Modular Program Report

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 Description

FDA requested execution of Modular Program #3 (MP3), version 1, to investigate the incidence use of quinine sulfate or diltiazem and outcomes of hemolytic-uremic syndrome (ICD-9 283.11), immune thrombocytopenic purpura (ICD-9 287.31), unspecified thrombocytopenia (ICD-9 287.49), other secondary thrombocytopenia (ICD-9 287.5), and thrombotic microangiopathy (ICD-9 446.6). The query was run against the Mini-Sentinel Distributed Database (MSDD) for the time period of January 1, 2006 through December 31, 2010. This results required a total of 5 runs of MP3. The package was distributed to 17 Data Partners in multiple versions between March 23, 2012 and April 24, 2012. Though these versions were distributed at different times, the MSDD was consistent throughout the entire requesting time period. A separate request (MSY3_MPR07), which investigates prevalent and incident use of Quinine Sulfate as well as incident Quinine Sulfate use among enrollees with a pre-existing Malaria diagnosis, was sent out and reported in conjunction with this request.

Results presented in this report provide counts of incident quinine sulfate and diltiazem users, dispensings, total days supplied, and events. To be considered incident, users must not have had a dispensing of quinine sulfate, diltiazem, ticlodipine, clopidogrel, or oral forms of several sulfa drugs in the prior 183 days. An event was considered incident if a user had not any event evaluated in this request (hemolytic-uremic syndrome, immune thrombocytopenic purpura, unspecified thrombocytopenia, other secondary thrombocytopenia, or thrombotic event) in the prior 183 days. Events were only considered in the inpatient and emergency department care settings. Results are given for each event category and a user may be counted in only one event category. The program was run for the entire time period (2006 - 2010) and results are given as such. Please see the Specifications for details into the exact parameters used in this report.

Request ID MSY3_MPR10

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

Modular Program Specifications

Modular Program #3, version 1, was used to investigate the incidence use of Quinine Sulfate or Diltiazem and outcomes of hemolytic-uremic syndrome (ICD-9 283.11), immune thrombocytopenic purpura (ICD-9 287.31), unspecified thrombocytopenia (ICD-9 287.49), other secondary thrombocytopenia (ICD-9 287.5), and thrombotic microangiopathy (ICD-9 446.6). The query period was from January 1, 2006 through December 31, 2010. The drug washout period was set to 0 days and event washout period was set to 183 days; the episode extension gap was set to 14 days, and both the minimum episode duration and minimum days supplied were set to 1 day. Age groups were split as follows: 00-19, 20-39, 40-64, 65+ years. In total, 10 different scenarios were examined in this report. See below for a description of each of these scenarios.

	Drug/Exposure Criteria			Event Criteria				
Scenario	Incident exposure	Incident w/ respect to:	Washout Period (days)	Event	Care Setting	Incident w/ respect to:	Washout Period (days)	Principal Dx
1	Quinine Sulfate	Quinine Sulfate, Diltiazem, Ticlodipine, Clopidogrel, and Sulfa drugs	183	Hemolytic-uremic syndrome	IP, ED	All events*	183	No
2	Quinine Sulfate	Quinine Sulfate, Diltiazem, Ticlodipine, Clopidogrel, and Sulfa drugs	183	Immune thrombocytopenic purpura	IP, ED	All events	183	No
3	Quinine Sulfate	Quinine Sulfate, Diltiazem, Ticlodipine, Clopidogrel, and Sulfa drugs	183	Other secondary thrombocytopenia	IP, ED	All events	183	No
4	Quinine Sulfate	Quinine Sulfate, Diltiazem, Ticlodipine, Clopidogrel, and Sulfa drugs	183	Thrombocytopenia unspecified	IP, ED	All events	183	No
5	Quinine Sulfate	Quinine Sulfate, Diltiazem, Ticlodipine, Clopidogrel, and Sulfa drugs	183	Thrombotic microangiopathy	IP, ED	All events	183	No
6	Diltiazem	Quinine Sulfate, Diltiazem, Ticlodipine, Clopidogrel, and Sulfa drugs	183	Hemolytic-uremic syndrome	IP, ED	All events	183	No
7	Diltiazem	Quinine Sulfate, Diltiazem, Ticlodipine, Clopidogrel, and Sulfa drugs	183	Immune thrombocytopenic purpura	IP, ED	All events	183	No
8	Diltiazem	Quinine Sulfate, Diltiazem, Ticlodipine, Clopidogrel, and Sulfa drugs	183	Other secondary thrombocytopenia	IP, ED	All events	183	No
9	Diltiazem	Quinine Sulfate, Diltiazem, Ticlodipine, Clopidogrel, and Sulfa drugs	183	Thrombocytopenia unspecified	IP, ED	All events	183	No
10	Diltiazem	Quinine Sulfate, Diltiazem, Ticlodipine, Clopidogrel, and Sulfa drugs	183	Thrombotic microangiopathy	IP, ED	All events	183	No

