1. An Evaluation of the Misuse and Abuse of Pregabalin using RADARS® System Programs in the United States and the European Union-

1.1. Introduction

When pregabalin abuse has been described in published case reports and surveys, a prior history of substance abuse and/or co-administration with opioids and other illicit drugs, was common. Pfizer's pharmacovigilance data indicate that case reports of abuse are relatively rare, less than 0.5% of the total number of adverse event reports, and a recent review of abuse case reports in the French pharmacovigilance database indicates that reports of abuse or dependence of pregabalin accounted for approximately 0.3% of total case reports related to this drug.[i] Recent systematic reviews of the literature suggest that abuse of pregabalin in the general population is low and that the risk of abuse is higher in patients with a prior history or concurrent substance abuse.

To obtain additional information about actual abuse of pregabalin, Pfizer commissioned a report using the RADARS® system program in the US, France, Germany and Italy. This evaluation assessed the non-medical use of prescription drugs and peer-reviewed published literature including case reports, systematic reviews and population surveys. A summary of these data are presented below (Section 1.1.1 to Section 1.1.9).

1.1.1. Rationale and background

Alpha$_2$-delta ligands (e.g., pregabalin and gabapentin) are widely used in neurology, psychiatry, and primary healthcare but are increasingly being reported globally as possessing a potential for misuse and abuse. These drugs are primarily prescribed as anticonvulsants, for the treatment of neuropathic pain as well as for the treatment of generalized anxiety disorders. Numerous international guidelines recommend pregabalin and gabapentin as first-line treatments for neuropathic pain. There has been a large increase in prescriptions of these drugs over the last decade. In the United States, pregabalin is listed as one of the 30 most prescribed medications as of 2011. Although pregabalin and gabapentin are prescribed for several approved therapeutic indications, there may be alternative motives for taking these drugs. There are reports of abuse of pregabalin and gabapentin from the European Union, from the US and globally. Abuse occurs at supra-therapeutic doses and is more prevalent among those with a current or past opioid use disorder. At dosages exceeding the therapeutic dosages, both drugs have anecdotally been reported by users to produce both sedative and dissociative/psychedelic effects. Reported pregabalin abuse among an addiction services population in Ireland suggests that pregabalin is an attractive drug to opioid dependent drug users. Further, concomitant opioid and gabapentin exposure has been found to be associated with a 49% higher risk of opioid-related death compared to opioid exposure alone. Both pregabalin and gabapentin may also be used off label to treat substance use disorders.

1.1.2. Research question and objectives

The primary objectives of this evaluation:

1. Summarize misuse and abuse data for pregabalin and each comparator within each country using the following data sources:

a) France, Germany, Italy:

i) Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System European Opioid Treatment Patient Survey (EUROPAD) Program

ii) RADARS® System Global Toxicosurveillance Network (GTNet) Program

iii) RADARS® System Survey of Non-Medical Use of Prescription Drugs Program

b) United States:

i. RADARS® System Treatment Center Programs Combined

ii. RADARS® System Survey of Non-Medical Use of Prescription Drugs Program

iii. RADARS® System Web Monitoring Program

iv. American Association of Poison Control Centers' (AAPCC's) National Poison Data System (NPDS)

2. Perform a statistical analysis of trends over time for pregabalin and each comparator to assess changes in misuse and abuse within each country and data source.

1.1.3. Study design

Objective 1: Summarize misuse and abuse data for pregabalin and each comparator

The MAH estimated rates or prevalence estimates for each of the outcomes (non-medical use, misuse, abuse, intentional exposures) by program for pregabalin and comparators within each country using descriptive statistics. No rates were calculated in the evaluation of data from the Web Monitoring Program.

Objective 2: Perform a statistical analysis of trends over time for pregabalin and each comparator

Trend analysis was performed for each drug and comparator for each of the outcomes by program within each country when continuous coverage for at least five year-quarters of data is available. Five continuous year-quarters of data allowed for a more accurate trend line to be fit; less than five continuous year-quarters of data were not as stable and have the potential for more variability. Trends were modeled using the rates of misuse and abuse.

This evaluation compared pregabalin at the active pharmaceutical ingredient level (Active Pharmaceutical Ingredient [API]; all branded and generic products combined) to the comparison groups in each country as presented below. The comparator drugs represent other central nervous system compounds that are known to be misused and abused, limited to the data available in each program in each country. No formal hypothesis tests were conducted between pregabalin and comparators.

France, Germany, and Italy:

1. EUROPAD Program:
    a) Gabapentin (branded and generic products with gabapentin as an API)
    b) Benzodiazepines (total drug class level [drug substances rollup; data on individual APIs are not collected])
    c) Opioid analgesics (branded and generic products with identified opioids as an API, combined into a single comparator group)
    d) Buprenorphine (branded and generic products with buprenorphine as an API)
    e) Methadone (branded and generic products with methadone as an API)
    f) Tramadol (branded and generic products with tramadol as an API)
    g) Heroin (all heroin mentions, regardless of form)
2. GTNet Program
    a) Gabapentin (branded and generic products with gabapentin as an API)
    b) Benzodiazepines (branded and generic products with identified benzodiazepines as an API, combined into a single comparator group)
    c) Opioid analgesics (branded and generic products with identified opioids as an API, combined into a single comparator group)
    d) Buprenorphine (branded and generic products with buprenorphine as an API)
    e) Methadone (branded and generic products with methadone as an API)
    f) Tramadol (France and Germany only) (branded and generic products with tramadol as an API)
3. Survey of Non-Medical Use of Prescriptions Drug Program
    a) Gabapentin (branded and generic products with gabapentin as an API)
    b) Baclofen (branded and generic products with baclofen as an API)
    c) Benzodiazepines (total drug class level [drug substances rollup; data on individual APIs are not collected])
    d) Opioid analgesics (branded and generic products with identified opioids as an API, combined into a single comparator group)
    e) Buprenorphine (branded and generic products with buprenorphine as an API)

f) Methadone (branded and generic products with methadone as an API)

g) Tramadol (branded and generic products with tramadol as an API)

h) Heroin (all heroin mentions, regardless of form)

United States:

1. Treatment Center Programs Combined:

a) Gabapentin (branded and generic products with gabapentin as an API)

b) Opioid analgesics (branded and generic products with identified opioids as an API, combined into a single comparator group)

c) Buprenorphine (branded and generic products with buprenorphine as an API)

d) Methadone (branded and generic products with methadone as an API)

e) Tramadol (branded and generic products with tramadol as an API)

f) Heroin (all heroin mentions, regardless of form)

2. AAPCC's NPDS

a) Gabapentin (cases coded to the Micromedex® Poisindex® generic code for gabapentin)

b) Baclofen (cases coded to the Micromedex Poisindex generic code for baclofen)

c) Benzodiazepines (cases coded to the Micromedex Poisindex generic code for benzodiazepines [individual APIs are not assigned separate Micromedex Poisindex generic codes])

d) Opioid analgesics (cases coded to the Micromedex Poisindex generic code for identified opioids, combined into a single comparator group)

e) Tramadol (cases coded to the Micromedex Poisindex generic code for tramadol)

f) Heroin (cases coded to the Micromedex Poisindex generic code for heroin)

3. Survey of Non-Medical Use of Prescriptions Drug Program

a) Gabapentin (branded and generic products with gabapentin as an API)

b) Baclofen (branded and generic products with baclofen as an API)

c) Benzodiazepines (total drug class level [drug substances rollup; data on individual APIs are not collected])

d) Opioid analgesics (branded and generic products with identified opioids as an API, combined into a single comparator group)

e) Buprenorphine (branded and generic products with buprenorphine as an API)

f) Methadone (branded and generic products with methadone as an API)

g) Tramadol (branded and generic products with tramadol as an API)

h) Heroin (all heroin mentions, regardless of form)

4. Web Monitoring Program

a) Gabapentin (branded and generic products with gabapentin as an API)

b) Opioid analgesics (branded and generic products with identified opioids as an API, combined into a single comparator group)

Surveillance periods for the evaluation included each RADARS® System data source for the period when pregabalin data collection began in that program in each country and included the last five years for NPDS.

a) France:

i. RADARS® System EUROPAD Program: 1st quarter 2015 – 4th quarter 2017

ii. RADARS® System GTNet Program: 1st quarter 2012 – 4th quarter 2016

iii. RADARS® System Survey of Non-Medical Use of Prescription Drugs Program: 2nd quarter 2017, 4th quarter 2017

b) Germany:

i. RADARS® System EUROPAD Program: 4th quarter 2014 – 4th quarter 2017

ii. RADARS® System GTNet Program: 1st quarter 2012 – 2nd quarter 2017

iii. RADARS® System Survey of Non-Medical Use of Prescription Drugs Program: 4th quarter 2017

c) Italy:

i. RADARS® System EUROPAD Program: 4th quarter 2014 – 4th quarter 2017

ii. RADARS® System GTNet Program: 1st quarter 2012 – 2nd quarter 2017

iii. RADARS® System Survey of Non-Medical Use of Prescription Drugs Program: 2nd quarter 2017, 4th quarter 2017

d) United States:

i. RADARS® System Treatment Center Programs Combined: 3rd quarter 2017 – 4th quarter 2017

ii. RADARS® System Survey of Non-Medical Use of Prescription Drugs Program: 3rd quarter 2016, 1st quarter 2017, 3rd quarter 2017

iii. RADARS® System Web Monitoring Program: 3rd quarter 2017 – 4th quarter 2017

iv. AAPCC's NPDS: 1st quarter 2013 – 4th quarter 2017

1.1.4. Setting

The surveillance population included the entire population enrolled by each data source, as described below.

EUROPAD Program

The surveillance population consisted of individuals seeking treatment for substance use disorders (other than alcohol) at sites that offer treatment for opioid use disorders in France, Germany, and Italy.

Treatment Center Programs Combined

The surveillance population consisted of patients entering treatment for opioid dependence in the United States.

GTNet Program

The surveillance population consisted of exposure cases recorded by participating poison centers in France, Germany, and Italy.

National Poison Data System

The surveillance population consisted of exposure cases recorded by 55 regional poison control centers in all 50 states covering 100% of the total United States population.

