

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213426Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 2, 2021
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 213426
Product Name and Strength:	Seglantis (celecoxib and tramadol hydrochloride) tablet, 44 mg and 56 mg
Applicant/Sponsor Name:	Esteve Pharmaceuticals, SA
OSE RCM #:	2019-1058-3
DMEPA 1 Safety Evaluator:	Cameron Clark, PharmD
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on August 25, 2021 for Seglantis. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container labels and carton labeling for Seglantis (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Clark, C. Label and Labeling Review for Seglantis (NDA 213426). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 AUG 17. RCM No.: 2019-1058-2.

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: August 30, 2021

To: Jaimin Patel
Regulatory Project Manager
**Division of Anesthesiology, Addiction Medicine, and Pain
Medicine (DAAP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA, CPH
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
L. Sheneé Toombs, PharmD, CPH
Senior Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: (Medication Guide (MG))

Drug Name (established name): TRADENAME (celecoxib and tramadol hydrochloride)

Dosage Form and Route: tablets, for oral use, C-IV

Application Type/Number, Supplement Number: NDA 213426

Applicant: Esteve

1 INTRODUCTION

On April 16, 2021, Esteve submitted for the Agency's review a resubmission of their New Drug Application (NDA) 213426 for TRADENAME (celecoxib and tramadol hydrochloride) tablets. The original application received a Complete Response (CR) letter on June 15, 2020. This resubmission provides responses to the questions in the CR letter along with revised labeling. The proposed indication is for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) on August 16, 2021 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TRADENAME (celecoxib and tramadol hydrochloride) tablets.

2 MATERIAL REVIEWED

- Draft TRADENAME (celecoxib and tramadol hydrochloride) tablets MG received on April 16, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 16, 2021.
- Draft TRADENAME (celecoxib and tramadol hydrochloride) tablets Prescribing Information (PI) received on April 16, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 16, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 24, 2021

To: Ning Hu, Clinical Reviewer
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Jaimin Patel, Regulatory Project Manager, DAAP

Lisa Basham, Associate Director for Labeling, DAAP

From: L. Sheneé Toombs, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRADENAME (celecoxib and tramadol hydrochloride) tablets, for oral use, C-IV

NDA: NDA 213426

In response to DAAP's consult request dated June 16, 2021, OPDP has reviewed the proposed product labeling (PI), and carton and container labeling for the original NDA/BLA submission for TRADENAME (celecoxib and tramadol hydrochloride) tablets, for oral use, C-IV.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DAAP on August 5, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on July 16, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Sheneé Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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LATOYA S TOOMBS
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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 17, 2021
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 213426
Product Name and Strength:	Seglantis (celecoxib and tramadol hydrochloride) tablet, 44 mg and 56 mg
Applicant/Sponsor Name:	Esteve Pharmaceuticals, SA
OSE RCM #:	2019-1058-2
DMEPA Safety Evaluator:	Cameron Clark, PharmD
DMEPA Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

As part of their Class 2 Resubmission, Esteve re-submitted the container labels, carton labeling, and prescribing information (PI) received on July 16, 2021 for Seglantis. The labeling included recommendations from our previous label and labeling reviews.^{a,b} On June 1, 2021, in response to a Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP) Information Request (IR), Esteve submitted a revised Prescribing Information that was updated to include the safety language update for DRESS and fetal toxicity in line with the recent changes to the listed drug, Celebrex. Thus, DAAP requested that we review the labels and labeling to determine if they are acceptable from a medication error perspective.

2 REGULATORY HISTORY

Esteve originally submitted NDA 213426 on May 15, 2019. We reviewed the container labels, carton labeling, and prescribing information. Our recommendations were conveyed to Esteve and they implemented all of our recommendations. However, on June 15, 2020, NDA 313426

^a Johnson, C. Label and Labeling Review for celecoxib and tramadol hydrochloride (NDA 213426). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 10. RCM No.: 2019-1058.

^b Johnson, C. Label and Labeling Review for celecoxib and tramadol hydrochloride (NDA 213426). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 DEC 13. RCM No.: 2019-1058-1.

received a Complete Response (CR) letter due to a facility inspection deficiency. On April 16, 2021, Esteve submitted their response to the deficiency in the CR letter as a class 2 resubmission. In their resubmission, Esteve submitted the same container labels and carton labeling that we had previously found to be acceptable from a medication error perspective with a minor revision of the statement “manufactured by” to “manufactured for” on the side panel of all labels and labeling.

On July 13, 2021, we found the proposed proprietary name, Seglentis, to be conditionally acceptable. Therefore, on July 16, 2021, Esteve, submitted a revised 90-count container label and carton labeling to replace the “TRADENAME” placeholder, with the proprietary name “Seglentis”. Esteve made additional changes to the container label and carton labeling which include:

- labels background/graphical layout change
- updated National Drug Code (NDC) for the new distributor
- updated manufacturer/packager entity name/location
- addition of new serialization (product identifier) labeling
- minor wording changes

3 CONCLUSION

The revised container label and carton labeling are unacceptable from a medication error perspective. The revised labeling does not include the format of the expiration date. Furthermore, the submission did not include the 30-count container label and carton labeling for our review.

4 RECOMMENDATIONS FOR ESTEVE PHARMACEUTICALS, SA

We recommend the following be implemented prior to approval of this NDA:

- A. As currently presented, the format for the expiration date is not defined on the 90-count container label or carton labeling. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a forward slash or a hyphen be used to separate the portions of the expiration date. Furthermore, include the format for the expiration date for the 30-count container label and carton labeling and submit the labeling for our review.
- B. As currently presented, the numbers “712268-02” and letters/numbers “SEG-US-0001” are located in close proximity to the lot number statement. These numbers/letters may be mistaken as the lot number. We recommend relocating these numbers/letters to a

different location on the container label so that they are not mistaken as the lot number.^c

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^c Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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MEMORANDUM TO FILE

Date of Consult: May 13, 2021

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through Tamara Johnson, M.D., MS,
Team Leader, Maternal Health, DPMH

To: Division of Anesthesiology, Addiction Medicine, and Pain (DAAP)

NDA Number: 213426

Drug: Tradename (Tramadol 44mg/ Celecoxib 56mg)

Applicant: Esteve Pharmaceuticals

Indication: The management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

BACKGROUND

The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) submitted a consult request to the Division of Pediatric and Maternal Health (DPMH) on May 13, 2021, requesting assistance in reviewing the labeling for compliance with the Pregnancy and Lactation Labeling Rule (PLLR) format and the summary of clinical published literature submitted by the applicant. This is a 2nd cycle resubmission for this new drug application via 505(b)2 pathway. The listed products relied upon are: Ultram, Ultram ER, and Celebrex – NDAs 020281, 021692, and 020998. DPMH completed an initial PLLR labeling review of NDA 213426 (by C. Mastroyannis, MD, dated February 20, 2020).

DPMH has conducted relevant reviews:

- July 27, 2020 - Tramadol oral solution, NDA 214044, labeling review by Jane Liedtka, MD, Reference ID: 4646291.¹
- October 13, 2015 - Labeling for the Ultram was reviewed for PLLR conversion, NDA 20281, by Miriam Dinatale, DO, Reference ID: 3829377

¹ DPMH did not rely on data in the Tramadol oral solution NDA or the agency's finding of safety and effectiveness for Tramadol oral solution to support labeling sections of this Tradename (Tramadol 44mg/ Celecoxib 56mg) NDA 213426. Rather, the cross-reference to the Tramadol oral solution consult is included to avoid duplicating background information relevant to this class of products.

- February 13, 2017 – Tramadol, Revisions to the Lactation subsection 8.2, TSI 1418, by Miriam Dinatale, DO, Reference ID: 4055175²

May 7, 2018 - Amlodipine Besylate and Celecoxib fixed dose, NDA 210045, labeling review by Christos Mastroyannis, MD, Reference ID: 4258383³

REVIEW

DPMH has reviewed the submission of April 16, 2021, by the applicant referring to the review of the relevant nonclinical and clinical published literature. The applicant has concluded that no new information or safety concerns have been identified that are not already included in the labeling regarding pregnancy, lactation and females and males of reproductive potential. This reviewer agrees with the applicant's conclusions. In addition, DPMH has performed a literature search in PubMed, Embase, the TERIS and Reprotox databases, and GG Briggs and RK Freeman in Drugs in Pregnancy and Lactation, and Hale TW Medications and Mother's Milk, for tramadol or celecoxib use in Pregnancy and Lactation and for any additional scientific publications on use of tramadol or celecoxib in pregnancy or lactation, or on adverse effects on fertility from February 20, 2020 (date of DPMH's initial NDA 213426 review) to present. No findings regarding any new safety concerns have been identified.

CONCLUSION

No additional comments/edits to the labeling are recommended, other than those initial recommendations provided in the February 20, 2020 DPMH review. DPMH will participate in the labeling discussions when they are scheduled. This memorandum will close out the consult request.

² DPMH did not rely on data in the Tramadol NDA or the agency's finding of safety and effectiveness for Tramadol to support labeling sections of this Tradename (Tramadol 44mg/ Celecoxib 56mg) NDA 213426. Rather, the cross-reference to the Tramadol consult is included to avoid duplicating background information relevant to this class of products

³ DPMH did not rely on data in the Amlodipine Besylate and Celecoxib fixed dose, NDA or the agency's finding of safety and effectiveness for Amlodipine Besylate and Celecoxib fixed dose NDA to support labeling sections of this Tradename (Tramadol 44mg/ Celecoxib 56mg) NDA 213426. Rather, the cross-reference to the Amlodipine Besylate and Celecoxib fixed dose, NDA 210045 consult is included to avoid duplicating background information relevant to this class of products

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/s/

CHRISTOS MASTROYANNIS
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology**

Integrated Review of Epidemiology and Drug Utilization

Date: January 31, 2020

Reviewers: Saranrat Wittayanukorn, PhD
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Ibrahim Ibrahim, Pharm D, MPH
Drug Use Team
Division of Epidemiology II

Quality Control: Sara Karami, PhD
Division of Epidemiology I

Secondary Reviewers: Rose Radin, PhD, MPH
Drug Abuse Team Lead
Rajdeep Gill, PharmD
Drug Utilization Team Lead
Division of Epidemiology II

Tertiary Reviewers: Tamra Meyer, PhD, MPH
Deputy Division Director (Acting)
Division of Epidemiology II
LCDR Grace Chai, PharmD
Associate Director for Special Initiatives (Acting)
Office of Surveillance and Epidemiology

Subject: Review of Recent Data on Use, Misuse, and Abuse of Tramadol and Comparator Drugs

Drug Name(s): Tramadol 44 milligram and Celecoxib 56 milligram tablet

Application Type/Number: NDA #213426

Applicant/sponsor: Esteve Pharmaceuticals

OSE RCM #: 2019-1152

**This document contains proprietary drug use data and data obtained by FDA under contracts and from CDC and AAPCC. The drug use data/information, CDC and AAPCC data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

