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 Description	The Dabigatran workgroup requested use of the Drug Utilization Program, Modular Program 1 (MP1) to assess uptake of dabigatran (approval date October 19, 2010). This program was developed for Mini-Sentinel Task Order 3 Activity: Drug Use Studies – Comparison to Nationally Projected Databases. The primary goal is an assessment of the uptake, persistence, and patterns of use of newly marketed drug products (e.g., New Molecular Entities [NMEs] approved in the last two years). Another goal is to create a reusable program (Modular Program) that can be used to easily repeat the analysis for other drugs of interest. For more details please refer to original protocol document. This program was distributed to 17 Data Partners on July 25, 2012. One Data Partner was excluded because their database does not overlap with the query period. This report contains data from 16 Data Partners and includes a maximum of 21 months of dabigatran follow-up (most Data Partners had >18 months of follow-up). Identification of new dabigatran users: Only new users of dabigatran are included, using the approval date as the first date for assessment. New use is defined with respect to use of the drug of interest, and not with respect to any other drugs. No pre-index enrollment criterion will be used to confirm a new use. Additional information about dabigatran is listed in **Table 1**. Follow-up: The assessment of uptake describes monthly use following approval. The maximum available follow-up will be used. Enrollment will not be required during the follow-up period. Reporting: The report describes dabigatran uptake and persistence. Since the primary objective is to assess drug use patterns for dabigatran across the Mini-Sentinel Distributed Database (MSDD), and because utilization of dabigatran is a potentially sensitive and proprietary topic, all count data will be presented in aggregate across the 16 participating Data Partners. When rates are presented, site information will be presented but sites will not be identified. MSOC has access to Data Partner and site-specific counts for follow-up assessment, as necessary, but only after FDA request and Data Partner approval. Uptake: The uptake assessment describes the number of new users in each month following approval. The number of new users is stratified by age group (< 20, 20-<50, 50-<65, and 65+ years) and sex. Age is calculated as of the date of the first dispensing. New users with no sex identifier (or with an unknown sex) or with a missing age at first dispensing are excluded. **Tables 2 to 4** provide information on the days supplied per dispensing. To assess the interval between the first and second dispensings, we present the percentage of days into the first dispensing that the second dispensing was filled (**Table 5**). **Tables 6 - New** provides counts and graphs of new users per month overall and by age group and sex. **Table 6 - Cum** provides monthly counts and graphs of the cumulative number of new users overall and by age group and sex. **Table 6 - Disp** provides monthly counts and graphs of the cumulative number of dispensings overall and by age group and sex. New users are counted once in the uptake assessment and their use is assigned to the month of their first dispensing. Persistence: Common measures of medication use include medication compliance (also referred to as adherence) and medication persistence. See the reference list for additional information on these measures. These terms are defined as follows (Cramer 2008): "Medication compliance (synonym: adherence) refers to the degree or extent of conformity to the recommendations about day-to-day treatment by the provider with respect to the timing, dosage, and frequency. It may be defined as "the extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen." Medication persistence refers to the act of continuing the treatment for the prescribed duration. It may be measured with a treament epsiode, defined as "the duration of time from initiation to discontinuation of therapy." This evaluation focuses on medication persistence, including measures of treatment episode length, gaps between treatment episodes, and the number of episodes per user. These measures will be assessed within four post-approval periods: 6, 12, 18, and 24 months. A treatment episode is calculated using the standard Mini-Sentinel medication stockpiling algorithm using an allowable gap of 10 days between episodes (i.e., gaps of 10-days or less are bridged to create continuous treatment episodes). **Table 7** provides information on the number of new users with one, two, and three episodes in the post-approval window, and the characteristics of the teatment episodes. **Figure 4** illustrates the number of treatment episodes within 12 months of approval and **Figure 5** illustrates the total days supplied per user.
Request ID	MSY3_MPR40

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Table 1. Drug of Interest

Drug Name	Approval Date	Labeled Indication
Dabigatran (Pradaxa)	19-Oct-10	A direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

Approval dates from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

Table 2. Distribution of Days Supplied (%) per Dispensing (All Data Partners Combined)

Days Supplied per Dispensing (in days)	Dabigatran (Pradaxa) October 19, 2010
Missing	0.0%
< 0	0.0%
0	0.0%
0-<1	0.0%
1-<15	1.0%
15-<33	86.8%
33-<66	1.0%
61-<99	11.0%
99-<499	0.1%
>=500	0.0%

Table 3. Descriptive Statistics for the Number of Days Supplied per Dispensing (all dispensings - All Data Partners Combined)

Statistic	Dabigatran (Pradaxa) October 19, 2010
Min	0
5th percentile	30
25th percentile	30
Mean	37
Median	30
75th percentile	30
95th percentile	90
Max	900

Table 4. Descriptive Statistics for Length of the First Treatment Episode* (in days - All Data Partners Combined)

Statistic	Dabigatran (Pradaxa) October 19, 2010
Min	1
5th percentile	30
25th percentile	30
Mean	113
Median	90
75th percentile	159
95th percentile	330
Max	686

*The length of a treatment episode is equal to the number of days supplied. Dispensings with a gap of less than 10 days are bridged together. A gap of more than 10 days between dispensings initiates the beginning of a new episode.