Survey of Non-Medical Use of Prescription Drugs Program

The surveillance population consisted of the adult general population *via* an online survey panel company. The sample is stratified by United States Census region and gender, mirroring the distribution of the population in both percentage and gender representation (approximately 50% female, 50% male within each region). The samples from France, Germany and Italy were

stratified by gender and Nomenclature des unités territoriales statistiques (NUTS) 1 level regions.

Web Monitoring Program

The Web Monitoring Program surveillance population consisted of individuals within the United States who post statements related to misuse and abuse on public social media accounts, online blogs, web forums and other internet sites.

1.1.5. Subjects and study size including dropouts

This evaluation was not intended to test a pre-specified statistical hypothesis; therefore a pre-determined sample size was not calculated.

1.1.5.1. Variables and data sources

1.1.5.1.1. Variables

Rates or prevalence estimates of four outcomes (non-medical use, misuse, abuse, and intentional exposures) were calculated separately for pregabalin and each comparator. Indication for all prescription and over-the-counter (OTC) drugs (pregabalin and comparators) cannot be obtained within the RADARS® System programs or NPDS data; therefore, outcomes may include off-label use or prescription drugs obtained through diversion. Medical records were not being accessed in this study. Outcome definitions were as follows:

Non-Medical Use

Non-medical use was described in the RADARS® System Survey of Non-Medical Use of Prescription Drugs Program. In the RADARS® System Survey of Non-Medical Use of Prescription Drugs Program, a non-medical use case was defined as a respondent who endorses "use without a doctor's prescription or for any reason other than what was recommended by their doctor."

Misuse

In the AAPCC's NPDS data, misuse was defined as those cases with a reason for exposure of intentional misuse. The definition for intentional misuse is "an exposure resulting from the intentional improper or incorrect use of a substance other than the pursuit of a psychotropic effect."

In the RADARS® System Survey of Non-Medical Use of Prescription Drugs Program, misuse was defined as those non-medical use cases with a reason of: "to self-treat my pain" or "to treat a medical condition, other than pain".

In the RADARS® System Web Monitoring Program, misuse was defined as "a mention that indicates the improper or incorrect use of a drug for reasons other than the pursuit of a high, psychotropic effect or other psychotropic effect."

Abuse

In the AAPCC's NPDS data, abuse was defined as those cases with a reason for exposure of intentional abuse. The definition for intentional abuse is "an exposure resulting from the intentional improper or incorrect use of a substance where the patient was likely attempting to gain a high, euphoric effect or some other psychotropic effect, including recreational use of a substance for any effect."

In the RADARS® System EUROPAD Program, an abuse case was defined as a survey response endorsing use "to get high" in the past 90 days.

In the RADARS® System Treatment Center Programs Combined, an abuse case was defined as a survey response endorsing use "to get high" in the past month.

In the RADARS® System Survey of Non-Medical Use of Prescription Drugs Program, an abuse case was defined as a survey response endorsing non-medical use of a product with a reason of "for enjoyment/to get high."

In the RADARS® System Web Monitoring Program, abuse was defined as "a mention that indicates the use of a drug to gain a high, euphoric effect or some other psychotropic effect."

Intentional exposures (misuse/abuse/diversion)

Intentional exposures were described in the RADARS® System GTNet Program. In the RADARS® System GTNet Program, intentional exposures were defined as any exposure resulting from the intentional improper or incorrect use of a substance.

1.1.5.1.2. Data sources

American Association of Poison Control Centers' National Poison Data System was used as well as five component data sources of the RADARS® System: EUROPAD Program, GTNet Program, Survey of Non-Medical Use of Prescription Drugs Program, Treatment Center Programs Combined, and Web Monitoring Program. Drug utilization data (estimates for dosage units dispensed and standard units) were obtained from a vendor, IQVIA™ (Danbury, CT) that provides information, services and technology for the healthcare industry, and used to generate rates adjusted for drug utilization. In addition, population data from the United States Census and EUROSTAT were used to generate population based rates.

1.1.6. Limitations of the research methods

IQVIA data were used as an indicator of quarterly drug utilization based upon a sample of data and a proprietary projection algorithm. Each of the RADARS® System programs and NPDS was based on self-reported information which presents a potential bias of ambiguous answers or incomplete data. NPDS and GTNet Program data represented a spontaneous reporting system while the Treatment Centers Combined, EUROPAD Program, and Survey of Non-Medical Use of Prescription Drugs Program data represented a non-probability sampling strategy.

Indication for all prescription and OTC drugs (pregabalin and comparators) cannot be obtained within the RADARS® System programs or NPDS data; therefore, outcomes may include off-

label use or prescription drugs obtained through diversion. This was a limitation common to all surveys. Medical records were not being accessed in this study.

1.1.7. Strengths of the research methods

The RADARS® System and NPDS data were usually available within three months of data capture allowing for near real-time data evaluation. An additional strength is the large catchment area covered; programs cover large areas of each country, and NPDS covers the entire United States. Cases arise from both large metropolitan areas as well as rural populations, thus providing results that are more broadly applicable than those from a smaller geographic region. The joint use of multiple RADARS® System programs and NPDS was a mosaic approach, allowing for the assessment of trends in various populations and in different settings to enhance the generalizability of the data and convergent validity. Comprehensive results from independent programs and data sources evaluate the totality of the evidence and provide better understanding of the trends of interest.

