 and December 31, 2012, by Exposure and Incidence Criteria

	New Users	New Episodes	Dispensings	Total Days Supplied	Days at Risk	Eligible Members	Member-Days	New Users/ 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing
Generic Name Clonazepam											
Incident with respect to generic only	1,080,906	1,080,906	2,480,642	72,238,695	72,162,451	92,787,598	78,445,957,632	11.65	66.83	2.29	29.12
Incident with respect to all clonazepam	1,073,281	1,073,281	2,452,569	71,342,655	71,252,297	92,779,844	78,439,008,746	11.57	66.47	2.29	29.09
Brand Name Klonopin											
Incident with respect to Klonopin only	22,468	22,468	44,549	1,328,677	1,330,451	93,154,270	79,513,058,099	0.24	59.14	1.98	29.83
Incident with respect to all clonazepam	13,566	13,566	23,416	647,204	639,667	92,779,844	78,809,307,883	0.15	47.71	1.73	27.64

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

	New Users	New Episodes	Dispensings	Total Days Supplied	Days at Risk	Eligible Members	Member-Days	New Users/ 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing
Generic Name Clonazepam											
<i>Incident with respect to generic only</i>											
0 to 21	80,612	80,612	175,280	4,684,653	4,692,889	27,996,639	22,469,477,354	2.88	58.11	2.17	26.73
22 to 44	469,448	469,448	1,017,296	27,389,007	27,384,660	36,682,013	24,698,352,920	12.80	58.34	2.17	26.92
45 to 64	419,951	419,951	1,019,473	30,870,844	30,841,863	26,889,788	23,160,292,834	15.62	73.51	2.43	30.28
65+	110,895	110,895	268,593	9,294,191	9,243,039	8,369,284	8,117,834,524	13.25	83.81	2.42	34.60
<i>Incident with respect to all clonazepam</i>											
0 to 21	80,091	80,091	173,510	4,628,869	4,635,229	27,996,343	22,469,180,879	2.86	57.80	2.17	26.68
22 to 44	466,805	466,805	1,007,700	27,109,530	27,098,143	36,679,757	24,696,747,491	12.73	58.07	2.16	26.90
45 to 64	416,189	416,189	1,005,050	30,390,404	30,356,917	26,885,031	23,156,083,154	15.48	73.02	2.41	30.24
65+	110,196	110,196	266,309	9,213,852	9,162,008	8,368,443	8,116,997,222	13.17	83.61	2.42	34.60
Brand Name Klonopin											
<i>Incident with respect to Klonopin only</i>											
0 to 21	2,042	2,042	4,071	113,826	114,498	28,008,372	22,518,858,633	0.07	55.74	1.99	27.96
22 to 44	8,978	8,978	16,839	460,077	460,937	36,854,913	25,079,626,030	0.24	51.24	1.88	27.32
45 to 64	9,720	9,720	20,322	641,811	642,154	27,133,840	23,654,140,242	0.36	66.03	2.09	31.58
65+	1,728	1,728	3,317	112,963	112,862	8,436,683	8,260,433,194	0.20	65.37	1.92	34.06
<i>Incident with respect to all clonazepam</i>											
0 to 21	1,389	1,389	2,417	63,740	63,180	27,996,343	22,489,257,280	0.05	45.89	1.74	26.37
22 to 44	5,393	5,393	8,977	228,768	225,925	36,698,617	24,836,084,106	0.15	42.42	1.66	25.48
45 to 64	5,701	5,701	10,131	296,283	293,203	26,924,059	23,316,867,966	0.21	51.97	1.78	29.25
65+	1,083	1,083	1,891	58,413	57,359	8,384,774	8,167,098,531	0.13	53.94	1.75	30.89

Table 3: Summary of Incident Clonazepam Use in the Mini-Sentinel Distributed Database (MSDD) between January 1, 2004 and December 31, 2012, by Exposure, Incidence Criteria, and Sex

	New Users	New Episodes	Dispensings	Total Days Supplied	Days at Risk	Eligible Members	Member-Days	New Users/ 1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing
Generic Name Clonazepam											
<i>Incident with respect to generic only</i>											
Female	699,008	699,008	1,535,078	44,514,544	44,473,798	47,260,783	40,240,486,946	14.79	63.68	2.20	29.00
Male	380,863	380,863	943,043	27,653,459	27,618,457	45,417,541	38,093,445,281	8.39	72.61	2.48	29.32
Unknown	1,035	1,035	2,521	70,692	70,196	109,274	112,025,405	9.47	68.30	2.44	28.04
<i>Incident with respect to all clonazepam</i>											
Female	694,005	694,005	1,516,819	43,930,834	43,882,108	47,255,541	40,235,689,382	14.69	63.30	2.19	28.96
Male	378,247	378,247	933,241	27,341,559	27,300,406	45,415,030	38,091,294,143	8.33	72.28	2.47	29.30
Unknown	1,029	1,029	2,509	70,262	69,783	109,273	112,025,221	9.42	68.28	2.44	28.00
Brand Name Klonopin											
<i>Incident with respect to Klonopin only</i>											
Female	14,924	14,924	29,073	865,181	866,528	47,495,665	40,936,307,676	0.31	57.97	1.95	29.76
Male	7,524	7,524	15,446	462,699	463,149	45,549,194	38,463,817,412	0.17	61.50	2.05	29.96
Unknown	20	20	30	797	774	109,411	112,933,011	0.18	39.85	1.50	26.57
<i>Incident with respect to all clonazepam</i>											
Female	9,137	9,137	15,490	427,633	422,968	47,255,541	40,480,875,608	0.19	46.80	1.70	27.61
Male	4,415	4,415	7,904	219,029	216,172	45,415,030	38,216,028,556	0.10	49.61	1.79	27.71
Unknown	14	14	22	542	527	109,273	112,403,719	0.13	38.71	1.57	24.64