*Events were incident with respect to all events evaluated in this request: hemolytic-uremic syndrome, immune thrombocytopenic purpura, other secondary thrombocytopenia, unspecified thrombocytopenia, and thrombotic microangiopathy

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 members are at risk for an event during a treatment episode (calculated using 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 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 treatment episodes to be considered the same treatment episode.

Exposure Extension Period - number of days post-treatment episode where outcomes/events are still attributed to 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 a member is eligible for an incident treatment episode (i.e., days that the member meets all inclusion criteria such a incidence, pre-existing condition, and enrollment requirements).

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 a treatment episode must have in order 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. 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 evaluates exposures 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

Table 1. Summary of Incident Quinine Sulfate and Diltiazem use in the MSDD between January 1, 2006 and December 31, 2010 by Event

	New Users	Dispensings	Total Days Supplied	Days at Risk	New Events	Dispensings/ User	Days Supplied/ User	Days Supplied/ Dispensing	Events/1M Days at Risk
Quinine Sulfate									
Hemolytic-uremic syndrome	45,779	68,796	2,626,332	2,640,234	1	1.5	57.4	38.2	0.38
Immune thrombocytopenic purpura	45,779	68,796	2,626,332	2,640,124	3	1.5	57.4	38.2	1.14
Thrombocytopenia unspecified	45,779	68,796	2,626,332	2,637,406	77	1.5	57.4	38.2	29.20
Other secondary thrombocytopenia	45,779	68,796	2,626,332	2,640,308	1	1.5	57.4	38.2	0.38
Thrombotic microangiopathy	45,779	68,796	2,626,332	2,640,229	2	1.5	57.4	38.2	0.76
Diltiazem									
Hemolytic-uremic syndrome	176,455	1,001,691	40,170,652	38,691,254	2	5.7	227.7	40.1	0.05
Immune thrombocytopenic purpura	176,455	1,001,691	40,170,652	38,684,426	30	5.7	227.7	40.1	0.78
Thrombocytopenia unspecified	176,455	1,001,691	40,170,652	38,580,530	815	5.7	227.7	40.1	21.12
Other secondary thrombocytopenia	176,455	1,001,691	40,170,652	38,690,264	22	5.7	227.7	40.1	0.57
Thrombotic microangiopathy	176,455	1,001,691	40,170,652	38,691,204	6	5.7	227.7	40.1	0.16

Figure 1a. Number of Incident Users and Dispensings between January 1, 2006 and December 31, 2010, by Drug Product