Table 5. Descriptive Statistics for the Interval between the First and Second Dispensing* for all Data Partners Combined

Statistic	Dabigatran (Pradaxa) October 19, 2010
Min	2%
5th percentile	68%
25th percentile	93%
Mean	122%
Median	103%
75th percentile	123%
95th percentile	227%
Max	10300%

*Calculated as the percentage of time (in days) into the first dispensing that the second dispensing was filled (calculated only for time between first and second dispensings). For example, if the first dispensing had a 30 day supply, and the second dispensing was filled 20 days after the first dispensing, the value would equal 20/30 or 66%. Values over 100% indicate the days supplied for the first dispensing is less than the time to the second dispensing.

Table 6. Number of New Users by Demographic and Number of Months Post Approval:

Dabigatran (Pradaxa) October 19, 2010

	Number of Months Post Approval*																							
Demographic	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Total	597	2,858	3,387	4,321	4,585	4,479	4,340	4,806	4,646	3,550	3,204	3,187	2,151	696	694	652	482	289	0	0	0	0	0	0
Male	338	1,676	1,963	2,401	2,560	2,455	2,447	2,710	2,588	1,963	1,721	1,740	1,216	453	467	440	309	189	0	0	0	0	0	0
Female	259	1,182	1,423	1,919	2,024	2,024	1,891	2,094	2,058	1,587	1,483	1,447	935	243	227	212	173	100	0	0	0	0	0	0
<20 years	0	0	1	1	0	0	0	0	1	2	1	0	0	1	1	0	2	1	0	0	0	0	0	0
20-<50 years	23	90	120	168	173	152	162	156	156	119	96	83	68	50	59	46	48	20	0	0	0	0	0	0
50-<65 years	107	657	656	748	801	837	819	884	861	645	467	509	401	279	253	248	159	121	0	0	0	0	0	0
65+ years	467	2,111	2,610	3,404	3,611	3,490	3,359	3,766	3,628	2,784	2,640	2,595	1,682	366	381	358	273	147	0	0	0	0	0	0
Male <20 years	0	0	0	1	0	0	0	0	0	1	1	0	0	1	1	0	1	1	0	0	0	0	0	0
Male 20-<50 years	16	70	85	122	129	118	123	118	121	93	69	63	54	34	48	36	38	16	0	0	0	0	0	0
Male 50-<65 years	76	499	494	552	590	612	601	662	632	479	339	367	304	213	193	189	109	94	0	0	0	0	0	0
Male 65+ years	246	1,107	1,384	1,726	1,841	1,725	1,723	1,930	1,835	1,390	1,312	1,310	858	205	225	215	161	78	0	0	0	0	0	0
Female <20 years	0	0	1	0	0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Female 20-<50 years	7	20	35	46	44	34	38	37	35	26	27	20	14	16	11	10	10	4	0	0	0	0	0	0
Female 50-<65 years	31	158	161	195	210	225	217	222	229	166	128	142	97	66	60	59	50	27	0	0	0	0	0	0
Female 65+ years	221	1,004	1,226	1,678	1,770	1,765	1,636	1,835	1,793	1,394	1,328	1,285	824	161	156	143	112	69	0	0	0	0	0	0

*maximum of 21 months, with most Data Partners with fewer than 18 months of follow-up