1.1.8. Country-Specific Results

Country-specific results are provided in the subsequent sections.

1.1.8.1. United States

The results in this section are for the United States only.

The Study Report for the United States can be found in Appendix 4

The tables and figures of the results section are available in Appendix 5

1.1.8.1.1. Survey of Non-Medical Use of Prescription Drugs Program

The 3rd quarter 2016 United States survey collected responses from 30,522 adults, and results from these respondents were weighted to represent the behaviors of 246,007,651 adults. The 1st quarter 2017 United States survey collected responses from 30,032 adults, and results from these respondents were weighted to represent the behaviors of 247,773,709 adults. The 3rd quarter 2017 United States survey collected responses from 30,010 adults, and results from these respondents were weighted to represent the behaviors of 249,485,228 adults.

1.1.8.1.1.1. Non-medical use

- During the study period there were substantial variations in the prevalence estimates of lifetime and last 90 day non-medical use of pregabalin, gabapentin, and baclofen relative to opioid comparators.

- In all launches of the survey (periodic surveys in different quarters) the prevalence of lifetime non-medical use of pregabalin was lower than lifetime prevalence of the opioid analgesics comparator group.

- In all launches, lifetime and last 90 day non-medical use of pregabalin was lower than opioid analgesics combined and benzodiazepines.

- Per dosage units dispensed, the rate of last 90 day non-medical use for pregabalin was less than methadone and buprenorphine for all launches.

- Pregabalin last 90 day non-medical use per dosage units dispensed was greater than dosage rates of last 90 day non-medical use for gabapentin, benzodiazepines and tramadol for all launches.

- Rates of pregabalin last 90 day non-medical use per dosage units dispensed were greater than opioid analgesic rates in the 1st quarter of 2017 and the 3rd quarter of 2017 launches.

- More than 25% of respondents to the Non-Medical Use of Prescription Drugs Program survey who non-medically used pregabalin tablets/capsules in their lifetime reported use via inhalation or injection.

1.1.8.1.1.2. Abuse

- During the study period, at least 80% of those reporting pregabalin abuse reported abuse of another comparator drug.

- Past month abuse of pregabalin among individuals entering treatment for opioid use disorders was less prevalent than abuse of all comparators per population, and rates were lower per dosage units dispensed for all comparators except gabapentin.

- Among those who abused pregabalin tablets/capsules, more than 30% reported inhalation use whereas 17.6% reported injection use

1.1.8.1.2. National Poison Data System

There were a total of 113,192 patients for the American Association of Poison Control Centers' National Poison Data System in the 1st Quarter 2013 through the 4th Quarter 2017

Misuse and abuse

- Rates of intentional abuse and misuse were stable per dosage units dispensed.

- Misuse of pregabalin via inhalation was rarely reported (four cases out of 760) and there were no cases of parenteral use reported.

- Inhalation/nasal use (47 cases out of 744) was more common among abuse cases. There were five cases reported that involved the parenteral route of administration.

- There were 47 individuals entering treatment for an opioid use disorder who reported past month abuse of pregabalin; seven reported of use via snorting and two reported use via injection.

1.1.8.1.3. Web Monitoring Program

- Misuse rather than abuse was the reason for use in a greater proportion of posts that involved pregabalin.

1.1.8.1.4. Limitations

The Survey of Non-Medical Use of Prescription Drugs Program survey instrument has undergone updates each launch. In the 3rd quarter of 2016 the survey required an affirmative endorsement of the following item prior to receiving addition questions about pregabalin:

"Have you ever used Pregabalin (e.g. Lyrica®), Gabapentin (Neurontin®, Horizant®, Gralise®, etc.), Baclofen (e.g. Lioresal®, Gablofen®, etc.), or Methocarbamol (e.g. Robaxin®, Robaxin®-750, etc.)?"

This item was removed from the 1st quarter 2017 launch. In the 3rd quarter 2017 launch, the survey randomized the order in which the opioid sections appeared to the survey respondents. This was to reduce the potential for bias due to an order effect. Prior to 3rd quarter 2017, fentanyl appeared first on the survey followed by buprenorphine; starting in 3rd quarter 2017 all opioids had equal chance of appearing first on the survey. These modifications should be considered when interpreting results.

IQVIA data are used as an indicator of quarterly drug utilization based upon a sample of data and a proprietary projection algorithm; hence the methodology is not well understood. Each of the RADARS® System programs was based on self-reported information which presents a potential bias of ambiguous answers or incomplete data. The National Poison Data System data represent a spontaneous reporting system while the Treatment Center Programs Combined data represent a non-probabilistic sampling strategy. The Survey of Non-Medical Use of Prescription Drugs Program utilizes a probability-based quota sampling strategy from a pre-selected subpopulation (ie, those who choose to participate in an online survey panel for modest compensation).

Some comparator drug groups were comprised of larger drug classes (e.g. opioid analgesics, benzodiazepines) whereas the target drug group (pregabalin) and others represent single active pharmaceutical ingredients (e.g. tramadol, gabapentin). This distinction should be considered when making interpretations.