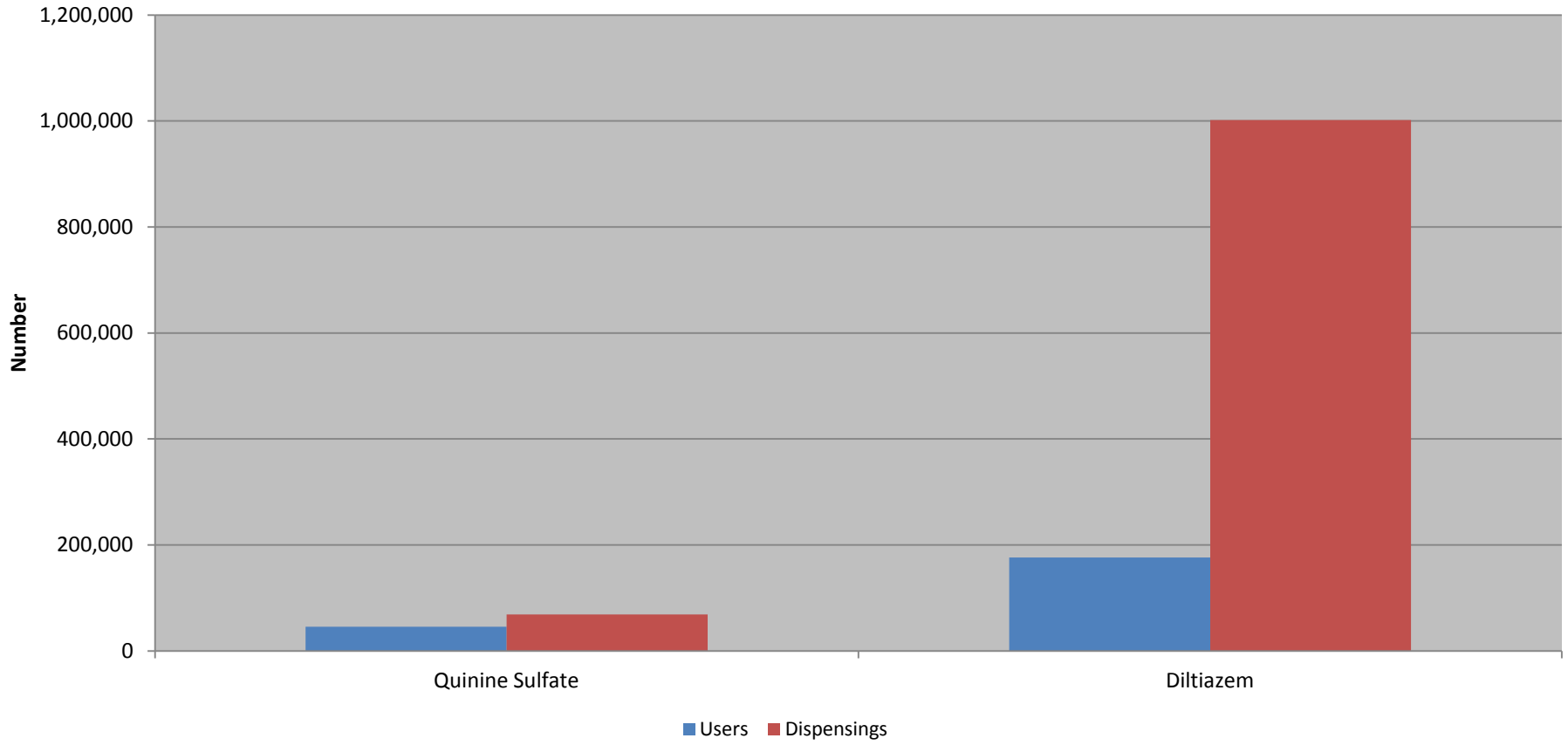

Figure 1b. Incident Days Supplied per User, Days Supplied per Dispensing, and Dispensings per User between January 1, 2006 and December 31, 2010, by Drug Product