Figure 1a. New Dabigatran Users by Age Group and Month from Drug Approval

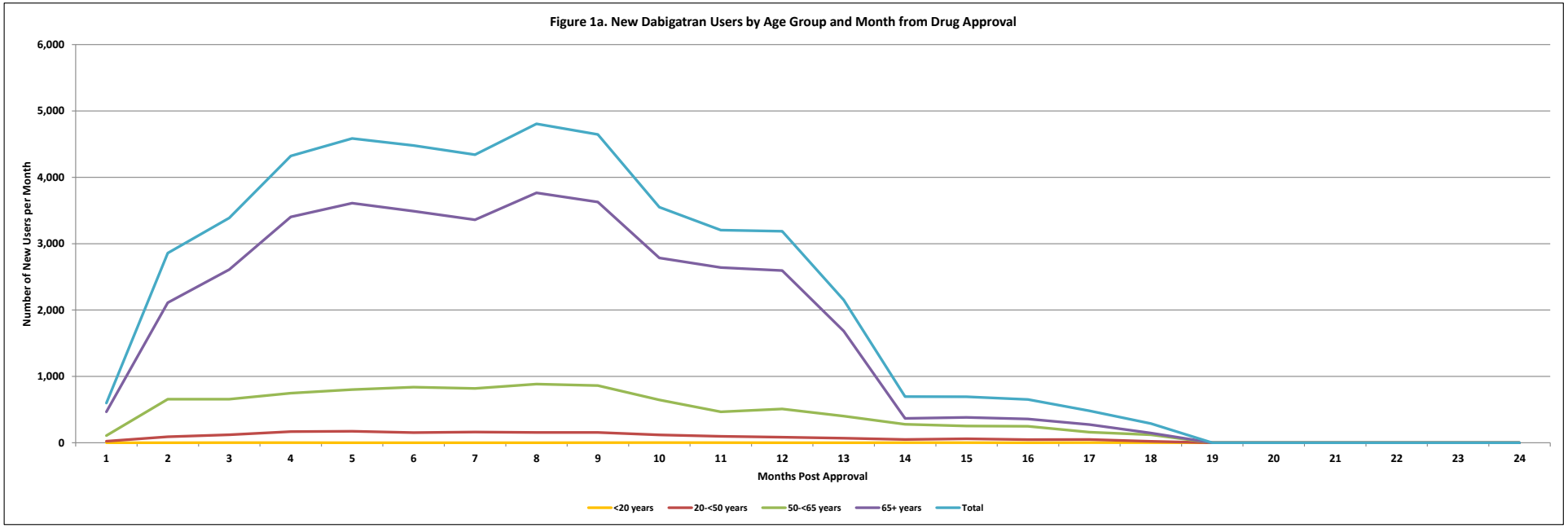

Figure 1b. Number of New Dabigatran Users Post Drug Approval by Sex

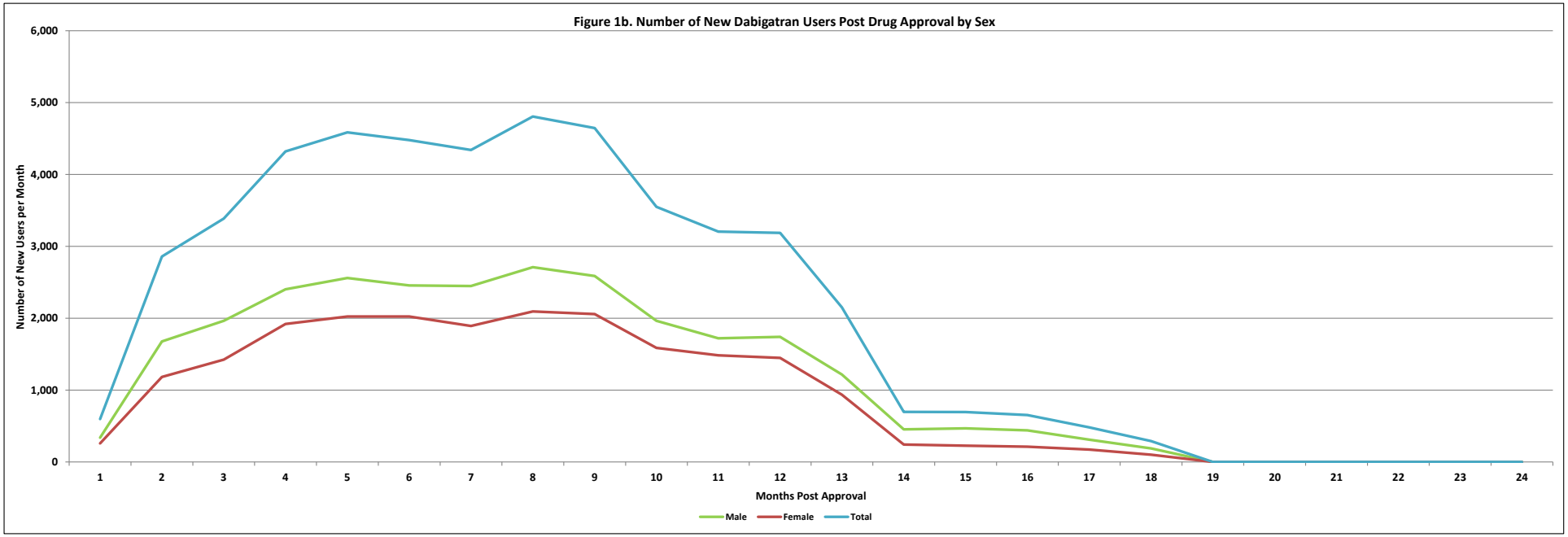

Table 7. Number of Cumulative New Users by Demographic and Number of Months Post Approval