All product codes must be redacted for public release**

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ABBREVIATIONS

AAPCC: American Association of Poison Control Centers
AD: Abuse-Deterrent
API: Active Pharmaceutical Ingredient
ASI-MV: Addiction Severity Index-Multimedia Version
CDC: Centers for Disease Control and Prevention
CSA: Controlled Substances Act
DAAP: Division of Anesthesiology, Addiction Medicine, and Pain Medicine
DEA: Drug Enforcement Administration
DIM: Drug-Involved Mortality
ED: Emergency Department
EUTRx: Total number of dispensed tablets, capsules, and so forth
ER: Extended-release
FDA: U.S. Food and Drug Administration
ICD-10: International Statistical Classification of Diseases and Related Health Problems-10th Revision
IR: Immediate-release
NAVIPPRO: National Addictions Vigilance Intervention and Prevention Program
NDA: New Drug Application
NFLIS: National Forensic Laboratory Information System
NPDS: National Poison Data System
NEISS-CADES: National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance
NSAID: Non-steroidal Anti-inflammatory Drug
NSDUH: National Survey on Drug Use and Health
NVSS-M: National Vital Statistics System-Mortality
MG: Milligram
OA: Opioid Analgesic
OSE: Office of Surveillance and Epidemiology
OTP: Opioid Treatment Program
PCC: Poison Control Center
PMR: Postmarket Requirement
RADARS: Researched Abuse, Diversion, and Addiction-Related Surveillance
RMPDC: Rocky Mountain Poison and Drug Center
SAMHSA: Substance Abuse and Mental Health Services Administration
SE: Single-entity
SKIP: Survey of Key Informants' Patients
SUD: Substance Use Disorders
TCP: Treatment Center Program
TRxs: Total number of prescriptions dispensed
U.S.: United States

EXECUTIVE SUMMARY

The Division of Anesthesiology, Addiction Medicine, and Pain Medicine consulted the Division of Epidemiology II to provide current information on tramadol misuse, abuse, associated adverse events, and utilization patterns for consideration at the Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee on January 15, 2020. The committees will discuss the New Drug Application of 213426, an immediate-release formulation tablet containing a fixed-dose combination of tramadol 44 milligram and celecoxib 56 milligram. We provide recent information related to opioid misuse/abuse, adverse events, and overdose deaths in the general population, among people seeking medical treatment for adverse effects of non-medical use, and among people entering or being assessed for treatment for opioid use disorder in the United States (U.S.). Recent drug utilization data come from U.S. outpatient retail pharmacies and office-based physician surveys.

Drug use

Tramadol-containing products (single-entity (SE) tramadol immediate-release (IR) and extended-release (ER) formulations and combination tramadol/acetaminophen IR formulations) accounted for 19% of the estimated total 169 million opioid analgesic (OA) prescriptions dispensed from retail pharmacies in 2018. Although the estimated absolute number of tramadol-containing prescriptions have declined, there was an apparent increase in SE tramadol as a percentage of the total OA prescriptions from 14% in 2012 to 19% in 2018. Single-entity tramadol (IR and ER) was the second most commonly dispensed opioid analgesic after prescriptions dispensed for hydrocodone/acetaminophen from U.S. retail pharmacies with approximately 32 million prescriptions or 2.2 billion tablets dispensed in 2018. Based on the number of prescriptions dispensed, SE tramadol IR was the most utilized product among tramadol-containing products, representing an estimated 95% of total prescriptions dispensed throughout the study period. Tramadol-containing product utilization increased from 2009 through 2014 by 64%, then declined by an estimated 22% from 2015 through 2018. The largest proportion of tramadol prescriptions were dispensed to patients over the age of 40 years. Primary care physicians prescribed the majority of the prescriptions dispensed. According to the U.S. office-based physician surveys, tramadol was mainly mentioned in association with the management of diseases of the musculoskeletal system and connective tissue, such as back pain.

Misuse, abuse, and related outcomes

Of the OAs we examined, hydrocodone and oxycodone were most commonly misused/abused across data sources, while tramadol's position relative to codeine and morphine depended on the data source. Most data sources suggested a decrease in misuse/abuse of tramadol and comparator OAs during the study period. In contrast, data from people presenting for opioid or substance use disorder treatment showed mixed results. Specifically, data from National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO) Addiction Severity Index-Multimedia Version (ASI-MV), 2013-2018, showed a decline in past-month abuse of tramadol and comparator OAs. However, data from Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System Treatment Center Program (TCP), 2014-2018, showed an increase in past-month abuse of tramadol from 5.1% to 7.8% of surveys, while comparator OAs declined.

It is unclear why RADARS TCP showed this increasing trend, and more research and confirmation are needed. One hypothesis is that data from RADARS TCP are from people with more advanced opioid use disorder, compared with NAVIPPRO which has a more heterogeneous population, including patients being assessed or treated for non-opioid substance use disorders. Tramadol may be relatively easier to obtain since there are fewer restrictions on its prescribing relative to schedule II opioids, and

tramadol may be trending toward an increasing percentage of total opioid analgesic outpatient prescriptions, as suggested by the results of the drug utilization analysis. However, the available data are insufficient to draw a conclusion.

Regarding related outcomes, there were more than 127,000 ED visits annually in 2016-2017 attributed to non-medical use of any OAs. Of the OAs we examined, ED visits involving non-medical use of tramadol as a percent of ED visits involving any OAs, were fewer than that for hydrocodone and oxycodone. In addition, mortality data from the Drug-involved Mortality database, 2011-2017, suggested that tramadol-involved overdose deaths increased. Overdose deaths involving morphine and oxycodone also increased over the study period, with a decline in the most recent year of data (2017), while overdose deaths involving hydrocodone decreased slightly over the study period. It was not clear whether the observed increase in overdose deaths involving tramadol is due to changes in use and abuse, or to other factors. For example, improved documentation of death certificates or increased surveillance after tramadol was placed in Schedule IV in 2014 may have driven the increase in death certificates mentioning tramadol involved in the overdose. Another source of uncertainty is that the overdose deaths involving tramadol may have involved multiple opioids, including fentanyl.

In conclusion, more than 95% of tramadol prescriptions were SE tramadol IR. Tramadol was mainly mentioned as being used for the management of diseases of the musculoskeletal system and connective tissue, such as back pain. The number of dispensed SE tramadol prescriptions gradually declined after the rescheduling in 2014. However, there was an increasing trend in tramadol as a percentage of the total opioid analgesic prescriptions in recent years. In addition, results from national surveys and poison center calls suggest that abuse and misuse of tramadol and comparator opioid analgesics have been declining among the general U.S. population in recent years. Tramadol was less frequently implicated in prescription opioid misuse, abuse, and related outcomes than were hydrocodone and oxycodone, while results were mixed for tramadol's position relative to codeine and morphine. Notably, tramadol abuse may have increased among people with opioid use disorder. Also, tramadol-involved overdose deaths increased from 2011 to 2017. It is uncertain whether the observed increase is due to changes in use and abuse, increased surveillance, improved documentation, or other factors.

APPEARS THIS WAY ON ORIGINAL

1 INTRODUCTION

The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) consulted the Division of Epidemiology II (DEPI) to provide current information on tramadol misuse, abuse, associated adverse events, and utilization patterns for consideration at the Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee on January 15, 2020. The committees will discuss the New Drug Application (NDA) of 213426, for a fixed-dose combination product containing tramadol 44 milligram (mg) and celecoxib 56 mg in tablet form.

Opioids were involved with 47,600 overdose deaths in the U.S. in 2017, 35% of which involved a prescription opioid and 1.9% of which involved tramadol.¹⁻³ In addition, the 2018 annual report from the U.S. National Forensic Laboratory Information System (NFLIS) indicates that tramadol was among the 25 drugs most frequently identified from drug seizures in 2018⁴, representing an increase from 5,344 in 2015⁵ to 8,850 reports in 2018.⁴ According to the World Health Organization, misuse, abuse, and dependence of tramadol, mostly obtained via diversion, may be increasing in Africa and the Middle East.⁶

Given the persistent contribution of prescription opioid analgesics (OAs) to the burden of opioid-related morbidity and mortality in the US, FDA aims to evaluate the impact of new opioid drug approval on public health at the time of approval. This review is designed to provide advisory committee members with a basis for considerations regarding the public health impact of new opioid drug approvals on the population at-large. The review includes current information on the scope and patterns of tramadol misuse/abuse, associated harms, and utilization patterns in the U.S., including data on other selected opioid-containing products for context.

1.1 REGULATORY HISTORY

Tramadol, an opioid agonist, was approved on March 3, 1995 under NDA 20281. Tramadol is indicated for the management of pain in adults that is severe enough to require an OA and for which alternative treatments are inadequate. The Drug Enforcement Administration (DEA) assigned tramadol to a Schedule IV controlled substance under the Controlled Substances Act in July 2014, with a low potential for abuse and low risk of dependence, relative to substances in Schedule III. The initial treatment with tramadol for adults not requiring rapid onset of analgesic effect is 25 mg per day. After titration, tramadol 50 to 100 mg can be administered as needed for pain relief every four to six hours, not to exceed 400 mg per day. Tramadol is available as a single-entity (SE) medication or in combination with acetaminophen. Tramadol products are available in immediate-release (IR) tablet and capsule, and extended-release (ER) tablet formulations, marketed by various manufacturers.

Celecoxib, a nonsteroidal anti-inflammatory drug (NSAID) was approved on December 31, 1998, and it is indicated for management of pain, including osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis in patients 2 years and older, ankylosing spondylitis, and primary dysmenorrhea. Celecoxib is available as a single-ingredient medication in immediate-release tablet and capsule formulations, marketed by various manufacturers.