1.1.8.1.5. Interpretation

In United States, estimates of extent of non-medical use, misuse, and abuse of pregabalin varied by launch. It is difficult to determine the extent to which this is due to survey design changes or changes in non-medical use patterns. When accounting for dosage units dispensed, non-medical use of pregabalin was more common than all comparators except for methadone and buprenorphine. Misuse was more likely to be the reason for non-medical use than abuse. Web posts mentioning pregabalin were more likely to discuss misuse than abuse. The majority of those reporting pregabalin abuse reported abuse of another comparator drug.

There were fewer intentional abuse and misuse exposures involving pregabalin reported to poison centers than calls involving each comparator. The rates of intentional abuse and intentional misuse exposures involving pregabalin were lower than all comparators except for

gabapentin. There were fewer endorsements of past month abuse of pregabalin than each comparator among respondents entering opioid treatment programs.

Abuse via routes that require tampering (inhalation or injection) were observed. Of the 47 past month abuse cases in treatment center programs, two reported injection use and seven reported inhalation use. Among 744 intentional abuse exposure cases involving pregabalin, five involved parenteral route of administration, 47 involved inhalation/nasal use.

1.1.8.1.6. Generalizability

Data from the Survey of Non-Medical Use of Prescription Drugs Program was generalizable to the national population due to the weighting scheme. The NPDS System captures all exposures reported to poison centers within the United States. The response region of the Treatment Center Programs Combined limits generalizability and could represent subpopulations of the United States rather than the whole nation.

1.1.8.1.7. Conclusions

Prevalence estimates of non-medical use of pregabalin and the routes of administration among those who use it non-medically have varied across survey launches. It is difficult to distinguish the extent to which this variation is due to survey design changes, as opposed to actual changes in non-medical use. In each launch, the primary reason for non-medical use was misuse and not abuse. This was also evidenced by the distribution of web posts involving pregabalin and by the exposure reason for calls to poison centers.

There were fewer intentional misuse and abuse exposures reported to poison centers than calls involving any of the comparators. The rate of misuse and abuse exposures per dosage units dispensed was lower than all comparators except rates of misuse for gabapentin. Among calls to poison centers, use *via* either the inhalation or parenteral route of administration was observed although less frequent than comparators except baclofen. Past month abuse among individuals seeking treatment for opioid use disorders was less common than for other products. The majority of those individuals reporting pregabalin abuse also reported abuse of another comparator drug.

1.1.8.2. France

The RADARS results in this section are for France only.

The Study Report for France can be found in Appendix 6

The tables and figures of the results section are available in Appendix 7

1.1.8.2.1. Non-medical use

- The national prevalence of last 90 day non-medical use of pregabalin was low: 0.5% in 2nd quarter 2017 and 0.1% in 4th quarter 2017.

- The prevalence of last 90 day non-medical use of pregabalin was similar to gabapentin, methadone, and buprenorphine.

- In 4th quarter 2017, the rate of last 90 day non-medical use of pregabalin adjusted by the standard units sold was similar to the rate for gabapentin and benzodiazepines but much lower than opioid analgesics, tramadol, methadone, or buprenorphine.

- Among those who non-medically used pregabalin in their lifetime, swallowed was the most frequent route of administration for both liquids and tablets/capsules.

- For liquid formulations, the proportions for inhalation and injection increased from 2nd quarter to 4th quarter 2017, though the confidence intervals do overlap.

1.1.8.2.2. Misuse

- In 4th quarter 2017, the prevalence of lifetime misuse of pregabalin (0.4%) was slightly less than the prevalence of lifetime non-medical use for any reason (0.7%).

- Among those who non-medically used pregabalin tablets/capsules, swallowed was the most frequent route of administration (68.1%).

- When compared to other drug groups, the proportion of swallowed cases was lower than the proportion of swallowed for all other comparators except gabapentin. Amongst other tablet/capsule comparators (excluding gabapentin), proportions of swallowed cases were higher, ranging from 80.9% to 95.0%.

- The proportion of swallowed cases for tablet/capsule formulations of gabapentin (18.6%) was lower than the proportion for pregabalin.

1.1.8.2.3. Abuse

- In 4th quarter 2017, the prevalence of lifetime abuse of pregabalin (0.1%) was much less than the prevalence of lifetime non-medical use for any reason (0.7%).

- Proportions of abuse by route of administration for pregabalin were calculated using a low denominator (less than 30). Therefore, estimates could be biased due to the weighting scheme, and interpretations should be considered accordingly.

- Lifetime abuse of pregabalin was associated with lifetime abuse of multiple drugs in 78% to 93 % of respondents.

1.1.8.2.4. EUROPAD program

There were a total of 800 patients for the RADARS® System EUROPAD Program in the 1st Quarter 2015 through 4th Quarter 2017.

Abuse

- The case count for abuse of pregabalin was much lower than other comparators except gabapentin.

- After adjustment for standard units, the rate for abuse of pregabalin was still lower than comparators other than gabapentin.

- Of 7 reported abuse cases, 5 indicated chewing as the route of administration for pregabalin.

1.1.8.2.5. GTNet program

There were a total of 213 patients for the RADARS® System GTNet Program in the 1st Quarter 2012 through 2nd Quarter 2017.

Intentional exposure

- There were only 2 cases of intentional exposure to pregabalin detected during the study period, one in 1st quarter of 2012 and one in 3rd quarter 2013.