Dabigatran (Pradaxa) October 19, 2010

	Number of Months Post Approval*																							
Demographic	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Total	597	3,455	6,842	11,163	15,748	20,227	24,567	29,373	34,019	37,569	40,773	43,960	46,111	46,807	47,501	48,153	48,635	48,924	48,924	48,924	48,924	48,924	48,924	48,924
Male	338	2,014	3,977	6,378	8,938	11,393	13,840	16,550	19,138	21,101	22,822	24,562	25,778	26,231	26,698	27,138	27,447	27,636	27,636	27,636	27,636	27,636	27,636	27,636
Female	259	1,441	2,864	4,783	6,807	8,831	10,722	12,816	14,874	16,461	17,944	19,391	20,326	20,569	20,796	21,008	21,181	21,281	21,281	21,281	21,281	21,281	21,281	21,281
<20 years	0	0	1	2	2	2	2	2	3	5	6	6	6	7	8	8	10	11	11	11	11	11	11	11
20-<50 years	23	113	233	401	574	726	888	1,044	1,200	1,319	1,415	1,498	1,566	1,616	1,675	1,721	1,769	1,789	1,789	1,789	1,789	1,789	1,789	1,789
50-<65 years	107	764	1,420	2,168	2,969	3,806	4,625	5,509	6,370	7,015	7,482	7,991	8,392	8,671	8,924	9,172	9,331	9,452	9,452	9,452	9,452	9,452	9,452	9,452
65+ years	467	2,578	5,188	8,592	12,203	15,693	19,052	22,818	26,446	29,230	31,870	34,465	36,147	36,513	36,894	37,252	37,525	37,672	37,672	37,672	37,672	37,672	37,672	37,672
Male <20 years	0	0	0	1	1	1	1	1	1	2	3	3	3	4	5	5	6	7	7	7	7	7	7	7
Male 20-<50 years	16	86	171	293	422	540	663	781	902	995	1,064	1,127	1,181	1,215	1,263	1,299	1,337	1,353	1,353	1,353	1,353	1,353	1,353	1,353
Male 50-<65 years	76	575	1,069	1,621	2,211	2,823	3,424	4,086	4,718	5,197	5,536	5,903	6,207	6,420	6,613	6,802	6,911	7,005	7,005	7,005	7,005	7,005	7,005	7,005
Male 65+ years	246	1,353	2,737	4,463	6,304	8,029	9,752	11,682	13,517	14,907	16,219	17,529	18,387	18,592	18,817	19,032	19,193	19,271	19,271	19,271	19,271	19,271	19,271	19,271
Female <20 years	0	0	1	1	1	1	1	1	2	3	3	3	3	3	3	3	4	4	4	4	4	4	4	4
Female 20-<50 years	7	27	62	108	152	186	224	261	296	322	349	369	383	399	410	420	430	434	434	434	434	434	434	434
Female 50-<65 years	31	189	350	545	755	980	1,197	1,419	1,648	1,814	1,942	2,084	2,181	2,247	2,307	2,366	2,416	2,443	2,443	2,443	2,443	2,443	2,443	2,443
Female 65+ years	221	1,225	2,451	4,129	5,899	7,664	9,300	11,135	12,928	14,322	15,650	16,935	17,759	17,920	18,076	18,219	18,331	18,400	18,400	18,400	18,400	18,400	18,400	18,400

*maximum of 21 months, with most Data Partners with fewer than 18 months of follow-up

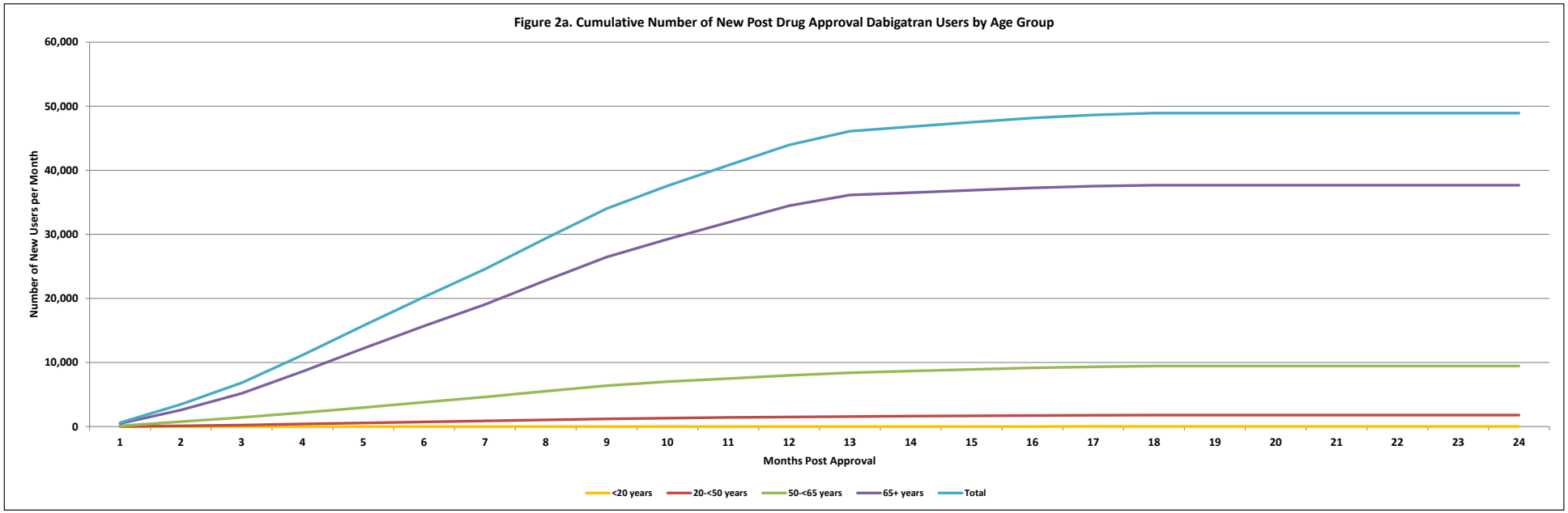
Figure 2a. Cumulative Number of New Post Drug Approval Dabigatran Users by Age Group
Number of New Users per Month
60,000
50,000
40,000
30,000
20,000
10,000
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Months Post Approval
<20 years
20-<50 years
50-<65 years
65+ years
Total