Esteve submitted a NDA under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for an IR formulation tablet containing a fixed-dose combination of racemic tramadol hydrochloride and celecoxib. The product is manufactured as a cocrystal of the two active pharmaceutical ingredients (APIs), and a 100 mg tablet contains 44 mg of tramadol and 56 mg of celecoxib. The dosing regimen

in adults for tramadol and celecoxib tablets is 200 mg every 12 hours, as needed, for the short-term management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

2 REVIEW METHODS AND MATERIALS

2.1 OVERVIEW AND FRAMEWORK

We examined several data sources to describe the utilization, abuse, misuse, and related adverse outcomes, associated with tramadol and comparator opioid analgesics (OAs) in recent years. These data sources collect information from various populations: the general population, people filling prescriptions in the outpatient retail setting, people seeking medical treatment for adverse effects of non-medical use, and individuals entering or being assessed for substance use disorder (SUD) treatment. We present major features of each data source in **Table 1** and list the opioid molecules we studied in **Table 2**. We provide a more detailed description of each data source and our analytic approach in the sections below. Unless otherwise indicated, we used standard regulatory definitions of misuse and abuse.⁷

Misuse: Intentional use, for therapeutic purposes, of a drug in a way other than prescribed or by an individual for whom it was not prescribed

Abuse: the intentional, non-therapeutic use of a drug product or substance, even once, for its desirable psychological or physiological effects

Table 1. Overview of data sources to assess the current landscape of prescription opioid misuse/abuse

Characteristic assessed	Population and data sources used	Use of data source(s)
Drug utilization	<u>Sales distribution data</u> IQVIA National Sales Perspectives (NSP), 2018	Determine the primary setting of care for utilization of tramadol-containing products
	<u>Prescription data</u> IQVIA National Prescription Audit (NPA) 2009-2018	Estimated number of dispensed prescriptions and units of opioid analgesics in U.S. outpatient retail pharmacies Estimated top 10 prescribers of tramadol-containing products in U.S. outpatient retail pharmacies
	<u>Diagnosis data</u> Syneos Health Research & Insights LLC., Treatment Answer with Pain Panel, 2018	Diagnoses associated with the use of tramadol-containing products based on surveys of a sample of office-based physicians
Scale of misuse/abuse of opioid analgesics	<u>General population</u> National Survey on Drug Use and Health (NSDUH), 2015-2018	Estimated number of individuals in the general U.S. population reporting misuse/abuse of prescription opioids

Characteristic assessed	Population and data sources used	Use of data source(s)
	<u>People seeking treatment for adverse effects of non-medical use</u> National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES), 2016-2017	Estimated number of emergency department (ED) visits and those resulting from non-medical use (including misuse and abuse) of prescription opioid analgesics
Relative frequency of misuse/abuse of tramadol and comparator opioid analgesics	<u>General population</u> NSDUH, 2015-2018	Prevalence of misuse/abuse for tramadol and comparator drugs in general population
	Monitoring the Future (MTF), 2009-2018	
	<u>Calls for advice after non-medical use</u> National Poison Data System (NPDS) exposure calls to Poison Control Centers (PCC)s: - 2009-2018: tramadol - 2014-2018: tramadol and comparator OAs	Drug exposures from calls to PCCs by specific opioids
	<u>People entering or being assessed for treatment for opioid or substance use disorders (OUD/SUD)</u> The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System Treatment Center Program (TCP), 2014-2018 Inflexxion National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™) Addiction Severity Index-Multimedia Version® (ASI-MV®), 2013-2018	Proportion of patients entering or being assessed for treatment for OUD/SUD reporting past thirty-day abuse of specific opioids
Routes of abuse for tramadol and comparator opioid analgesics	<u>Calls for advice after non-medical use</u> NPDS exposure calls to PCC, 2009-2018	Routes of abuse for single-substance exposure calls
	<u>People entering or being assessed for treatment for OUD/SUD</u> RADARS TCP, 2017-2018	Product-specific routes of abuse among people entering or being assessed for SUD treatment RADARS TCP and NAVIPPRO™
	Inflexxion NAVIPPRO™ ASI-MV®, 2017-2018	
Morbidity and mortality involving tramadol and comparator opioid analgesics	<u>People seeking treatment for adverse effects of non-medical use</u> NEISS-CADES, 2016-2017	Assess outcomes such as need for healthcare intervention associated with specific opioids
	<u>Calls for advice after non-medical use</u> NPDS exposure calls to PCCs,	Assess severity of medical outcomes for drug exposures

Characteristic assessed	Population and data sources used	Use of data source(s)
	-2009-2018: tramadol	from calls to PCCs by specific opioids
	<u>General population</u> Drug-involved Mortality (DIM) data for overdose deaths, 2011-2016	Assess overdose deaths associated with specific opioids

Table 2. Tramadol and other selected opioids

Opioid products
Tramadol
Comparator opioid analgesics • Codeine • Hydrocodone • Morphine • Oxycodone

2.2 DRUG UTILIZATION

2.2.1 PRODUCTS INCLUDED

This analysis is focused on utilization of tramadol-containing products which are available as single-entity (SE) IR and ER formulations as well as combination tramadol products (tramadol/acetaminophen) (Table 3 below). For comparison, we examined utilization patterns of the top 20 OAs including all extended-release/long-acting (ER/LA) and immediate-release (IR) formulations primarily utilized in the outpatient retail pharmacy (see Table 1 in Appendix 7.1). We did not include injectable formulations of OAs, opioid-containing medication-assisted therapy (MAT) products and opioid-containing cough/cold products in this drug utilization review.

TABLE 3.

Drug Name	Approval Date	NDA*
Single Ingredient Tramadol Products		
Tramadol Immediate-Release (IR)		
Ultram® Tablet	3/3/1995	20281
Rybix ODT®	5/5/2005 (marketed 5-2010)	21693
Tramadol Extended-Release (ER)		
Ultram ER® Tablet	9/9/2005	21692
Ryzolt ER® Tablet	12/30/2008	21745
Conzip Capsule ER ®	5/7/2010	22370
Tramadol Combination Immediate-Release (IR)		
Ultracet Tablet® (acetaminophen/tramadol HCl)	8/15/2001	21123

*There are multiple FDA approved ANDAs for Ultram, Ultram ER, Conzip and Ultracet. Rybix ODT, Ryzolt and Ultram ER are discontinued, however branded generic products are still in the market. ODT (oral disintegrating tablet), NDA (new drug application), ANDA (abbreviated new drug application)

2.2.2 DATA SOURCES USED

This drug utilization review was conducted using proprietary databases available to the FDA (See **Appendix A1** for full database descriptions).

2.2.2.1 Determining Settings of Care

The primary setting of care for utilization of tramadol-containing products was determined based on sales volume (bottles or packages) from manufacturers in 2018 using the IQVIA National Sales Perspectives™ (NSP) database. The NSP database measures the volume of drug products, both prescription and over-the-counter products sold from manufacturers and distributors into retail and mail-order pharmacies, and non-retail settings such as clinics and hospitals.

2.2.2.2 Prescription Data

The estimated number of prescriptions and units (e.g., tablets, capsules) dispensed from U.S. outpatient retail pharmacies from 2009 through 2018 was determined using data obtained from the IQVIA National Prescription Audit™ (NPA) database. This database was also used to provide the top 10 prescriber specialties based on the estimated number of prescriptions dispensed for tramadol-containing products from U.S. retail pharmacies in 2018. The NPA database measures the rate of drug movement out of retail pharmacies into the hands of consumers via formal prescriptions in the U.S., providing a national level estimate of the drug activity.

2.2.2.3 Office-Based Physician Survey Data

Diagnoses associated with the use of tramadol-containing products as reported by U.S. office-based physician surveys in 2018 was examined using the Syneos Health Research & Insights LLC., TreatmentAnswers™ with Pain Panel database. Diagnoses data are reported as drug use mentions based on International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes with 95% confidence intervals. The survey consists of data from over 3,200 office-based physicians representing 30 specialties across the U.S. that report on all patient activity during one typical workday per month.

2.3 NATIONAL SURVEY ON DRUG USE AND HEALTH (NSDUH)

Data Source

The National Survey on Drug Use and Health (NSDUH) is an annual survey funded by the Substance Abuse and Mental Health Services Administration (SAMHSA) designed to provide nationally-representative estimates of illicit and prescription drug misuse/abuse in the general U.S. population. Strengths of this data source include an in-person survey, and predominantly stable survey design in recent years with the ability to assess temporal changes in drug misuse/abuse in the general U.S. population.

NSDUH uses a multistage probability sample design to provide annual, nationally-representative estimates for non-institutionalized residents of the U.S. who are aged 12 years and above. Population subgroups not covered by the survey include individuals residing within institutional facilities (e.g., jails, nursing homes), as well as those without a permanent address (e.g., homeless individuals). The survey is conducted in a face-to-face manner, and during the year 2018, the interview final response rate was 66.5%, for a total of 67,791 completed interviews.⁸

Starting in 2015, NSDUH has asked about past-year use and misuse/abuse of certain prescription drugs and drug classes. However, separate estimates were not created for the use and misuse of codeine products for 2015 because of concerns that respondents in 2015 might have overreported the use and

non-medical use of codeine products if they confused Tylenol® with codeine 3 or 4. NSDUH made changes to the questionnaire in 2016, and estimates have been produced for the use and misuse of codeine products for 2016 and later.

Definition

NSDUH defines *misuse* of a drug as the following: “use in any way not directed by a doctor, including use without a prescription of one’s own; use in greater amounts, more often, or longer than told.” Since NSDUH’s definition of misuse includes intentional, non-therapeutic use of a drug to obtain a desired psychological or physiological effect (i.e., abuse), this review labels it *misuse/abuse*. NSDUH defines “any use of pain relievers” as any use of pain relievers for any reason, either use of one’s own prescription pain reliever as directed by a physician, or misuse/abuse.

Search Strategy and Analysis

We extracted available data from reports and detailed tables from the 2015-2018 National Survey on Drug Use and Health made publicly available by SAMHSA through their website⁹ that related to past-year misuse/abuse of tramadol and comparator opioid analgesics.¹⁰ We reported national estimates in terms of numbers of individuals, percent of the total population, and percent of past-year any-users.

Appendix B1 provides additional details on tramadol and comparator opioid analgesics.

2.4 AMERICAN ASSOCIATION OF POISON CONTROL CENTERS (AAPCC), NATIONAL POISON DATA SYSTEM (NPDS)

Data Source

The American Association of Poison Control Centers (AAPCC) maintains the National Poison Data System (NPDS), which captures data on calls to U.S. poison control centers (PCCs) on a near real-time basis. As of 2017, the NPDS data came from 55 PCCs and covered the entire U.S. population.¹¹ These PCCs receive calls for exposures to substances through the Poison Help Line 24 hours per day, offer medical advice, and document reported events in the database. PCC healthcare professionals systematically follow-up on reported exposures to document their medical outcome. Quality control measures are used to ensure data accuracy and completeness.

In 2017, there were 2.1 million human exposure calls to PCCs, and 60% were for individuals under the age of 20. Almost 80% of calls related to an unintentional exposure, 19% were for intentional exposures, and the remainder for other reasons. Analgesics, including opioid products, were the most common class of substances involved in human exposures, accounting for 11% of calls (N=283,784).¹¹

Note that exposures do not necessarily represent a poisoning or overdose, as the AAPCC does not completely verify the accuracy of every report made to member center, and some callers are not necessarily experiencing symptoms or side effects when they call. Additional exposures may go unreported to PCCs, and the calls to PCCs represent an unknown proportion of all non-medical use of OAs.¹¹

Definition

- **Intentional Abuse:** “an exposure resulting from the intentional improper or incorrect use 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.”
- **Intentional Misuse:** “an exposure resulting from the intentional improper or incorrect use for reasons other than the pursuit of a psychotropic effect.”