- Case counts of comparators (excluding gabapentin) were much higher, between eight and 70 times larger.

- While no cases of intentional exposure to pregabalin were detected in the latter 3 years of the study, the calculated slope of the trend over time was not significant.

- Trends in exposures to opioid analgesics and methadone were significantly decreasing; no other comparator was significant.

- For all comparators, most intentional exposures were through an oral route of administration.

1.1.8.2.6. Limitations

IQVIA data were used as an indicator of quarterly drug utilization based upon a sample of data and a proprietary projection algorithm; hence the methodology is not well understood. Each of the RADARS® System programs was based on self-reported information which presents a potential bias of ambiguous answers or incomplete data. GTNet Program data represent a spontaneous reporting system while the EUROPAD Program and Survey of Non-Medical Use of Prescription Drugs Program data represent a non-probability sampling strategy. The GTNet Program and EUROPAD Program do not cover the entire population of France. There were 9 poison centers located in France, of which only 1 is included within the GTNet Program. This center, Centre Antipoison et de Toxicovigilance de Paris covers roughly 19% of the population in France. The EUROPAD Program had 22.1% coverage in France. Some comparator drug groups were comprised of larger drug classes (eg, opioid analgesics, benzodiazepines) whereas the target drug group (pregabalin) and others represent single active pharmaceutical ingredients (e.g. tramadol, gabapentin). This distinction should be considered when making interpretations.

1.1.8.2.7. Interpretation

Relative to other substances with misuse and abuse potential, the frequency of pregabalin cases for the four outcomes (non-medical use, misuse, abuse, and intentional exposure) was low. However, all outcomes had some cases involving pregabalin, even if infrequent. In all programs

and outcomes, oral use was the predominant route of administration for pregabalin, and cases of inhalation and injection were infrequent. The Survey of Non-Medical Use of Prescription Drugs Program provides data on both misuse and abuse; the prevalence of abuse was much lower than the prevalence of misuse, indicating that within the general population, the reasons for non-medical use of pregabalin for medical purposes are more frequent than for enjoyment or a high feeling.

Data over time from two programs suggests overall decreases in exposure and non-medical use of pregabalin, but results are not conclusive. The final program, the EUROPAD Program, did not look at trends over time. In the GTNet Program, the trend over time in intentional exposure to pregabalin was not significant, but only 2 cases were detected. These cases were in the first half of the study period. In the Survey of Non-Medical Use of Prescription Drugs, the last 90 day prevalence of non-medical use of pregabalin was lower in the 4th quarter than in the 2nd quarter, though only two time points are represented in this descriptive trend.

1.1.8.2.8. Generalizability

Data from the Survey of Non-Medical Use of Prescription Drugs Program was generalizable to the national population due to the weighting scheme. Coverages of the GTNet and EUROPAD Programs limit generalizability and may represent subpopulations of France rather than the whole nation.

1.1.8.2.9. Conclusions

The presence of non-medical use, misuse, abuse, and intentional exposure to pregabalin in France was infrequent in three RADARS® System programs and generally lower than opioid analgesic and benzodiazepine comparators. Even when rates were adjusted for standard units sold, rates of the outcomes for pregabalin were generally lower than comparators; however, in some cases, standard units adjusted rates for pregabalin were similar to other molecules, such as methadone or buprenorphine. The predominant route of administration for pregabalin was the oral route. In one program with comparable data, the frequency of abuse was much lower than that of misuse.

1.1.8.3. Germany

The RADARS results in this section are for Germany only.

The Study Report for Germany can be found in Appendix 8

The tables and figures of the results section are available in Appendix 9

1.1.8.3.1. Non-Medical Use

- In the 4th quarter of 2017, it was estimated that 711.893 of every 100,000 adults non-medically used pregabalin in the last 90 days in Germany. This was higher than reported non-medical use of gabapentin, benzodiazepines, tramadol, baclofen, methadone, or buprenorphine. However, it was lower than non-medical use of opioid analgesics.

- Relative to the standard units in 4th quarter 2017, there was an estimated 476.764 adults reporting non-medical use of pregabalin NMU for every 100,000 standard units sold. This value was greater than benzodiazepines. The rate was similar to gabapentin and tramadol. It was lower than opioid analgesics, baclofen, methadone, and buprenorphine.

1.1.8.3.2. Misuse

- In the 4th quarter 2017, the prevalence of lifetime misuse of pregabalin was 2.0%. This was greater than the prevalence for gabapentin, benzodiazepines, tramadol, baclofen, methadone, and buprenorphine.

- The prevalence of lifetime misuse of pregabalin was lower than the prevalence of misuse of opioid analgesics.

1.1.8.3.3. Abuse

- In the 4th quarter 2017, the prevalence of lifetime abuse of pregabalin (0.2%) was much less than the prevalence of lifetime misuse (2.0%).

- The prevalence of pregabalin abuse was lower than abuse of opioid analgesics, benzodiazepines, and buprenorphine. It was similar to tramadol and methadone and greater than gabapentin and baclofen.

- Of those reporting abuse of pregabalin, 80 % also reported lifetime abuse of a comparator drug.