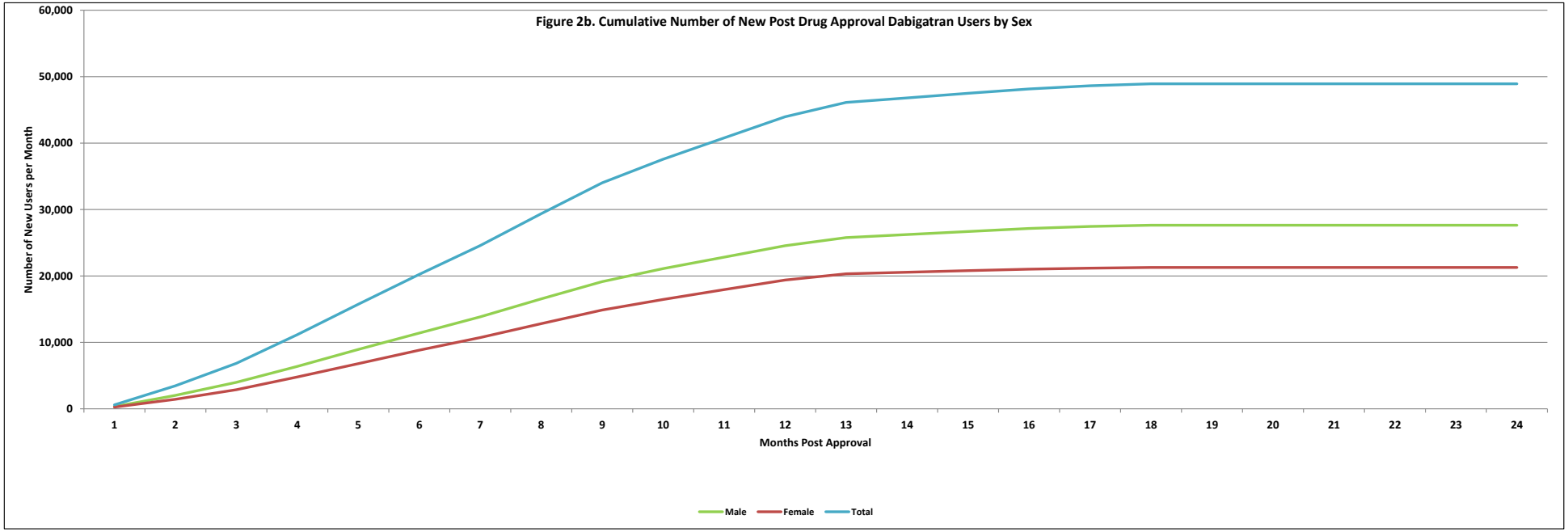
Figure 2b. Cumulative Number of New Post Drug Approval Dabigatran Users by Sex
Number of New Users per Month
60,000
50,000
40,000
30,000
20,000
10,000
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Months Post Approval
Male
Female
Total

Table 8. Number of Dispensings by Demographic and Number of Months Post Drug Approval

Dabigatran (Pradaxa) October 19, 2010

	Number of Months Post Approval*																							
Demographic	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Total	604	3,344	5,366	8,459	11,118	13,266	14,967	18,084	19,896	18,184	17,775	18,775	13,324	4,919	4,996	4,835	4651	3179	120	115	87	0	0	0
Male	343	1,952	3,115	4,776	6,250	7,396	8,363	10,125	11,062	9,870	9,277	9,844	7,268	3,307	3,338	3,164	3110	2093	68	65	51	0	0	0
Female	261	1,392	2,250	3,681	4,866	5,868	6,600	7,953	8,828	8,311	8,498	8,931	6,056	1,612	1,658	1,671	1541	1086	52	50	36	0	0	0
<20 years	0	0	1	2	2	1	1	1	2	3	3	0	1	2	1	1	3	2	0	0	0	0	0	0
20-<50 years	23	99	176	291	378	431	496	578	600	478	394	394	320	263	283	242	240	173	4	7	2	0	0	0
50-<65 years	107	759	1,107	1,614	2,084	2,563	2,852	3,454	3,721	3,050	2,382	2,628	2,305	1,877	1,853	1,770	1713	1184	37	35	27	0	0	0
65+ years	474	2,486	4,082	6,552	8,654	10,271	11,618	14,051	15,573	14,653	14,996	15,753	10,698	2,777	2,859	2,822	2695	1820	79	73	58	0	0	0
Male <20 years	0	0	0	1	1	0	0	0	0	1	1	0	0	1	1	0	1	1	0	0	0	0	0	0
Male 20-<50 years	16	76	131	221	275	325	380	435	467	368	288	295	253	209	228	191	190	140	3	4	1	0	0	0
Male 50-<65 years	76	576	827	1,198	1,549	1,903	2,115	2,562	2,735	2,271	1,745	1,882	1,696	1,445	1,413	1,364	1318	903	28	25	20	0	0	0
Male 65+ years	251	1,300	2,157	3,356	4,425	5,168	5,868	7,128	7,860	7,230	7,243	7,667	5,319	1,652	1,696	1,609	1601	1049	37	36	30	0	0	0
Female <20 years	0	0	1	1	1	1	1	1	2	2	2	0	1	1	0	1	2	1	0	0	0	0	0	0
Female 20-<50 years	7	23	45	70	103	106	115	141	131	109	106	99	67	54	55	51	50	33	1	3	1	0	0	0
Female 50-<65 years	31	183	279	414	533	658	734	889	983	777	637	746	609	432	440	406	395	281	9	10	7	0	0	0
Female 65+ years	223	1,186	1,925	3,196	4,229	5,103	5,750	6,922	7,712	7,423	7,753	8,086	5,379	1,125	1,163	1,213	1094	771	42	37	28	0	0	0