Search parameters used for tramadol and the comparator drugs of interest are summarized below in **Table 4. NPDS Search parameters- tramadol and other selected opioids**

Report name	Case Log (Product Code)
Month/year of query	10/2019
Date range for query (tramadol)	1/1/2009- 12/31/2018
Date range for query (other selected opioids: codeine, hydrocodone, morphine, oxycodone)	1/1/2014- 12/31/2018
Call type	Exposure
Case status	Closed
Species	Human

Data Analysis

To define the search criteria, generic codes and product codes for pharmaceutical preparations containing tramadol, codeine, hydrocodone, morphine, and oxycodone were identified by using MicroMedex® Solutions and the 2019 AAPCC Pharmaceutical and Non-Pharmaceutical Generic Code List – February 2019 version (product codes are included in **Appendix C1**). Data on closed, human exposure calls to tramadol (1/1/2009 – 12/31/2018) were extracted. In addition, we also extracted comparator opioid analgesics (1/1/2014-12/31/2018) to compare trends in recent years among tramadol and comparators. All data were extracted on 10/18/2019. In brief, we included oral solid, oral liquid formulations, or formulation unknown. We also included opioid-containing cough and cold products primarily because, for codeine, we expect those products to comprise a substantial proportion of both dispensing and abuse, as well as of exposures where formulation was unknown. The advantage of including oral liquid OAs and cough-cold products is capturing the cases with exposure to unknown formulation products as part of an API-level analysis. More information on formulation inclusion and exclusion is included in **Appendix C1**. At the time of extraction, AAPCC had completed its standard processes for outcome adjudication and quality control for all these data and had locked the data to ensure reliability. In addition, the search excluded observations that had medical outcome classified as “confirmed non-exposure.”

Analysis of NPDS consisted of five components:

1. Trends
 - a. Trends in exposures by reason of exposure and related medical outcomes by year
 - Exposure calls involving tramadol were extracted for the ten-year period (2009-2018). Data were stratified by reason for exposure (intentional: abuse, misuse, suspected suicide, unknown (intent that is suspected to be intentional but cannot be categorized further); unintentional; adverse reaction; withdrawal; unknown; and other) and severity of related medical outcomes (minor effect, moderate effect, major effect, and death) across years. Variable definitions are included in **Appendix C2**.
2. Reason for exposure by age group
 - a. Exposure calls involving tramadol products were aggregated for the ten-year period. Data were stratified by age group (0-11; 12-17; 18-25; 26-39; 40-64; 65 and older; unknown). Variable definitions are included in **Appendix C2**.

3. Cases of intentional abuse or misuse

We analyzed data from calls involving exposure to tramadol that had been classified as either of two, mutually-exclusive AAPCC categories for *reason for exposure*: “intentional abuse,” or “intentional misuse.” We evaluated the calls using categories defined by AAPCC (variable definitions are included in **Appendix C2**).

a. By co-exposures

- Data on multiple-substance exposures were aggregated for the ten-year period and stratified by co-exposures (prescription opioids, heroin/illicit fentanyl analogue, alcohol, marijuana, and stimulants, including prescription and illicit)

b. By route of use

- Data on exposure calls involving tramadol products were aggregated for the ten-year period and stratified by number of substances involved (single and multiple) and route of use (oral, nasal/inhalation, injection, other, and unknown). In the NPDS data, multiple routes can be reported for a single substance. For these cases, we counted each route mentioned by the caller separately. As a result, the totals for each individual route may exceed the total number of exposures for that product.

c. By severity of medical outcomes for cases with related clinical effects

- Data on exposure calls involving tramadol products were aggregated for the ten-year period and stratified by substance exposures (single and multiple) and medical outcome (“minor effect,” “moderate effect,” “major effect,” and “death”). Variable definitions are included in **Appendix C2**. *Medical outcome* was characterized for the subset of calls with a “Related” clinical effect. NPDS defines “Related” clinical effects as exposures where the following criteria are satisfied: the timing and severity of clinical effects are reasonable for the reported exposure, the clinical effect is consistent with the anticipated substance, and the clinical assessment is made by a physician. Exposures with “Related” clinical effects were identified if any listed clinical effect for a given exposure call involving the drug of interest was designated as “(R)”.

4. Comparative analysis

a. Trends in intentional misuse/abuse exposure calls of tramadol and other selected opioids by year

- Data on exposure calls involving misuse/abuse of tramadol and other selected opioids were aggregated for a recent five-year period (2014-2018). Variable definitions are included in **Appendix C2**.

b. Intentional exposure cases

- Data on exposure calls involving intentional exposure of tramadol and other selected opioids were aggregated for a recent five-year period (2014-2018). Variable definitions are included in **Appendix C2**.

c. Cases of misuse/abuse by route of use

- Data on single-substance exposures to tramadol and other selected opioids were aggregated for the five-year period and stratified by route of use.

5. Map of tramadol misuse/abuse exposure call percentages by State
 - a. Data on exposure calls involving tramadol products in 2018, as well as the subset of misuse/abuse exposure calls of tramadol products were extracted and stratified by States. In addition, we also extracted data on exposure calls involving total human exposure calls and stratified by State. We then calculated the percentage of exposure calls that involved tramadol, as well as misuse/abuse exposure calls involving tramadol as a percentage of total human exposure calls, by State in 2018.

All NPDS results were replicated independently using the same criteria by a separate analyst for quality control. Results from the two independent analyses agreed.

2.5 RESEARCHED ABUSE, DIVERSION, AND ADDICTION-RELATED SURVEILLANCE (RADARS®) SYSTEM TREATMENT CENTER PROGRAM (TCP)

Data Source

The Rocky Mountain Poison and Drug Center (RMPDC), a private subsidiary of Denver Health, operates the RADARS® System (RADARS) to collect product-specific data on drug abuse for surveillance, reporting, and research. Pharmaceutical manufacturers, government, and non-government agencies support RADARS by contracting for its services, while Denver Health retains exclusive ownership of all data and systems. RADARS TCP provides survey data from two RADARS System programs:

- The Opioid Treatment Program includes a convenience sample of primarily publicly-funded, medication-assisted maintenance treatment programs in urban and rural areas throughout the US.
- The Survey of Key Informants' Patients Program includes a convenience sample of primarily privately-funded treatment centers, most of which do not use medication-assisted treatment.

In the TCP, the coverage area is defined quarterly as the three-digit ZIP codes where at least one survey respondent resided. In 2018, the coverage area included approximately 50% of the U.S. population, drawing from 185 participating sites and three-digit ZIP codes in 46 states and the District of Columbia.

These two programs use the same core data collection form, enabling data to be combined, and complement each other by providing information from patients entering both private and public opioid addiction treatment programs. Patients enrolling in the study complete a self-administered, anonymous questionnaire within the first week of admission. Surveys include questions about prescription or illicit drugs used in the past month for “getting high” (i.e., abuse). Surveys also include questions relating to the route of abuse. These programs estimate past-month prevalence and route-specific rates of prescription and illicit drugs among their respective populations:

Search Strategy and Analysis

FDA obtained surveillance data from RADARS® TCP through an ongoing contract with the RMPDC:

- First, we examined trends in the percentage of respondents endorsing abuse of a specific opioid molecule from 2014 through 2018 from consistent sites that contributed at least one survey in each study year and in at least 75% of study quarters in the study period.
- In addition, we examined respondents endorsing past-month abuse and routes of abuse as percentages of all respondents from 2017 through 2018, using data from all sites because only two years of data were available. In this report, numerators represent the total number of

endorsements and denominators represent the total number of respondents for that year. Therefore, the total percentages for each product may exceed 100%.

For this review, we used results of analyses in which RADARS excluded careless responses, *i.e., surveys with 24 or more opioid item endorsements or endorsements of 9 or more consecutive items that were deemed careless responses.*

2.6 NATIONAL ADDICTIONS VIGILANCE INTERVENTION AND PREVENTION PROGRAM (NAVIPPRO™)

Data Source

Inflexxion, Inc., a subsidiary of IBH Solutions, operates the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™), a product-specific, surveillance system for monitoring prescription drug abuse.¹² One of the components of NAVIPPRO surveillance is the Addiction Severity Index-Multimedia Version® (ASI-MV®), a computer-administered version of ASI assessment via patient self-report. ASI-MV® is used in the assessment of addiction severity, and includes questions relating to use or abuse of specific products such as route of administration and the source of the prescription medication. A convenience sample of adults seeking treatment or being assessed for substance use disorder treatment at participating facilities across the U.S. constitutes the study population. In 2018, NAVIPPRO™ included 390 treatment sites in 36 states in its full sample, with 65 treatment sites in 15 states being consistent sites that provided at least one assessment in each calendar quarter from 2013 to 2018.

Search Strategy and Analysis

FDA obtained surveillance data collected from the NAVIPPRO™ ASI-MV® through an ongoing contract with Inflexxion.

- The number and percent of respondents endorsing abuse of specific opioid molecules in each calendar year (2013 through 2018).
- The number and percent of respondents endorsing abuse of specific products and routes of abuse from January 2017 through December 2018. In this report, numerators represent the total number of endorsements and denominators represent the total number of assessments in that calendar year.

For this review, we first examined trends in the percentage of respondents endorsing abuse of specific opioid molecules from 2013 through 2018 from consistent sites. We compared overall trends between data from all sites and consistent sites and found similar trends. In addition, we examined the percent of respondents endorsing past-month abuse and route of administration from 2017 through 2018, using data from all sites because only two years of data were available.

2.7 NATIONAL ELECTRONIC INJURY SURVEILLANCE SYSTEM -- COOPERATIVE ADVERSE DRUG EVENT SURVEILLANCE (NEISS-CADES)

Data Source

Cases and national estimates of the number of emergency department (ED) visits for drug-related adverse events were based on data from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, a national stratified probability sample of approximately 60 hospitals with a minimum of 6 beds and a 24-hour ED in the United States and its territories. The NEISS-CADES project, which has been described in detail

elsewhere, is a joint effort of the Centers for Disease Control and Prevention, the US Consumer Product Safety Commission, and the US Food and Drug Administration.¹³⁻¹⁶

In brief, trained data abstractors located at each participating hospital review clinical records of every ED visit to identify clinician-diagnosed drug related adverse events attributed to medications used for any reason. Abstractors record up to 4 medications implicated in each adverse event, and narrative descriptions of the incident (including intent of drug use, clinical diagnoses and manifestations).

Definition

Non-medical use includes pharmaceutical abuse, therapeutic misuse (use other than as directed by a clinician), and opioid overdoses without indication of intent.^{17,18} (**Table 5**). Of note, cases involving inadequate therapy, drug withdrawal, detoxification treatment, harms from ED treatment, and deaths are not included.

Table 5. Definition of non-medical use^{17,18}

Category	NEISS-CADES Definition
Abuse	Clinician diagnosis of abuse (for current ED visits) or documented recreational use (e.g., “to get high”)
Therapeutic misuse	Documented therapeutic intent, but the pharmaceutical was not used as directed (e.g., taking someone else’s prescription medication for pain, intentionally taking larger doses than prescribed or recommended)
Overdoses without indication of intent	Cases of overdose without indication of intent have insufficient documentation to categorize the case as abuse, therapeutic, or self-harm (e.g., patients found unresponsive by paramedics and patients unable or unwilling to provide description of circumstances or intent). Appendix F1 provides definitions for intent of drug use.