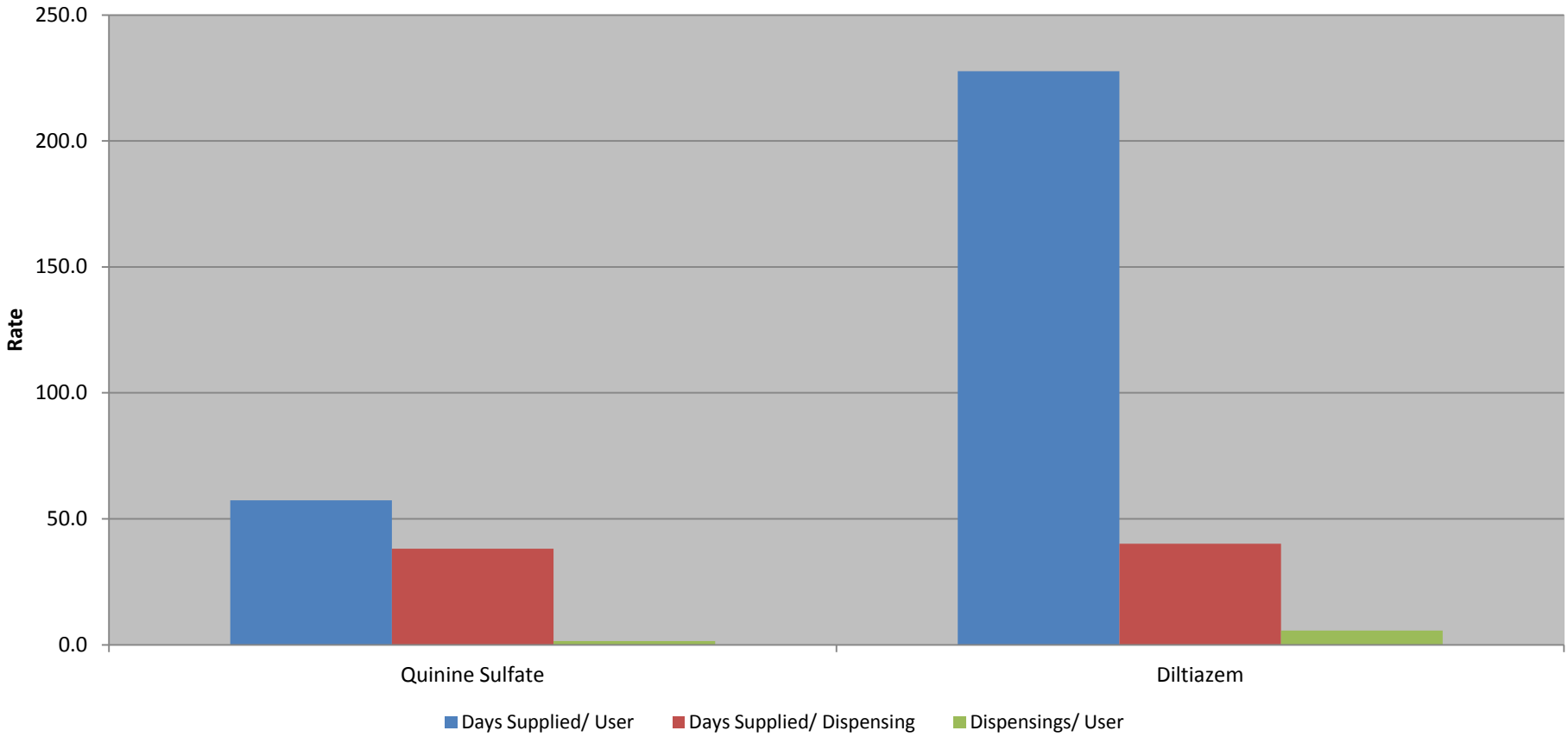

Figure 1c. Events per 1 Million Days at Risk between January 1, 2006 and December 31, 2010, by Event and Drug Product