*maximum of 21 months, with most Data Partners with fewer than 18 months of follow-up

Figure 3a. Number of Total Dispensings Post Drug Approval for Dabigatran Users by Age Group

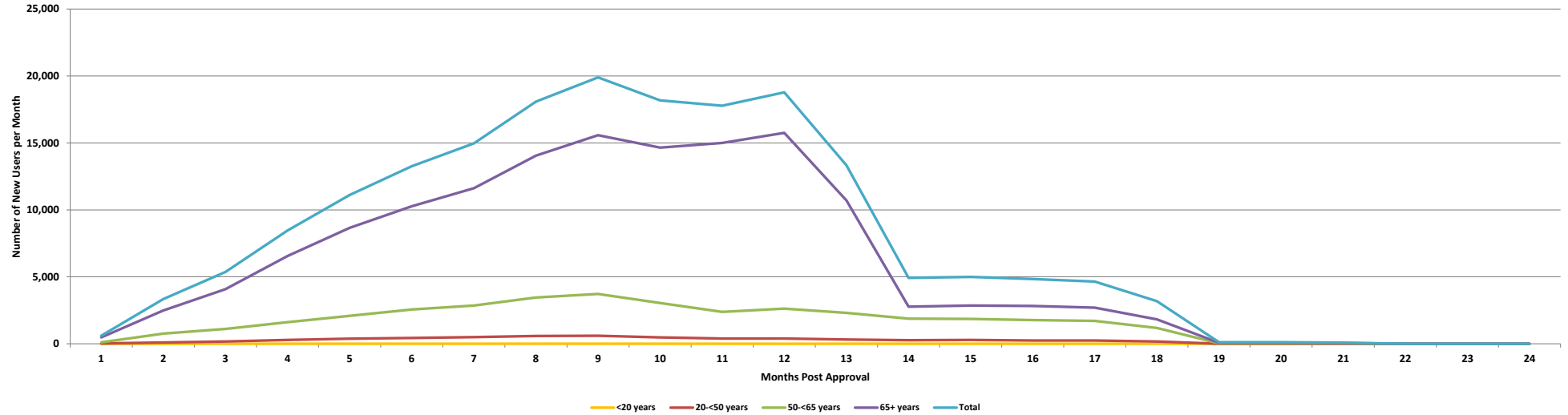

Figure 3b. Number of Total Dispensings Post Drug Approval for Dabigatran Users by Sex