Data Analysis

We tabulated the number of ED visits in the NEISS-CADES sample that were related to non-medical use of tramadol and other selected opioids. To allow calculation of national estimates, each NEISS-CADES case is assigned a sample weight derived from the inverse probability of selection, adjusted for nonresponse and post-stratified to adjust for the number of annual hospital ED visits. We estimated the projected national number of such visits by using the SURVEYFREQ procedure in SAS version 9.4 (SAS Institute, Cary, North Carolina). Estimates based on <20 cases or total estimates <1,200 are considered statistically unstable and are not shown. Additionally, estimates with a coefficient of variation >30% may be statistically unstable and are noted. We also examined the number of ED visits for non-medical use of tramadol, by adverse event manifestation during 2016-2017.

Inclusion criteria:

Tramadol and comparator opioid analgesics, including hydrocodone, morphine, and oxycodone

Cases were identified by searching for “tramadol”, “hydrocodone”, “morphine”, and “oxycodone” in all fields for the generic name of an involved drug (generic1 – generic4).

Codeine comparator

Cases were identified by searching for “codeine” in all fields for the generic name of an involved drug (generic1 – generic4). Codeine analgesics and codeine-containing cough and cold products were included in the analysis.

Exclusion criteria:

Tramadol and other selected opioids, including hydrocodone, morphine, and oxycodone

Cases that involved only unspecified opioids (e.g., diagnosis of opioid overdose but no indication if prescription opioid or heroin) were excluded from the analysis. Opioid-containing cough and cold products were excluded from the analysis. In addition, cases of ED visits resulting from assault were excluded from the analysis.

Codeine comparator

Cases that involved only unspecified opioids (e.g., diagnosis of opioid overdose but no indication if prescription opioid or heroin) were excluded from the analysis. In addition, cases of ED visits resulting from assault were excluded from the analysis.

2.8 MONITORING THE FUTURE (MTF)

Data Source

Monitoring the Future (MTF) is an annual survey of U.S. adolescents, college students, and adult high school graduates that monitors substance use and related attitudes.^{19,20} Relevant to this review, MTF surveys high school seniors on use and misuse/abuse of prescription drugs. It produces national estimates through a complex sampling design and weighted analysis. In 2018, approximately 14,500 high school seniors participated by completing the paper questionnaire during school hours. Academic researchers at the University of Michigan conduct MTF with grant support from the National Institute on Drug Abuse, National Institutes of Health.^{19,20}

Definition

MTF defines misuse of prescription drugs as “use outside of a doctor’s orders.” An example, quoting a question from the survey is as follows: “*What narcotics other than heroin have you taken during the last year without a doctor’s orders?*” As MTF’s definition includes intentional, non-therapeutic use of a drug to obtain a desired psychological or physiological effect (i.e., abuse), this review labels it *misuse/abuse*.

Search Strategy and Analysis

We extracted national estimates of the past-year prevalence of misuse/abuse of tramadol and comparator opioid analgesics among high school seniors, from the published results²⁰ of the MTF, 2009-2018.

2.9 NATIONAL VITAL STATISTICS SYSTEM – MORTALITY (NVSS-M) AND DRUG-INVOLVED MORTALITY (DIM) LINKED DATA

Data source

The National Vital Statistics System (NVSS) data contain vital registration data for the U.S. The National Center for Health Statistics (NCHS) collects vital registration data from 50 states, the District of Columbia, and U.S. territories, including live births, deaths, and fetal deaths. The National Vital Statistics System Mortality (NVSS-M) data include cause of death, demographic, and geographic information from all death certificates in the U.S. In NVSS-M, cause of death is classified by *International Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* codes.

Overdose deaths were defined using ICD-10 underlying cause-of-death codes: X40–X44 (accidental self-poisoning), X60–X64 (intentional self-poisoning), X85 (homicide), and Y10–Y14 (undetermined poisonings).

The Drug-Involved Mortality (DIM) data consists of NVSS-M data linked with information extracted from the literal text information from death certificates.²¹ The method used to extract information on DIM has been previously described.²² Briefly, the literal text fields contain information written on the death certificate, including the cause of death, manner, circumstances, and other factors contributing to the death. The API or substance mentioned in a literal text field is assumed to be involved in the death unless contextual information indicates otherwise. **Appendix H1** provides more information on the method used to extract information.

Search Strategy and Analysis

We extracted DIM data for tramadol and other opioids from recent, published study reports by Hedegaard, et al.^{3,23} Specifically, we abstracted information from overdose deaths, January 1, 2011 through December 31, 2017, where tramadol and the comparator OAs--codeine, hydrocodone, morphine, and oxycodone--were mentioned in the literal text as contributing to the death. The selected ICD-10 codes limited deaths to those caused by acute intoxication from drugs (i.e., overdose) as opposed to chronic exposure or adverse effects experienced due to therapeutic or prophylactic dosages. For overdose deaths involving these substances, we examined trends in the annual number of opioid-involved drug overdose deaths and the annual age-adjusted rate of overdose deaths per 100,000 population stratified by opioid.

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3. RESULTS

3.1 DRUG UTILIZATION

3.1.1 SETTINGS OF CARE

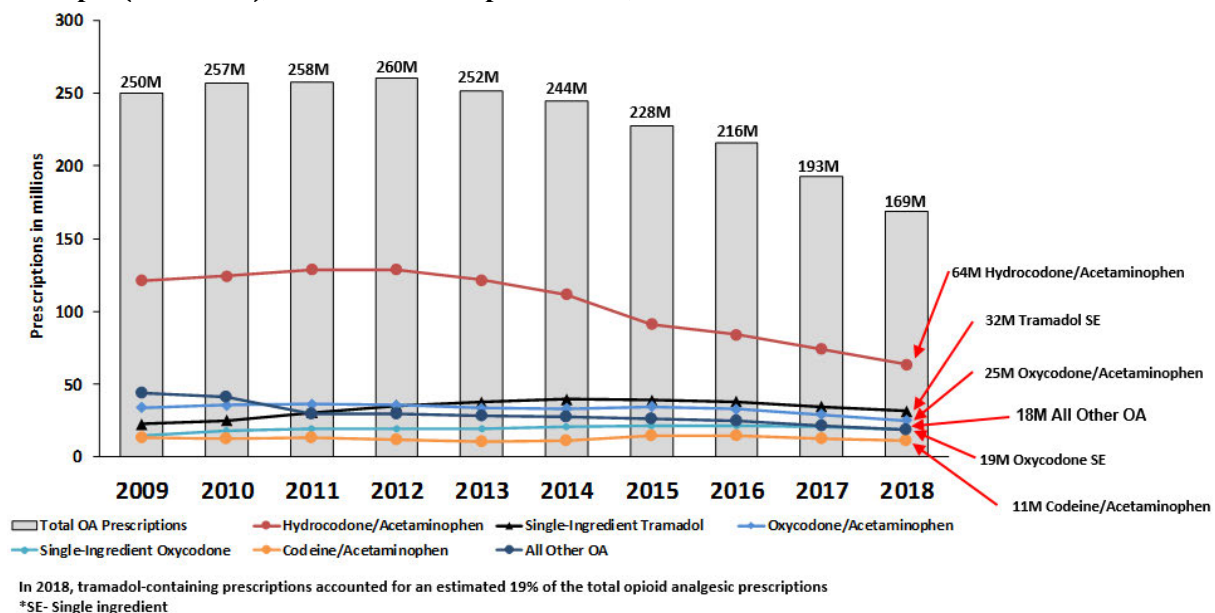
Based on manufacturer sales distribution data in 2018, approximately 58% of all bottles or packages of tramadol-containing products were sold from manufacturers and wholesalers to retail pharmacies, followed by 37% to non-retail pharmacies, and 5% to mail-order/specialty pharmacies.¹ As a result of these distribution patterns, we focused our analysis on the retail pharmacy setting only, the setting where the majority of drug product was distributed.

3.1.2 PRESCRIPTION DATA

3.1.2.1 Total Opioid Analgesics (OA)

In 2018, tramadol-containing prescriptions accounted for an estimated 32.6 million or 19% of the total 169 million OA prescriptions dispensed from U.S. retail pharmacies. SE tramadol was the third most dispensed OA from 2009 to 2012, and from 2013 onwards, it was the second most dispensed OA after combination hydrocodone/acetaminophen. SE tramadol, combination oxycodone/acetaminophen, SE oxycodone, and combination codeine/acetaminophen, collectively comprised 91% of the total OA market as shown in **Figure 1** below. **Table 1** in **Appendix A** provides the total OA prescriptions dispensed through U.S. retail pharmacies from 2009 through 2018.

Figure 1. Estimated number of dispensed prescriptions for all opioid analgesics (grey bar) and the top 5 (solid lines), from U.S. retail pharmacies, 2009-2018



Data Source: IQVIA National Prescription Audit™. 2009-2018. Data extracted October 2019. File: USC02200 Launch MVP_1_Oct-03-2019.xlsx. Of note, changes were made in the underlying data and methodology of the proprietary database IQVIA NPA to account for a dynamic pharmaceutical market, including a change to manage prescription claims that are voided or reversed. Prescription volumes dispensed from the retail pharmacies have been historically adjusted back to January 2017. Data prior to January 2017 have not been adjusted to the new methodology. In 2018, an estimated 2% of total prescription claims for opioid analgesics dispensed from U.S. retail pharmacies appear to have been voided or reversed. Thus, annual estimates prior to 2017 may be overstated by a low margin if we assume voids and reversals do not change substantively over time

¹ IQVIA™ National Sales Perspectives. Year 2018. Extracted September 2019. File NSP Tramadol_Sept-03-2019.xlsx