- There were fewer respondents who endorsed pregabalin (17) than endorsed abuse of gabapentin (35), benzodiazepines (127), opioid analgesics (81), tramadol (19), methadone (115), and buprenorphine (40).

1.1.8.3.4. Intentional Exposure

- The average quarterly rate of intentional exposures involving pregabalin per 100,000 persons was 0.029. This was greater than gabapentin and tramadol; similar to methadone and buprenorphine, and lower than benzodiazepines and opioid analgesics.

- Per 100,000 standard units sold, the rate of intentional exposures involving pregabalin (0.030) was greater than gabapentin and tramadol, and similar to opioid analgesics. The pregabalin rate was lower than buprenorphine, benzodiazepines, and methadone.

- On average, pregabalin population rates increased by 10.2% each quarter during the study period. Drug utilization rates increased 7.8% per quarter, on average.

1.1.8.3.5. Limitations

IQVIA data were used as an indicator of quarterly drug utilization based upon a sample of data and a proprietary projection algorithm; hence the methodology is not well understood. Each of

the RADARS® System programs was based on self-reported information which presents a potential bias of ambiguous answers or incomplete data. The Survey of Non-Medical Use of Prescription Drugs Program utilizes a probability-based quota sampling strategy from a pre-selected subpopulation (i.e. those who choose to participate in an online survey panel for modest compensation).

The EUROPAD Program utilizes a non-probabilistic convenience sampling strategy comprised of centers in Essen, Oberhausen, and Muelheim an der Ruhr. Coverage is determined by the location of the treatment center. Approximately 1.2% of the population within Germany is covered. Because a small percentage of the population is covered and one treatment facility was represented from each region, results may not be generalizable to the entire population and rates are underestimates of the extent of abuse among individuals entering treatment facilities within the coverage area.

The GTNet Program data represent a spontaneous reporting system. Participating poison centers cover the federal states of Bremen, Hamburg, Niedersachsen, and Schleswig-Holstein in Germany; approximately 18 % of the population. Given the limited coverage results may not be generalizable to the entire population.

Some comparator drug groups were comprised of larger drug classes (e.g. opioid analgesics, benzodiazepines) whereas the target drug group (pregabalin) and others represent single active pharmaceutical ingredients (e.g. tramadol, gabapentin). This distinction should be considered when making interpretations between comparators.

1.1.8.3.6. Interpretation

In Germany, the extent of non-medical use and misuse of pregabalin was higher than comparator substances with the exception of opioid analgesics. When accounting for standard units sold, non-medical use of pregabalin was less frequent than comparator substances except for tramadol and benzodiazepines. Abuse of gabapentin was relatively rare, particularly in contrast to opioid analgesics and benzodiazepines. Use of pregabalin *via* inhalation or injection (both requiring tampering) was rare but present in all data sources. Intentional exposures involving pregabalin increased per population and per dosage units dispensed between January 2011 and June 2017.

1.1.8.3.7. Generalizability

Data from the Survey of Non-Medical Use of Prescription Drugs Program was generalizable to the national population due to the weighting scheme and sampling techniques. Data from the GTNet Program was generalizable due to the coverage of the German population. Geographic coverage of the EUROPAD Program limits generalizability, and data may represent subpopulations of Germany rather than the whole nation.

1.1.8.3.8. Conclusions

Non-medical use and misuse of pregabalin in Germany was more common than non-medical use of some prescription medications (gabapentin, benzodiazepines, tramadol, baclofen, methadone, and buprenorphine). Non-medical use of pregabalin was less common than non-medical use of opioid analgesics. Non-medical use of pregabalin was less than comparator substances except for tramadol and benzodiazepines when adjusting for standard units sold. Abuse of pregabalin

and use via inhalation or injection was rare relative to other medications but cases were observed. Intentional exposures involving pregabalin were less common than exposures involving benzodiazepines or opioid analgesics. However, per quarter, intentional exposures were increasing, and these increases were greater than all comparators per population and per standard units sold.

1.1.8.4. Italy

The RADARS results in this section are for Italy only.

The Study Report for Italy can be found in Appendix 10

The tables and figures of the results section are available in Appendix 11

1.1.8.4.1. Non-medical use

- The national prevalence of last 90 day non-medical use of pregabalin of was low: 0.3% in 2nd quarter 2017 and 0.1% in the 4th quarter 2017.
- The prevalence of last 90 day non-medical use of pregabalin was similar to other single molecule comparator groups: gabapentin, tramadol, baclofen, methadone, and buprenorphine.
- In the 4th quarter 2017, the rate of last 90 day non-medical use of pregabalin adjusted by the standard units sold was similar to the rate for gabapentin and benzodiazepines, but much lower than opioid analgesics, tramadol, or buprenorphine.
- Among those who non-medically used pregabalin in their lifetime, swallowed was the most frequent route of administration for both tablets/capsules.
- For tablet/capsule formulations, the proportion for swallowed decreases from 2nd quarter to 4th quarter while the proportion for chewed and then swallowed increased.

1.1.8.4.2. Misuse

- In the 4th quarter 2017, the prevalence of lifetime misuse of pregabalin (0.9%) was slightly less than the prevalence of any lifetime non-medical use (1.0%).
- Among those who non-medically used pregabalin tablets/capsules, swallowed was the most frequent route of administration (70.9%). However, the proportion of those who chewed and then swallowed was also notable (36.6%).
- Proportions of injection or inhalation were low (5.3% for both).