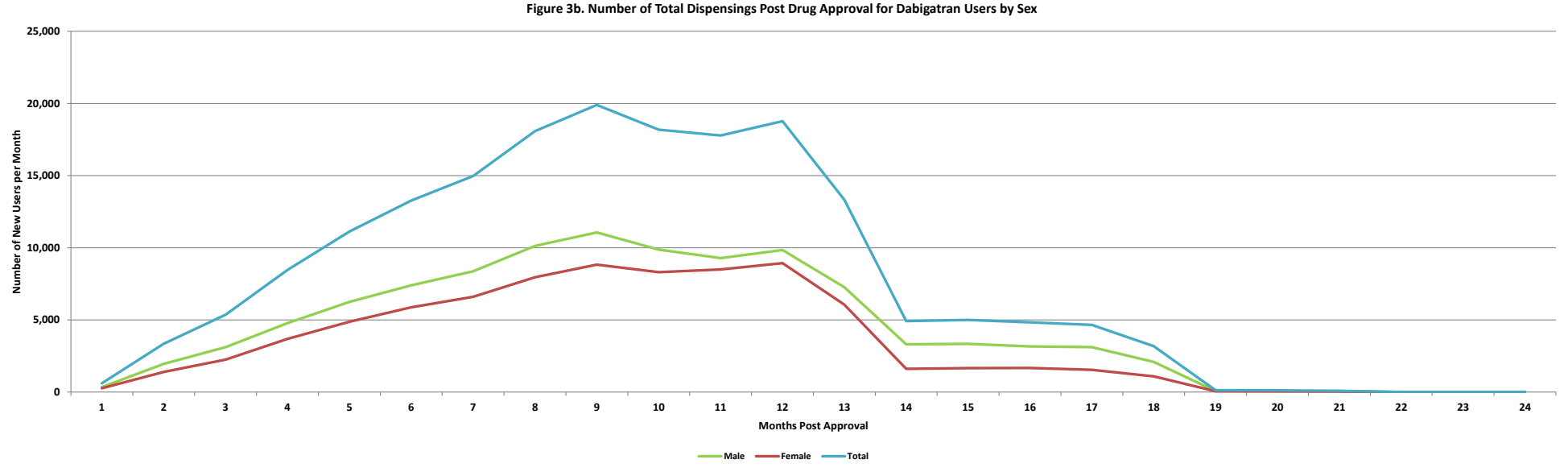

Table 9. Medication Persistence Measures*: Dabigatran (Pradaxa) October 19, 2010

Measure	Months Post Approval 0-6	0-12	0-18	0-24**
Total number of new users	24,540	46,072	48,885	48,885
Users with only one treatment episode				
N (users)	15,927	33,591	36,106	36,106
N (%) users who are right censored†	18 (0.1%)	24 (0.1%)	24 (0.1%)	24 (0.1%)
Total days supplied in episode‡	2,703,091	4,324,247	4,521,026	4,521,026
Total duration of episodes (days)	2,753,280	4,401,751	4,601,259	4,601,259
Range across Data Partners:				
Mean number of days supplied	37.0 - 420.0	37.0 - 315.0	37.0 - 315.0	37.0 - 315.0
Mean number of days	37.0 - 424.0	37.0 - 320.5	37.0 - 320.5	37.0 - 320.5
Median number of days supplied	30.0 - 420.0	30.0 - 375.0	30.0 - 375.0	30.0 - 375.0
Median number of days	30.0 - 424.0	30.0 - 384.0	30.0 - 384.0	30.0 - 384.0
Users with exactly two treatment episodes				
Treatment Episode #1				
N (users)	5,583	8,690	8,972	8,972
N (%) users who are right censored	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total days supplied in episode	480,039	657,037	668,619	668,619
Total duration of first episode (days)	492,000	672,520	684,274	684,274
Range across Data Partners:				
Mean number of days supplied	30.0 - 169.7	30.0 - 128.8	30.0 - 119.9	30.0 - 119.9
Mean number of days	30.0 - 174.2	30.0 - 131.8	30.0 - 122.7	30.0 - 122.7
Median number of days supplied	30.0 - 105.0	30.0 - 90.0	30.0 - 90.0	30.0 - 90.0
Median number of days	30.0 - 105.0	30.0 - 90.0	30.0 - 90.0	30.0 - 90.0
Episode Gap¥ #1				
Total days between treatment episodes	206,696	295,071	301,437	301,437
Range of means (days)	18.5 - 124.0	25.3 - 124.0	25.3 - 124.0	25.3 - 124.0
Range of medians (days)	14.5 - 124.0	15.0 - 124.0	15.0 - 124.0	15.0 - 124.0
Treatment Episode #2				
N (%) users who are right censored	1 (0.0%)	2 (0.0%)	2 (0.0%)	2 (0.0%)
Total days supplied in episode	655,170	878,633	894,867	894,867
Total duration of second episode (days)	671,572	899,553	916,009	916,009
Range across Data Partners:				
Mean number of days supplied	30.0 - 175.5	30.0 - 145.7	30.0 - 138.9	30.0 - 138.9
Mean number of days	30.0 - 179.3	30.0 - 148.4	30.0 - 141.7	30.0 - 141.7
Median number of days supplied	30.0 - 150.0	30.0 - 90.0	30.0 - 90.0	30.0 - 90.0
Median number of days	30.0 - 155.0	30.0 - 95.0	30.0 - 93.0	30.0 - 93.0
Post-Approval Window (All Episodes Combined)				
Total days supplied in post-approval window	1,135,209	1,535,670	1,563,486	1,563,486
Total duration of episodes (days)	1,163,572	1,572,073	1,600,283	1,600,283
Range across Data Partners:				
Mean number of days supplied	70.0 - 341.7	70.0 - 274.5	70.0 - 258.8	70.0 - 258.8
Mean number of days	70.7 - 349.2	70.7 - 280.2	70.7 - 264.3	70.7 - 264.3
Median number of days supplied	60.0 - 390.0	60.0 - 240.0	60.0 - 210.0	60.0 - 210.0
Median number of days	60.0 - 397.5	60.0 - 244.0	60.0 - 212.0	60.0 - 212.0
Users with three or more treatment episodes				
N (users)	3,030	3,791	3,807	3,807
N (%) users who are right censored	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total days supplied in post-approval window	642,792	759,746	761,306	761,306
Total duration of episodes (days)	660,561	780,124	781,694	781,694

*Number of treatment episodes and total days supplied are aggregated across all participating Data Partners

**Run date for this request was July 25, 2012, thus only a maximum of 21 months of follow-up are included

†Users are right censored when the days supplied exceeds the observation period. For example, if a user began taking a drug 5 months after the approval date and has a 90 day supply, this user will be right censored in the 0-6 months after approval observation period.