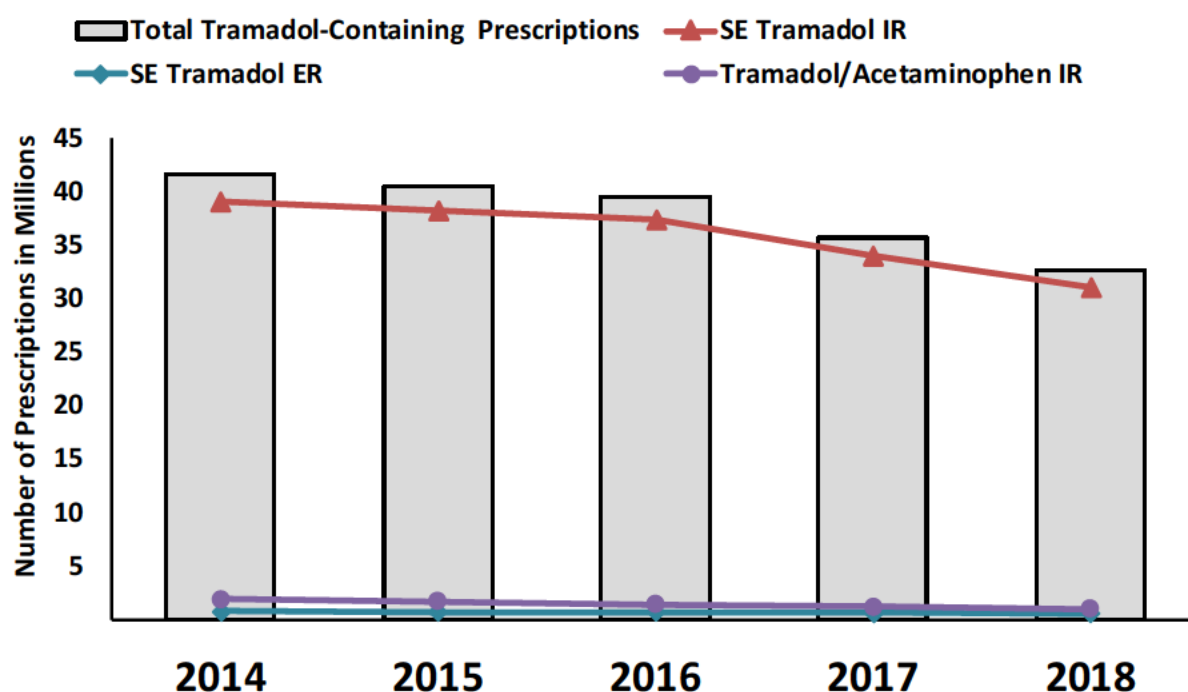
Approximately 11 billion units (tablets, capsules, etc.) of OA were dispensed from U.S. retail pharmacy settings in 2018. **Table 2 in Appendix A** provides the total OA units dispensed from U.S. retail pharmacy settings from 2009 through 2018. Similar to dispensed prescription data, the top five most dispensed OA units (SE tramadol, combination oxycodone/acetaminophen, combination hydrocodone/acetaminophen, SE oxycodone, and combination codeine/acetaminophen) collectively comprised 90% of the total units dispensed in 2018.

3.1.2.2 Tramadol-Containing Products

Figure 2 below and **Table 3 in Appendix A** provides the estimated number of prescriptions dispensed for tramadol-containing formulations from U.S. retail pharmacies from 2014 through 2018. An estimated total of 33 million prescriptions were dispensed for tramadol-containing products in 2018, a decrease of 22% from 42 million prescriptions dispensed in 2014.

SE Tramadol IR was the most utilized tramadol product in 2018 at 31 million prescriptions or 95% of the total tramadol-containing prescriptions dispensed, followed by the IR combination tramadol/acetaminophen at 3% or 945,000 prescriptions dispensed. Tramadol ER accounted for 2% or 560,000 prescriptions dispensed in 2018.

Figure 2. Estimated number of dispensed prescriptions for tramadol-containing products from U.S. retail pharmacies, 2014-2018



Data Source: IQVIA National Prescription Audit™, 2014-2018. Data extracted October 2019. File: NPA 2019-1557 tramadol IR&ER 2014-2018. 10-30-19.xlsx.

Of note, there are changes in the underlying data and methodology of the proprietary database IQVIA NPA to account for a dynamic pharmaceutical market, including a change to manage prescription claims that are voided or reversed. Prescription volumes dispensed from the retail pharmacies have been historically adjusted back to January 2017. Data prior to January 2017 have not been adjusted to the new methodology. In 2018, an estimated 2% of total prescription claims for opioid analgesics dispensed from U.S. retail pharmacies appear to have been voided or reversed.

3.1.2.3 Tramadol-Containing Products by Age

Table 4 in Appendix A provides data on tramadol-containing prescriptions by patient age in 2018. These data exclude prescriptions written by veterinary medicine specialty. Patients aged 40 to 59

years had the most dispensed prescriptions for SE tramadol IR in 2018 (35% or 11 million prescriptions), followed by patients aged 60-74 years (33% or 10 million prescriptions). Similar trends were observed for dispensed tramadol ER prescriptions.

For combination tramadol/acetaminophen patients aged 60-74 years were dispensed the most prescriptions (33% or 309,000 prescriptions) followed by patients aged 40-59 years (28% or 260,000) and 75+ years (25% or 238,000) in 2019.

3.1.2.4 Tramadol-Containing Products by Prescriber Specialties

In 2018, the combined specialties of family practice, general practice, and internal medicine accounted for an estimated 37% or (b) (4) prescriptions of total dispensed tramadol-containing prescriptions from U.S. retail pharmacies followed by nurse practitioners and physician assistants (20%) and osteopathic medicine specialty (10%) in 2018 (**Table 5 in Appendix A**).

3.1.3 OFFICE-BASED PHYSICIAN SURVEY DATA

Table 6 in Appendix A provides the top diagnoses (ICD-10-CM) associated with the use of tramadol-containing products as reported by U.S office-based physician surveys in 2018. Diseases of the musculoskeletal system and connective tissue (M00-M99) such as dorsalgia (M54) accounted for approximately 52% of all reported diagnoses associated with the use of SE tramadol IR. Injury, poisoning and certain external cause consequences (S00-T88) accounted for 18%, followed by factors influencing health status and health services (Z00-Z99) and neoplasms (C00-D49) at 7% and 5%, respectively.

Diseases of the musculoskeletal system and connective tissue (M00-M99) accounted for approximately 53% of total drug use mentions of all reported diagnoses associated with the use of tramadol/acetaminophen. Tramadol ER was only associated with diseases of the musculoskeletal system and connective tissue (M00-M99).

A review of concurrent use(s) of tramadol-containing products with other molecules showed that tramadol was mainly mentioned as being used alone or in combination with ibuprofen, meloxicam and naproxen from the non-steroidal anti-inflammatory drug (NSAID) class of medications (see **Table 6 in Appendix A** for the medications used in combination with tramadol).

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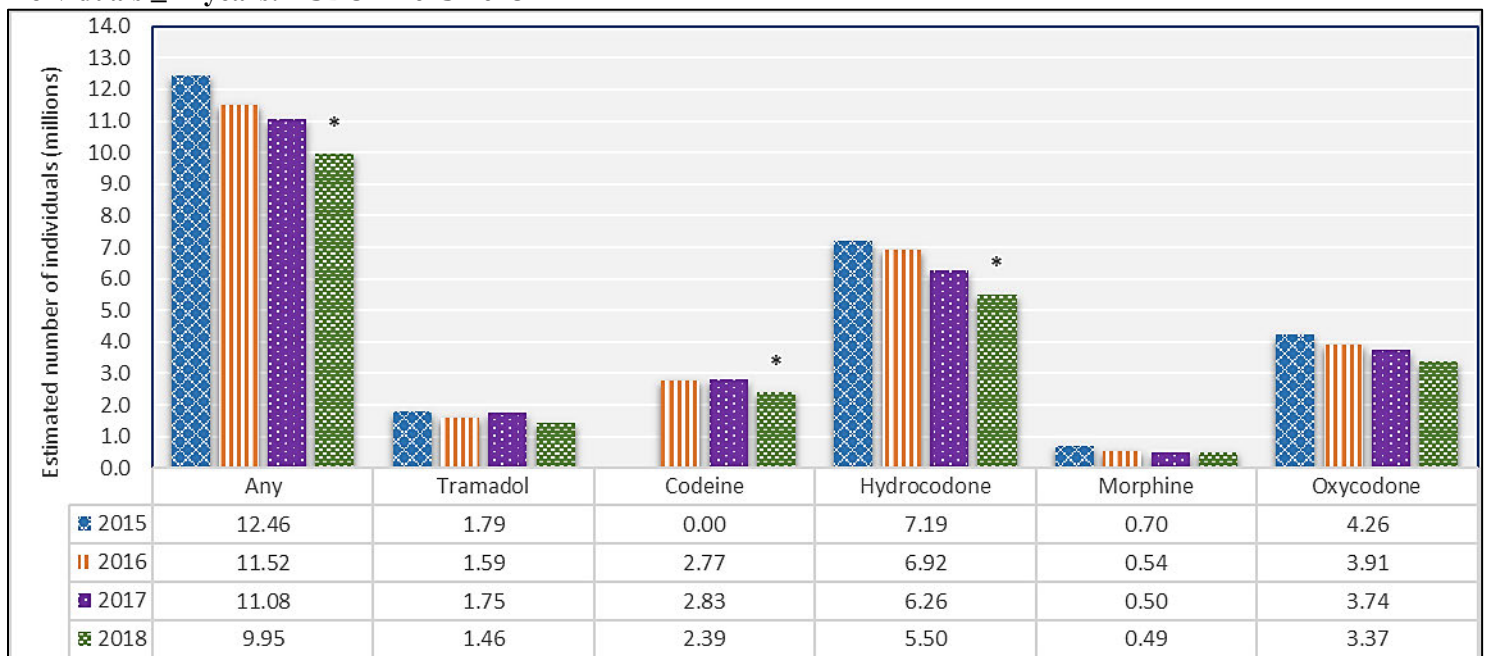
3.2 NSDUH

In 2018, the nationally-projected survey results estimated that more than 86 million U.S. individuals aged 12 or older had used prescription opioid analgesics for any reason during the previous year (**Appendix B2**). Of these, approximately 10 million people, 3.6% of the population, reported any past-year misuse/abuse of prescription opioids (**Figures 3A-3B**). The estimated number of people reporting any past-year misuse/abuse of opioid analgesics declined by 10.2% from 2017 to 2018, a statistically significant decrease.

In 2018, approximately 18 million individuals had used tramadol-containing products for any reason in the past year (**Appendix B2**). Of these, approximately 1.5 million individuals, or 0.5% of the U.S. population reported any past-year misuse/abuse of tramadol. The estimated number of people reporting past-year misuse/abuse of tramadol in 2018 was similar to the 2017 estimate and lower than the 2015 estimate of 1.8 million people (**Figures 3A-3B**).

The top three misuse/abused opioid analgesics in the general U.S. population in 2018 were hydrocodone, oxycodone and codeine, with misuse/abuse occurring among 5.5 million, 3.4 million and 2.4 million individuals, respectively. For each comparator opioid analgesic, the estimated number of individuals who reported use for any reason or misuse/abuse either remained stable from 2017 to 2018, or slightly decreased (**Appendix B2**). For example, the estimated past-year misuse/abuse of hydrocodone was estimated at 2% of the U.S. population in 2018, compared with 2.3% in 2017 (**Figures 3A-3B**). **Appendix B2** provides additional details on the results, presented in a table format.