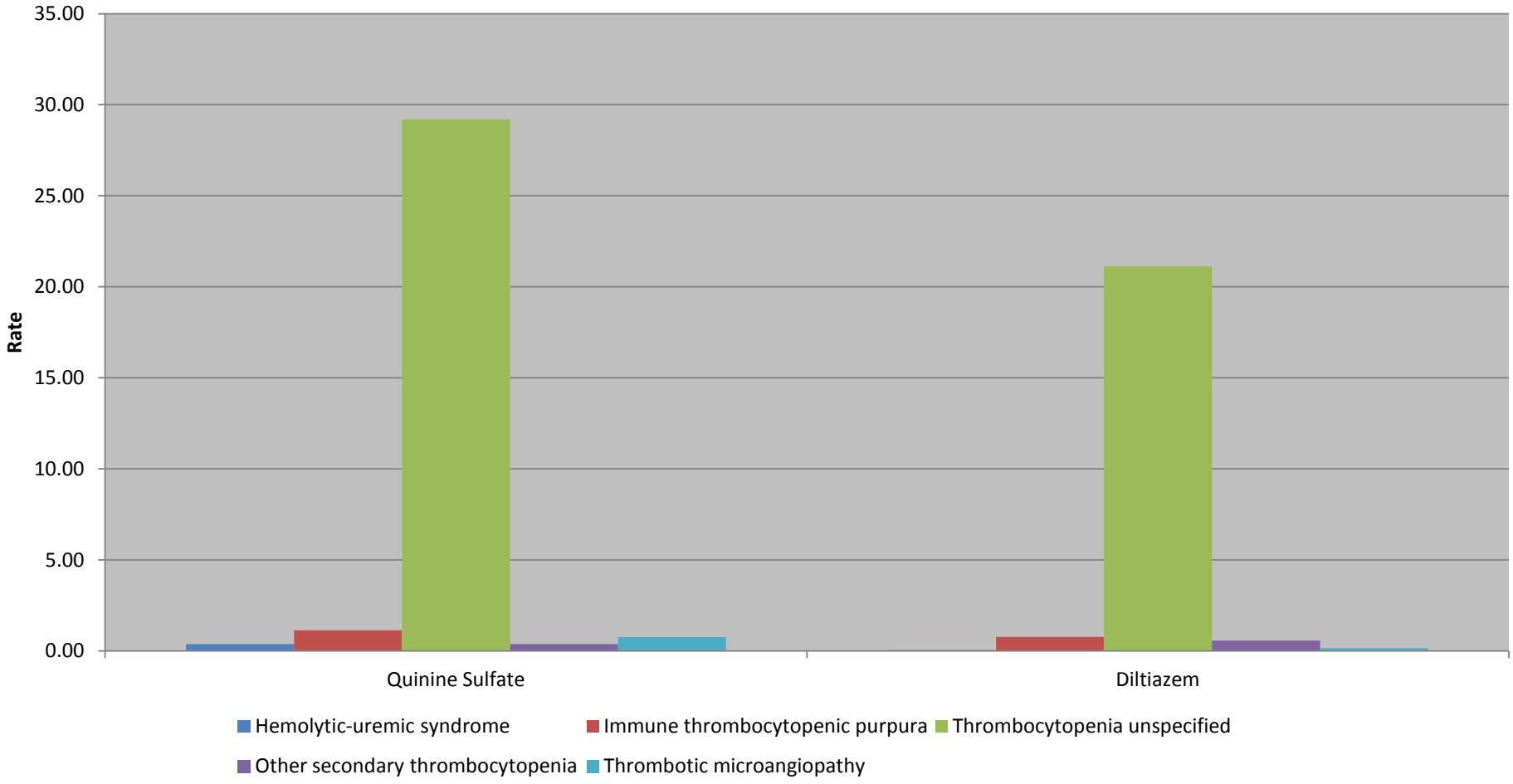

Table 2. Summary of Incident Quinine Sulfate and Diltiazem use in the MSDD between January 1, 2006 and December 31, 2010 by Event and Age Group

	New Users	Dispensings	Total Days Supplied	Days at Risk	New Events	Dispensings/ User	Days Supplied/ User	Days Supplied/ Dispensing	Events/1M Days at Risk
Quinine Sulfate									
Hemolytic-uremic syndrome	45,779	68,796	2,626,332	2,640,234	1	1.5	57.4	38.2	0.38
00 to 19	419	456	6,733	6,738	0	1.1	16.1	14.8	0.00
20 to 39	3,346	4,051	92,247	92,222	0	1.2	27.6	22.8	0.00
40 to 64	22,836	34,483	1,188,891	1,197,450	0	1.5	52.1	34.5	0.00
65+	19,178	29,806	1,338,461	1,343,824	1	1.6	69.8	44.9	0.74
Immune thrombocytopenic purpura	45,779	68,796	2,626,332	*2,640,124*	3	1.5	57.4	38.2	1.14
00 to 19	419	456	6,733	6,738	0	1.1	16.1	14.8	0.00
20 to 39	3,346	4,051	92,247	92,222	0	1.2	27.6	22.8	0.00
40 to 64	22,836	34,483	1,188,891	1,197,269	2	1.5	52.1	34.5	1.67
65+	19,178	29,806	1,338,461	1,343,895	1	1.6	69.8	44.9	0.74
Thrombocytopenia unspecified	45,779	68,796	2,626,332	*2,637,406*	77	1.5	57.4	38.2	29.20
00 to 19	419	456	6,733	6,667	1	1.1	16.1	14.8	149.99
20 to 39	3,346	4,051	92,247	92,103	3	1.2	27.6	22.8	32.57
40 to 64	22,836	34,483	1,188,891	1,196,382	35	1.5	52.1	34.5	29.25
65+	19,178	29,806	1,338,461	1,342,254	38	1.6	69.8	44.9	28.31
Other secondary thrombocytopenia	45,779	68,796	2,626,332	*2,640,308*	1	1.5	57.4	38.2	0.38
00 to 19	419	456	6,733	6,738	0	1.1	16.1	14.8	0.00
20 to 39	3,346	4,051	92,247	92,222	0	1.2	27.6	22.8	0.00
40 to 64	22,836	34,483	1,188,891	1,197,435	1	1.5	52.1	34.5	0.84
65+	19,178	29,806	1,338,461	1,343,913	0	1.6	69.8	44.9	0.00
Thrombotic microangiopathy	45,779	68,796	2,626,332	*2,640,229*	2	1.5	57.4	38.2	0.76
00 to 19	419	456	6,733	6,738	0	1.1	16.1	14.8	0.00
20 to 39	3,346	4,051	92,247	92,222	0	1.2	27.6	22.8	0.00
40 to 64	22,836	34,483	1,188,891	1,197,445	1	1.5	52.1	34.5	0.84
65+	19,178	29,806	1,338,461	1,343,824	1	1.6	69.8	44.9	0.74