‡Total days of treatment episodes are calculated as [Episode End Date - Episode Start Date + 1] and include any gaps of 10 days or less that have been bridged.

¥A gap of more than 10 days between dispensings initiates the beginning of a new episode.

Table for Figure 4. Distribution of Users by Number of Treatment Episodes within 12 Months of Approval for All Data Partners Combined (% of Users)

	Dabigatran (Pradaxa)
Number of Treatment Episodes	October 19, 2010
1 Episode	***72.0%***
2 Episodes	***19.4%***
3 Episodes	***5.8%***
4+ Episodes	***2.8%***

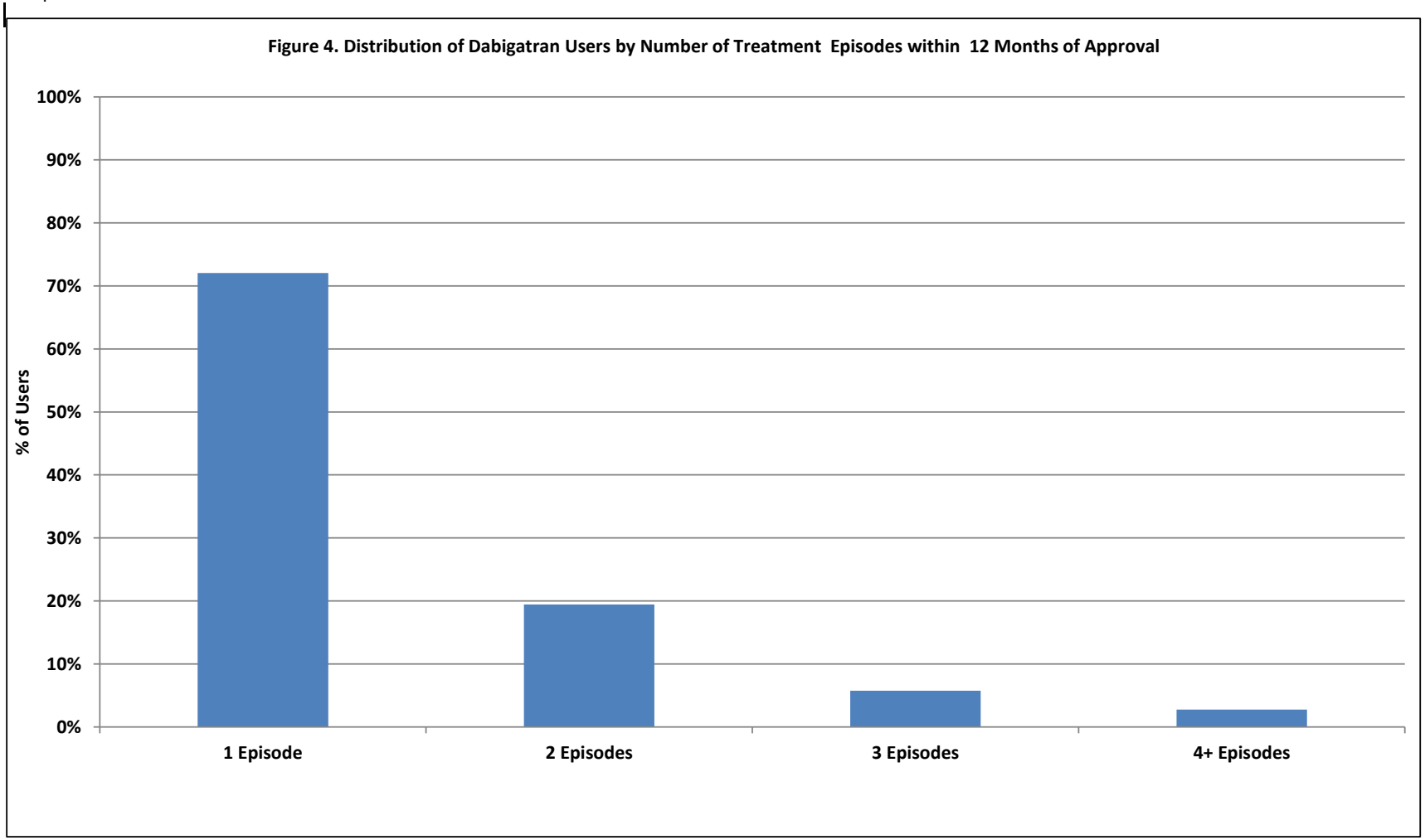

Table for Figure 5. Distribution of Total Days Supplied per Dabigatran User for All Data Partners Combined

Total Days Supplied per User	Dabigatran (Pradaxa) October 19, 2010
30+ Days	***99.1%***
90+ Days	***64.3%***
180+ Days	***34.9%***
270+ Days	***16.1%***
360+ Days	***5.6%***

Figure 5. Distribution of Total Days Supplied per Dabigatran User for All Data Partners Combined