1.1.8.4.3. Abuse

- In the 4th quarter 2017, the prevalence of lifetime abuse of pregabalin (0.1%) was much less than the prevalence of lifetime non-medical use of any opioid (1.6%).

- Lifetime abuse of comparator along with lifetime abuse of pregabalin was reported by 57% in the 2nd quarter 2017 and 86% in the 4th quarter 2017.

- The case count for abuse of pregabalin was much lower than other comparators except gabapentin; only a single case of each was observed from 2015 to 2017. Comparatively, there were 11 cases involving tramadol and 18 involving buprenorphine. Heroin was involved in 128 cases and had the highest case count.

1.1.8.4.4. Intentional exposure

- There were 38 cases of intentional exposure to pregabalin detected during the study period.

- The case count for gabapentin is much smaller (n=14) and is similar to the case count for buprenorphine (n=41).

- A total of 38 cases of intentional exposure to pregabalin indicated a route of administration, and all of these cases were orally administered.

- Trends in rates for exposures to opioid analgesics, benzodiazepines, methadone and buprenorphine were significantly decreasing; trends in pregabalin and gabapentin were not significant (Table 27). These trend results were generally observed for both population-adjustment and standard units adjustment.

1.1.8.4.5. Limitations

IQVIA data were used as an indicator of quarterly drug utilization based upon a sample of data and a proprietary projection algorithm; hence the methodology was not well understood. Each of the RADARS® System programs was based on self-reported information which presents a potential bias of ambiguous answers or incomplete data. The Survey of Non-Medical Use of Prescription Drugs Program utilizes a probability-based quota sampling strategy from a pre-selected subpopulation (ie, those who choose to participate in an online survey panel for modest compensation).

The EUROPAD Program utilizes a non-probabilistic convenience sampling strategy currently comprised of centers in Puglia, Italy. Coverage was determined by the location of the treatment center. Approximately 7.0% of the population within Italy is covered. Because a small percentage of the population was covered results may not be generalizable to the entire population and rates may be underestimates of the extent of abuse among individuals entering treatment facilities within the coverage area.

The GTNet Program data represent a spontaneous reporting system. The participating poison centre (located in Milan) covers all regions within Italy but only takes approximately 67.5% of the total calls from the population. Given the limited coverage, results may not be generalizable to the entire population.

Some comparator drug groups are comprised of larger drug classes (e.g. opioid analgesics, benzodiazepines) whereas the target drug group (pregabalin) and others represent single active

pharmaceutical ingredients (e.g. tramadol, gabapentin). This distinction should be considered when making interpretations between comparators.

1.1.8.4.6. Interpretation

Relative to other substances with misuse and abuse potential, the frequency of pregabalin cases for the four outcomes (non-medical use, misuse, abuse, and intentional exposure) was low. However, all outcomes had some cases involving pregabalin, even if infrequent. In all programs and outcomes, oral use was the predominant route of administration for pregabalin, and cases of inhalation and injection were infrequent. The Survey of Non-Medical Use of Prescription Drugs Program provides data on both misuse and abuse; the prevalence of abuse was much lower than the prevalence of misuse, indicating that within the general population, the reasons for non-medical use of pregabalin for medical purposes were more frequent than for enjoyment or a high feeling. Trend analysis from two programs, the GTNet Program and Survey of Non-Medical Use of Prescription Drugs Program, were inconclusive.

1.1.8.4.7. Generalizability

Data from the Survey of Non-Medical Use of Prescription Drugs Program was generalizable to the national population due to the weighting scheme. Data from the GTNet Program was generalizable due to the coverage of 100% of the Italian population. Geographic coverage of the EUROPAD Program limits generalizability, and data may represent subpopulations of Italy rather than the whole nation.

1.1.8.5. Conclusions

The presence of non-medical use, misuse, abuse, and intentional exposure to pregabalin in Italy was infrequent in three RADARS® System programs and generally lower than opioid analgesic and benzodiazepine comparators. Even when rates were adjusted for standard units sold, rates of the outcomes for pregabalin were generally lower than comparators. The predominant route of administration for pregabalin was the oral route. In one program with comparable data, the frequency of abuse was much lower than that of misuse.

1.1.9. Overall RADARS® Conclusion

In summary, the 2018 RADARS® data showed that the rate of abuse of pregabalin was low and the pattern of reported pregabalin abuse varied by country. For the study period, the rate of abuse was highest in Germany, followed by the US, then France and Italy. Opioid analgesics were the most abused drugs in all countries, followed in decreasing order by buprenorphine, methadone, benzodiazepines, and other drugs that were studied. Pregabalin was rarely abused alone; the majority of patients reporting pregabalin abuse also reported abuse of another comparator drug. These data demonstrate low rates of abuse of pregabalin and rarely, sole abuse of pregabalin.

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[i] Bossard JB, Ponte C, Dupouy J, et al. Disproportionality analysis for the assessment of abuse and dependence potential of pregabalin in the French pharmacovigilance database. Clin Drug Invest 2016; 36(9):735-42.