Figure 3A. Number of individuals reporting past-year misuse/abuse of prescription opioid analgesics, individuals ≥12 years: NSDUH 2015-2018

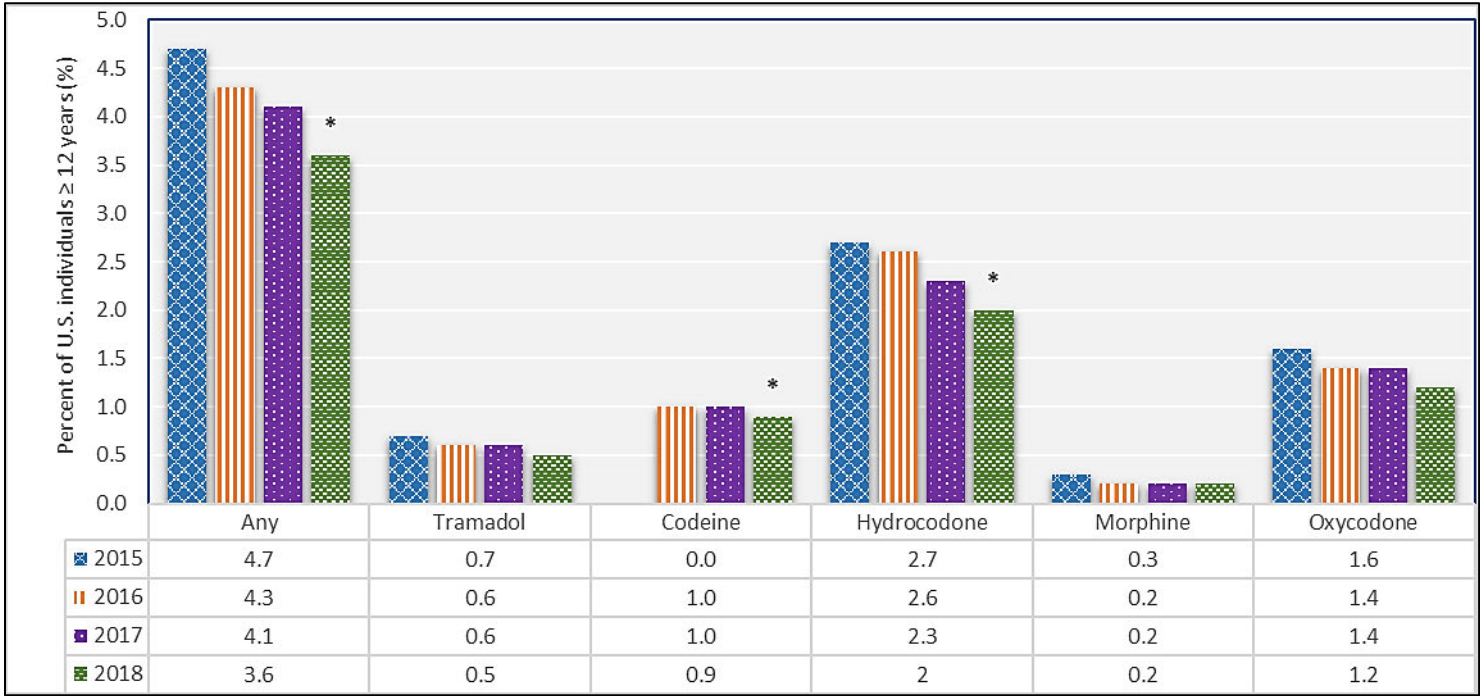


* represent statistically significant changes relative to prior year.

Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health (NSDUH), 2017 and 2018 Detailed Tables. Tables 1.98A-B <https://www.samhsa.gov/data/nsduh/reports-detailed-tables-2018-NSDUH>; 2016 and 2017 Detailed Tables. Tables 1.97A-B <https://www.samhsa.gov/data/nsduh/reports-detailed-tables-2016-2017-NSDUH>

[tables-2017-NSDUH](#); 2014 and 2015. Detailed Tables. Tables 1.139A-B <https://www.samhsa.gov/data/report/results-2015-national-survey-drug-use-and-health-detailed-tables>

Figure 3B. Past-year misuse/abuse of prescription opioid analgesics as a percentage of U.S. individuals ≥12 years: NSDUH 2015-2018



* represent statistically significant changes relative to prior year.

Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health (NSDUH), 2017 and 2018 Detailed Tables. Tables 1.98A-B <https://www.samhsa.gov/data/nsduh/reports-detailed-tables-2018-NSDUH>; 2016 and 2017 Detailed Tables. Tables 1.97A-B <https://www.samhsa.gov/data/nsduh/reports-detailed-tables-2017-NSDUH>; 2014 and 2015. Detailed Tables. Tables 1.139A-B <https://www.samhsa.gov/data/report/results-2015-national-survey-drug-use-and-health-detailed-tables>

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3.3 AAPCC NPDS

The analysis of NPDS consisted of five components: trends, reason for exposure by age group, characteristics of calls involving misuse/abuse, comparative analysis of calls involving tramadol *versus* comparator opioid analgesics, and map of population rates of calls involving tramadol exposure.

3.1 Trends

Over 10 years (January 1, 2009 to December 31, 2018), the annual number of exposure calls involving tramadol increased from 10,521 calls in 2009 to 12,964 in 2012, then declined to 8,762 in 2018 (**Table 6**). More than 60% of these calls were due to intentional exposures. Also, there was a decline over time in intentional misuse/abuse as a percentage of calls involving tramadol, from 15.2% (1,600 calls) of tramadol exposure calls in 2009 to 10.6% (929 calls) in 2018. Looking at severity of related clinical effects, tramadol, single-substance exposures were most commonly classified as having a minor effect, while multiple-substance exposure calls were most commonly classified as having a moderate effect. These descriptive characteristics and additional information are shown in **Table 6**.

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Table 6. Exposure calls involving tramadol: U.S., NPDS, 2009-2018

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
All Exposure Calls (n)	10,521	11,399	12,473	12,964	12,835	12,605	11,952	11,551	10,359	8,762
Gender, n (%)										
Female	6160 (58.5)	6741 (59.1)	7392 (59.3)	7716 (59.5)	7746 (60.4)	7577 (60.1)	7416 (62)	7273 (63)	6572 (63.4)	5554 (63.4)
Male	4324 (41.1)	4609 (40.4)	5047 (40.5)	5208 (40.2)	5047 (39.3)	4982 (39.5)	4494 (37.6)	4246 (36.8)	3768 (36.4)	3186 (36.4)
Unknown	37 (0.4)	49 (0.4)	34 (0.3)	40 (0.3)	42 (0.3)	46 (0.4)	42 (0.4)	32 (0.3)	19 (0.2)	22 (0.3)
Reason for Exposure										
Intentional	6,370	6,912	7,640	7,965	7,775	7,646	7,328	7,096	6,397	5,390
<i>Intentional Abuse</i>	659 (10.3)	765 (11.1)	878 (11.5)	936 (11.8)	740 (9.5)	709 (9.3)	608 (8.3)	502 (7.1)	477 (7.5)	377 (7.0)
<i>Intentional Misuse</i>	942 (14.8)	1093 (15.8)	1116 (14.6)	1139 (14.3)	1123 (14.4)	1004 (13.1)	925 (12.6)	902 (12.7)	744 (11.6)	552 (10.2)
<i>Suspected Suicide</i>	4356 (68.4)	4616 (66.8)	5159 (67.5)	5382 (67.6)	5428 (69.8)	5511 (72.1)	5397 (73.7)	5332 (75.1)	4856 (75.9)	4224 (78.4)
<i>Intentional Unknown*</i>	413 (6.5)	438 (6.3)	487 (6.4)	508 (6.4)	484 (6.2)	422 (5.5)	398 (5.4)	360 (5.1)	320 (5)	237 (4.4)
Unintentional	3,289	3,616	3,833	4,024	4,136	4,018	3,799	3,697	3,259	2,802
Adverse Reaction	630	657	735	692	628	660	548	513	467	367
Withdrawal	56	38	58	75	51	50	44	37	31	30
<i>Withdrawal, single-substance</i>	41	32	45	62	36	38	30	23	24	17
Other**	5	3	5	4	14	6	5	5	8	3
Unknown Reason	171	173	202	204	231	225	228	203	197	170
Related Medical Outcomes***, n (%)										
Single Substance										
Minor Effect	974 (50.1)	1087 (51.2)	1140 (51.1)	1248 (52.2)	1225 (52.1)	1198 (52.9)	1138 (54.3)	1154 (55.9)	941 (53.8)	786 (52.4)
Moderate Effect	816 (42.0)	852 (40.2)	907 (40.6)	952 (39.9)	937 (39.9)	893 (39.4)	792 (37.8)	782 (37.9)	660 (37.8)	598 (39.8)
Major Effect	150 (7.7)	181 (8.5)	180 (8.1)	181 (7.6)	186 (7.9)	173 (7.6)	164 (7.8)	126 (6.1)	142 (8.1)	115 (7.7)
Death	4 (0.2)	2 (0.1)	5 (0.2)	7 (0.3)	2 (0.1)	3 (0.1)	2 (0.1)	3 (0.1)	5 (0.3)	1 (0.1)
Multiple Substance										
Minor Effect	1385 (46.7)	1484 (45.6)	1625 (43.9)	1695 (43.3)	1678 (42.0)	1650 (41.1)	1634 (41.9)	1591 (41.0)	1469 (40.3)	1239 (40.1)
Moderate Effect	1251 (42.2)	1369 (42.1)	1587 (42.9)	1675 (42.8)	1826 (45.7)	1846 (46.0)	1795 (46.0)	1815 (46.8)	1680 (46.2)	1443 (46.7)
Major Effect	308 (10.4)	364 (11.2)	401 (10.8)	444 (11.4)	429 (10.7)	477 (11.9)	444 (11.4)	441 (11.4)	445 (12.2)	366 (11.9)
Death	21 (0.7)	35 (1.1)	88 (2.4)	98 (2.5)	64 (1.6)	40 (1.0)	31 (0.8)	33 (0.8)	48 (1.3)	41 (1.3)

NPDS: National Poison Data System

*Intentional unknown defined as exposures that are deemed to be intentional although the specific motive is undetermined.

**Other included other malicious, contamination and tampering

***Medical outcomes among individuals with a related clinical effect.

3.2 Reason for exposure by age group

During the 10-year period, the age group that had the largest share of its intentional exposure calls classified as abuse was the 12-17 year age group (969 calls, 14.5% of calls for intentional exposure in that age group), and the age group that had the largest share of its intentional exposure calls classified as misuse was age ≥ 65 years (584 calls, 20.4% of calls for intentional exposure in that age group) (Table 7). For the youngest age group, 0-11 years, most exposure calls were for an unintentional exposure. In the 12-17 years age group and older age groups, suspected suicide was the most frequent reason for exposure (Table 7).