Table 2. Summary of Incident Quinine Sulfate and Diltiazem use in the MSDD between January 1, 2006 and December 31, 2010 by Event and Age Group

	New Users	Dispensings	Total Days Supplied	Days at Risk	New Events	Dispensings/ User	Days Supplied/ User	Days Supplied/ Dispensing	Events/1M Days at Risk
Diltiazem									
Hemolytic-uremic syndrome	176,455	1,001,691	40,170,652	38,691,254	2	5.7	227.7	40.1	0.05
00 to 19	603	1,992	60,505	60,371	0	3.3	100.3	30.4	0.00
20 to 39	12,433	46,977	1,526,316	1,506,655	0	3.8	122.8	32.5	0.00
40 to 64	82,394	461,680	17,245,432	16,746,642	1	5.6	209.3	37.4	0.06
65+	81,025	491,042	21,338,399	20,377,586	1	6.1	263.4	43.5	0.05
Immune thrombocytopenic purpura	176,455	1,001,691	40,170,652	38,684,426	30	5.7	227.7	40.1	0.78
00 to 19	603	1,992	60,505	60,371	0	3.3	100.3	30.4	0.00
20 to 39	12,433	46,977	1,526,316	1,506,652	1	3.8	122.8	32.5	0.66
40 to 64	82,394	461,680	17,245,432	16,745,176	6	5.6	209.3	37.4	0.36
65+	81,025	491,042	21,338,399	20,372,227	23	6.1	263.4	43.5	1.13
Thrombocytopenia unspecified	176,455	1,001,691	40,170,652	38,580,530	815	5.7	227.7	40.1	21.12
00 to 19	603	1,992	60,505	59,805	5	3.3	100.3	30.4	83.61
20 to 39	12,433	46,977	1,526,316	1,505,046	14	3.8	122.8	32.5	9.30
40 to 64	82,394	461,680	17,245,432	16,720,357	200	5.6	209.3	37.4	11.96
65+	81,025	491,042	21,338,399	20,295,322	596	6.1	263.4	43.5	29.37
Other secondary thrombocytopenia	176,455	1,001,691	40,170,652	38,690,264	22	5.7	227.7	40.1	0.57
00 to 19	603	1,992	60,505	60,371	0	3.3	100.3	30.4	0.00
20 to 39	12,433	46,977	1,526,316	1,506,578	2	3.8	122.8	32.5	1.33
40 to 64	82,394	461,680	17,245,432	16,746,866	1	5.6	209.3	37.4	0.06
65+	81,025	491,042	21,338,399	20,376,449	19	6.1	263.4	43.5	0.93
Thrombotic microangiopathy	176,455	1,001,691	40,170,652	38,691,204	6	5.7	227.7	40.1	0.16
00 to 19	603	1,992	60,505	60,371	0	3.3	100.3	30.4	0.00
20 to 39	12,433	46,977	1,526,316	1,506,650	1	3.8	122.8	32.5	0.66
40 to 64	82,394	461,680	17,245,432	16,746,627	3	5.6	209.3	37.4	0.18
65+	81,025	491,042	21,338,399	20,377,556	2	6.1	263.4	43.5	0.10

Table 3. Summary of Incident Quinine Sulfate and Diltiazem use in the MSDD between January 1, 2006 and December 31, 2010 by Event and Sex