Table 4: Summary of Incident Clonazepam Use in the Mini-Sentinel Distributed Database (MSDD) between January 1, 2004 and December 31, 2012, by Exposure, Incidence Criteria, and Year

	New Users	New Episodes	Dispensings	Total Days Supplied	Days at Risk	Eligible Members	Member-Days	New Users/1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing
Generic Name Clonazepam											
<i>Incident with respect to generic only</i>											
2004	66,694	66,694	202,699	6,005,654	6,046,833	19,451,267	4,311,746,009	3.43	90.05	3.04	29.63
2005	86,681	86,681	220,762	6,578,446	6,608,547	21,371,703	6,153,021,037	4.06	75.89	2.55	29.80
2006	80,019	80,019	197,516	5,971,028	6,004,349	22,758,183	6,422,418,308	3.52	74.62	2.47	30.23
2007	92,518	92,518	236,742	7,144,749	7,176,528	25,461,537	6,846,612,782	3.63	77.23	2.56	30.18
2008	154,009	154,009	365,210	10,695,963	10,736,607	46,561,404	10,577,427,392	3.31	69.45	2.37	29.29
2009	200,118	200,118	455,044	13,130,947	13,155,120	47,494,293	13,598,845,290	4.21	65.62	2.27	28.86
2010	181,067	181,067	400,148	11,494,494	11,508,911	45,627,864	13,116,492,233	3.97	63.48	2.21	28.73
2011	150,663	150,663	295,777	8,311,732	8,266,628	44,012,793	12,611,638,689	3.42	55.17	1.96	28.10
2012	69,137	69,137	106,744	2,905,682	2,658,928	25,506,359	4,807,755,892	2.71	42.03	1.54	27.22
<i>Incident with respect to all clonazepam</i>											
2004	65,495	65,495	196,567	5,828,137	5,865,391	19,447,109	4,310,610,826	3.37	88.99	3.00	29.65
2005	84,814	84,814	214,332	6,383,243	6,410,661	21,368,219	6,151,396,885	3.97	75.26	2.53	29.78
2006	79,195	79,195	194,265	5,863,007	5,894,334	22,756,504	6,421,664,210	3.48	74.03	2.45	30.18
2007	92,123	92,123	234,979	7,084,244	7,114,393	25,460,431	6,846,139,955	3.62	76.90	2.55	30.15
2008	153,124	153,124	362,122	10,591,401	10,630,361	46,558,019	10,576,602,497	3.29	69.17	2.36	29.25
2009	199,129	199,129	452,072	13,029,353	13,051,615	47,491,696	13,597,828,712	4.19	65.43	2.27	28.82
2010	180,436	180,436	398,184	11,426,469	11,439,728	45,626,240	13,115,836,981	3.95	63.33	2.21	28.70
2011	149,928	149,928	293,463	8,237,144	8,192,437	44,011,999	12,611,316,435	3.41	54.94	1.96	28.07
2012	69,037	69,037	106,585	2,899,657	2,653,377	25,505,833	4,807,612,245	2.71	42.00	1.54	27.21
Brand Name Klonopin											
<i>Incident with respect to Klonopin only</i>											
2004	4,599	4,599	10,390	282,842	286,323	19,549,622	4,348,071,799	0.24	61.50	2.26	27.22
2005	4,863	4,863	8,808	248,202	250,226	21,513,374	6,211,793,522	0.23	51.04	1.81	28.18
2006	2,076	2,076	3,810	116,177	116,799	22,937,139	6,491,058,617	0.09	55.96	1.84	30.49
2007	1,754	1,754	3,520	108,343	108,615	25,709,182	6,932,918,747	0.07	61.77	2.01	30.78
2008	2,433	2,433	4,694	145,499	145,071	46,975,353	10,710,914,336	0.05	59.80	1.93	31.00
2009	3,002	3,002	6,586	212,936	212,425	47,973,207	13,781,307,881	0.06	70.93	2.19	32.33
2010	2,013	2,013	3,877	126,171	124,990	46,183,799	13,318,665,192	0.04	62.68	1.93	32.54
2011	1,252	1,252	2,170	66,656	66,187	44,622,191	12,825,255,334	0.03	53.24	1.73	30.72
2012	476	476	694	21,851	19,815	25,902,229	4,893,072,671	0.02	45.91	1.46	31.49

Table 4: Summary of Incident Clonazepam Use in the Mini-Sentinel Distributed Database (MSDD) between January 1, 2004 and December 31, 2012, by Exposure, Incidence Criteria, and Year

	New Users	New Episodes	Dispensings	Total Days Supplied	Days at Risk	Eligible Members	Member-Days	New Users/1K Eligible Members	Days Supplied/ User	Dispensings/ User	Days Supplied/ Dispensing
<i>Incident with respect to all clonazepam</i>											
2004	2,905	2,905	5,567	144,720	144,226	19,447,109	4,311,139,096	0.15	49.82	1.92	26.00
2005	3,264	3,264	5,333	141,861	140,441	21,404,289	6,159,822,060	0.15	43.46	1.63	26.60
2006	1,286	1,286	2,083	56,346	55,748	22,833,834	6,441,312,014	0.06	43.81	1.62	27.05
2007	1,030	1,030	1,833	53,611	53,200	25,574,536	6,877,259,624	0.04	52.05	1.78	29.25
2008	1,448	1,448	2,631	75,370	74,629	46,708,995	10,617,935,210	0.03	52.05	1.82	28.65
2009	1,582	1,582	2,735	81,224	80,142	47,708,240	13,656,313,669	0.03	51.34	1.73	29.70
2010	1,129	1,129	1,934	56,716	55,680	45,917,417	13,196,325,276	0.02	50.24	1.71	29.33
2011	683	683	983	28,474	27,612	44,359,403	12,706,236,037	0.02	41.69	1.44	28.97
2012	239	239	317	8,882	7,989	25,712,333	4,842,964,897	0.01	37.16	1.33	28.02

Appendix A: List of Dates of Available Data for Each Data Partner as of Request Send Date (August 9, 2013)

DP ID	Start Date	End Date
DP0001	1/1/2004	12/31/2012
DP0002	1/1/2004	6/30/2012
DP0003	1/31/2004	12/31/2012
DP0004	1/1/2004	12/31/2012
DP0005	1/1/2004	12/31/2012
DP0006	1/1/2004	12/31/2012
DP0007	1/1/2004	12/31/2011
DP0008	1/1/2004	6/30/2012
DP0009	1/1/2004	9/30/2012
DP0010	1/1/2004	12/31/2012
DP0011	6/2/2007	10/31/2012
DP0012	1/2/2008	11/30/2012
DP0013	1/1/2004	4/30/2012
DP0014	1/2/2008	9/30/2012
DP0015	1/2/2005	9/30/2012
DP0016	1/1/2004	12/31/2012
DP0017	1/1/2004	12/31/2011
DP0018	1/2/2006	12/30/2012

Appendix B: List of Generic and Brand Names Included in this Request

Code Type	Generic Name	Brand Name
National Drug Code		Klonopin
National Drug Code	Clonazepam	Clonazepam
National Drug Code	Clonazepam	Ceberclon
National Drug Code	Clonazepam	Klonopin

Appendix C: Modular Program Specifications for Query ID MSY4MPR27 - Clonazepam

Modular Program #3 (MP3) will be used to investigate use of clonazepam in the Mini-Sentinel Distributed Database. The query period will be from January 1, 2004 to December 31, 2012. The enrollment gap will be set to 45 days, and minimum episode duration and minimum days supplied will both be set to 0 days. MP3 is normally used to examine an event or outcome among individuals with a particular exposure. However, in this case, a dummy event is used because we only wish to examine clonazepam treatment episodes. Age groups will be split as follows: 0-21, 22-44, 45-64, 65+ years. In total, four different scenarios will be examined in this request with differing exposures and incidence criteria. See below for a description of each of these scenarios.

Scenario	Drug/Exposure						Event/Outcome									
	Incident exposure	Incident w/ respect to:	Episode Gap (days)	Washout (days)	Washout Type	Exposure Extension Period	Event/ Outcome	Care Setting	Principal Dx	Event incident w/ respect to:	Incident Only Care Setting	Washout (days)	Washout Type	Incident Only		
														Principal Dx	Blackout Period	
1	Brand Klonopin	All Clonazepam	10	183	Sing	0	Dummy	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
2	Generic Clonazepam	All Clonazepam	10	183	Sing	0	Dummy	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3	Brand Klonopin	Brand Klonopin	10	183	Sing	0	Dummy	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
4	Generic Clonazepam	Generic Clonazepam	10	183	Sing	0	Dummy	N/A	N/A	N/A	N/A	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 Edition (CPT-4) codes checked against "Optum 2012 Current Procedure Codes & Relative Values Data File" provided by OptumInsight