	New Users	Dispensings	Total Days Supplied	Days at Risk	New Events	Dispensings/ User	Days Supplied/ User	Days Supplied/ Dispensing	Events/1M Days at Risk
Quinine Sulfate									
Hemolytic-uremic syndrome	45,779	68,796	2,626,332	2,640,234	1	1.5	57.4	38.2	0.38
Female	28,031	41,632	1,588,209	21,409,991	1	1.5	56.7	38.1	0.63
Male	17,720	27,122	1,037,117	17,258,705	0	1.5	58.5	38.2	0.00
Unknown	28	42	1,006	22,558	0	1.5	35.9	24.0	0.00
Immune thrombocytopenic purpura	45,779	68,796	2,626,332	2,640,124	3	1.5	57.4	38.2	1.14
Female	28,031	41,632	1,588,209	21,406,908	3	1.5	56.7	38.1	1.88
Male	17,720	27,122	1,037,117	17,254,960	0	1.5	58.5	38.2	0.00
Unknown	28	42	1,006	22,558	0	1.5	35.9	24.0	0.00
Thrombocytopenia unspecified	45,779	68,796	2,626,332	2,637,406	77	1.5	57.4	38.2	29.20
Female	28,031	41,632	1,588,209	21,356,759	36	1.5	56.7	38.1	22.56
Male	17,720	27,122	1,037,117	17,201,218	41	1.5	58.5	38.2	39.40
Unknown	28	42	1,006	22,553	0	1.5	35.9	24.0	0.00
Other secondary thrombocytopenia	45,779	68,796	2,626,332	2,640,308	1	1.5	57.4	38.2	0.38
Female	28,031	41,632	1,588,209	21,409,761	0	1.5	56.7	38.1	0.00
Male	17,720	27,122	1,037,117	17,257,945	1	1.5	58.5	38.2	0.96
Unknown	28	42	1,006	22,558	0	1.5	35.9	24.0	0.00
Thrombotic microangiopathy	45,779	68,796	2,626,332	2,640,229	2	1.5	57.4	38.2	0.76
Female	28,031	41,632	1,588,209	21,409,971	2	1.5	56.7	38.1	1.25
Male	17,720	27,122	1,037,117	17,258,675	0	1.5	58.5	38.2	0.00
Unknown	28	42	1,006	22,558	0	1.5	35.9	24.0	0.00
Diltiazem									
Hemolytic-uremic syndrome	176,455	1,001,691	40,170,652	38,691,254	2	5.7	227.7	40.1	0.05
Female	97,376	554,400	22,258,728	21,409,991	2	5.7	228.6	40.1	0.09
Male	78,954	446,610	17,888,725	17,258,705	0	5.7	226.6	40.1	0.00
Unknown	125	681	23,199	22,558	0	5.4	185.6	34.1	0.00
Immune thrombocytopenic purpura	176,455	1,001,691	40,170,652	38,684,426	30	5.7	227.7	40.1	0.78
Female	97,376	554,400	22,258,728	21,406,908	18	5.7	228.6	40.1	0.84
Male	78,954	446,610	17,888,725	17,254,960	12	5.7	226.6	40.1	0.70
Unknown	125	681	23,199	22,558	0	5.4	185.6	34.1	0.00

Table 3. Summary of Incident Quinine Sulfate and Diltiazem use in the MSDD between January 1, 2006 and December 31, 2010 by Event and Sex

	New Users	Dispensings	Total Days Supplied	Days at Risk	New Events	Dispensings/ User	Days Supplied/ User	Days Supplied/ Dispensing	Events/1M Days at Risk
Diltiazem, continued									
Thrombocytopenia unspecified	176,455	1,001,691	40,170,652	38,580,530	815	5.7	227.7	40.1	21.12
Female	97,376	554,400	22,258,728	21,356,759	376	5.7	228.6	40.1	17.61
Male	78,954	446,610	17,888,725	17,201,218	438	5.7	226.6	40.1	25.46
Unknown	125	681	23,199	22,553	1	5.4	185.6	34.1	44.34
Other secondary thrombocytopenia	176,455	1,001,691	40,170,652	38,690,264	22	5.7	227.7	40.1	0.57
Female	97,376	554,400	22,258,728	21,409,761	12	5.7	228.6	40.1	0.56
Male	78,954	446,610	17,888,725	17,257,945	10	5.7	226.6	40.1	0.58
Unknown	125	681	23,199	22,558	0	5.4	185.6	34.1	0.00
Thrombotic microangiopathy	176,455	1,001,691	40,170,652	38,691,204	6	5.7	227.7	40.1	0.16
Female	97,376	554,400	22,258,728	21,409,971	5	5.7	228.6	40.1	0.23
Male	78,954	446,610	17,888,725	17,258,675	1	5.7	226.6	40.1	0.06
Unknown	125	681	23,199	22,558	0	5.4	185.6	34.1	0.00