Table 7. Tramadol intentional exposure calls by age group: U.S., NPDS, 2009-2018

Reason for Exposures by Age Group (year)	0-11	12-17	18-25	26-39	40-64	65 and older	Unknown
Intentional Exposures							
Intentional, n (%)	169	6,671	14,313	20,349	23,680	2,858	2,479
<i>Intentional Abuse</i>	8 (4.7)	969 (14.5)	1823 (12.7)	1949 (9.6)	1483 (6.3)	122 (4.3)	297 (12.0)
<i>Intentional Misuse</i>	67 (39.7)	554 (8.3)	2200 (15.4)	2945 (14.5)	2627 (11.1)	584 (20.4)	563 (22.7)
<i>Suspected Suicide</i>	57 (33.7)	4812 (72.1)	9596 (67.0)	14369 (70.6)	18244 (77.0)	1932 (67.6)	1251 (50.5)
<i>Intentional Unknown</i>	37 (21.9)	336 (5.1)	694 (4.9)	1086 (5.3)	1326 (5.6)	220 (7.7)	368 (14.8)
Unintentional, n	15,386	841	1,816	3,638	7,041	5,891	1,860
Adverse Reaction, n	17	134	860	1,425	1,747	912	802
Withdrawal, n	5	0	56	152	136	68	53
<i>Withdrawal, single-substance</i>	3	0	46	121	91	44	43
Other*, n	5	7	9	13	15	2	7
Unknown Reason, n	61	111	206	397	750	288	191
NPDS: National Poison Data System							
*Other included other malicious, contamination and tampering							

3.3 Cases of tramadol exposure calls involving misuse/abuse

Characteristics of all tramadol exposure calls involving misuse/abuse are described in Tables 8-10. Overall, tramadol, single-substance exposure calls involving misuse/abuse accounted for 59.2% of total misuse/abuse exposure calls involving tramadol.

- a. By co-exposures: among tramadol, multiple-substance exposure calls involving misuse/abuse, the most common co-exposures were: other prescription opioids (25.6%), benzodiazepines (21.1%), and alcohol (19.4%) (Table 8).

Table 8. Tramadol, multiple-substance exposure calls involving misuse/abuse: U.S., NPDS, 2009-2018

Characteristics	Multiple-substance exposures N (% of column) *
Total misuse/abuse (n)	6,610
Co-Exposures	
Benzodiazepines	1395 (21.1)
Prescription opioids	1693 (25.6)
Heroin/illicit fentanyl analogue	113 (1.7)
Alcohol	1284 (19.4)
Marijuana	275 (4.2)
Stimulants (prescription and illicit)	458 (6.9)
NPDS: National Poison Data System	
*The counts of each co-exposure are not mutually exclusive.	

- b. By route of misuse/abuse: among tramadol, single-substance exposure calls involving misuse/abuse, almost all exposures (99.1%) occurred via the oral route (**Table 9**). Similarly, findings from multiple-substance exposure calls involving misuse/abuse yielded consistent results. Of note, we restricted our main analysis to single-substance calls since route cannot be mapped to a specific drug in multiple-substance exposure calls.

Table 9. Percentage of misuse/abuse exposure calls reporting specific exposure routes[^] for tramadol: U.S., NPDS, 2009-2018

Misuse/abuse		
Characteristics	Single substance exposures N (% of column)	Multiple-substance exposures N (% of column)
Number of Misuse/abuse exposure call (n)	9,581	6,610
Route of misuse/abuse*		
Oral**	9498 (99.1)	6504 (98.4)
Nasal/inhalation	67 (0.7)	369 (5.6)
Injection	26 (0.3)	107 (1.6)
Other***	10 (0.1)	30 (0.5)
Unknown	12 (0.1)	134 (2)
NPDS: National Poison Data System		
[^] Routes are represented as percentage of exposure calls reporting a specific route over all of the single or multiple-substance exposure calls for the opioid. One exposure call may be associated with more than one exposure route, thus the total % for each column may exceed 100%. Route cannot be mapped to a specific drug in multiple-substance exposure calls.		
*The counts of each route are not mutually exclusive.		
**Oral included aspiration/with ingestion.		
*** Other includes exposure routes categorized as bite/sting, dermal, ocular, otic, vaginal, rectal, and/or other		

- c. By severity of medical outcomes for cases with related clinical effects: among tramadol, single-substance exposure calls involving misuse/abuse and with a medical outcome classified as related to the exposure, moderate effect was the most common category of related medical outcome (48.9%), followed by minor effect (42.2%), and major effect (8.8%). Similarly, findings from multiple-substance exposure calls involving misuse/abuse yielded consistent results (Table 10).

Table 10. Severity of medical outcomes for misuse/abuse cases with related clinical effects- by single and multiple-substance: U.S., NPDS, 2014-2018

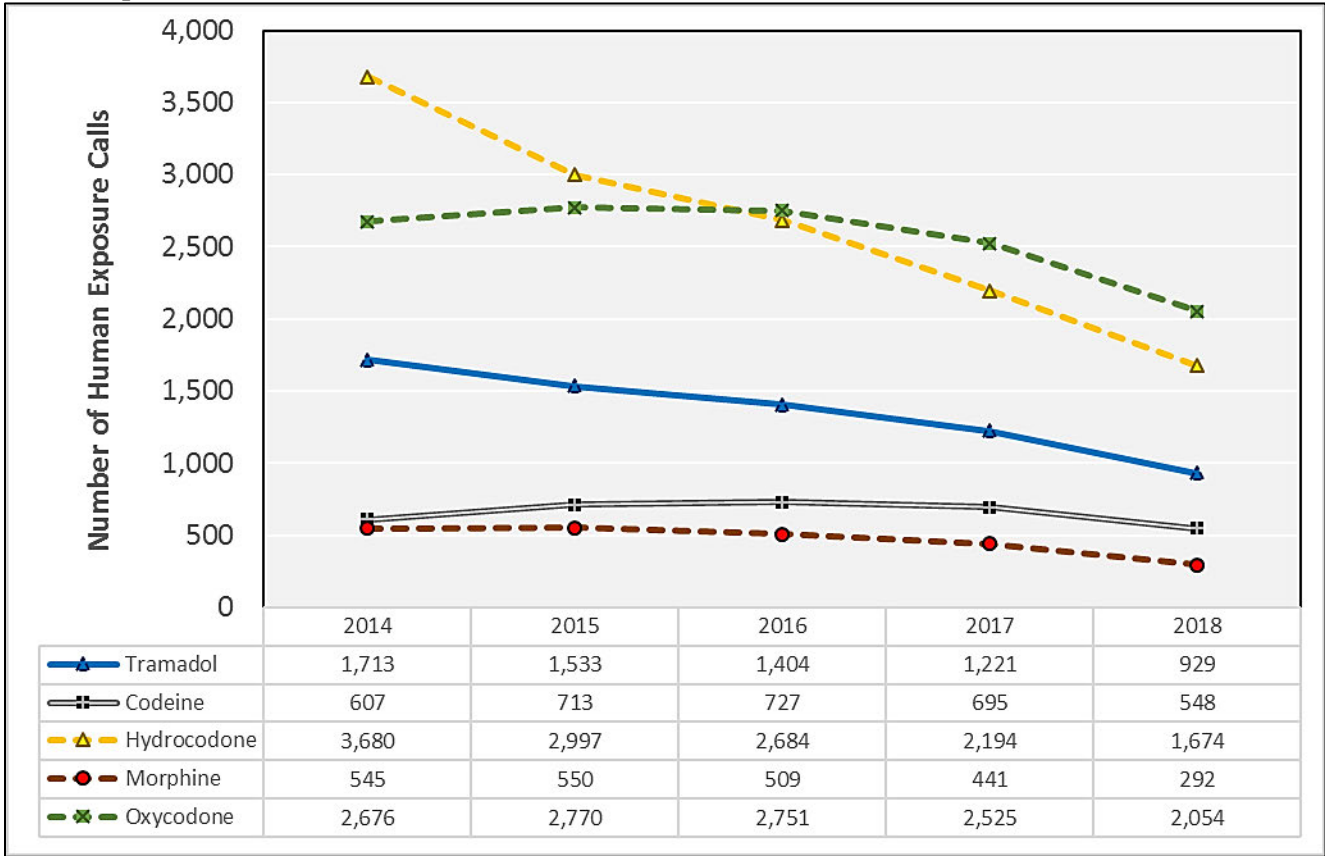
Medical Outcomes	Single substance exposures	Multiple-substance exposures
Total, n	2,138	1,845
Minor effect, n (%)	903 (42.2)	787 (42.6)
Moderate effect	1,045 (48.9)	896 (48.6)
Major Effect	187 (8.8)	131 (7.1)
Death	3 (0.1)	31 (1.7)
NPDS: National Poison Data System		
*Related clinical effect cannot be mapped to specific drug in multiple-substance exposure		

3.4 Comparative analysis

- a. Trends in intentional misuse/abuse exposure calls of tramadol and comparator opioid analgesics by year: From 2014 through 2018, the annual number of exposure calls involving tramadol misuse/abuse declined from 1,713 to 929 calls (Figure 4). Similarly, calls involving misuse/abuse of each comparator opioid analgesic declined from 2014 to 2018. Across years, there were higher number of exposure calls involving oxycodone and hydrocodone misuse/abuse, while there were fewer number of exposure calls involving morphine and codeine.

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Figure 4. Number of intentional misuse/abuse exposure calls per year of tramadol and other selected opioids: U.S., NPDS, 2014-2018



NPDS: National Poison Data System

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When stratifying calls by abuse or misuse, tramadol, codeine, and morphine had higher exposure calls involving misuse than abuse (**Table 11**).

Table 11. Number of exposure calls per year involving tramadol and comparator by intentional abuse and misuse: U.S., NPDS, 2014-2018

	2014	2015	2016	2017	2018
Intentional Abuse					
Tramadol	709	608	502	477	377
Codeine	256	267	335	349	271
Hydrocodone	1,634	1,309	1,106	965	690
Morphine	303	337	310	260	170
Oxycodone	1,465	1,511	1,568	1,543	1,240
Intentional Misuse					
Tramadol	1,004	925	902	744	552
Codeine	351	446	392	346	277
Hydrocodone	2,046	1,688	1,578	1,229	984
Morphine	242	213	199	181	122
Oxycodone	1,211	1,259	1,183	982	814
NPDS: National Poison Data System					

- b. Intentional exposure cases: across all intentional exposure calls of tramadol and four other selected opioids (codeine, hydrocodone, morphine, and oxycodone) over the five-year period (2014-2018), hydrocodone was involved in the most intentional exposure calls followed by oxycodone, and tramadol (60,799, 42,543, and 33,857 intentional exposure calls, respectively) (**Table 12**). Out of the five opioids, oxycodone was involved in the most intentional abuse exposure calls (7,327 calls) followed by hydrocodone (5,704 calls), and tramadol (2,673 calls), respectively. Out of the five opioids, hydrocodone was involved in the most intentional misuse exposure calls (7,525 calls) followed by oxycodone (5,449 calls) and tramadol (4,127 calls), respectively. Abuse was a more common reason for intentional exposure to either morphine or oxycodone (respective percentages: 18.4% and 17.2%) than it was for intentional exposures to either tramadol (7.9%) or hydrocodone (9.4%). Across the five opioid molecules examined, the proportions of intentional exposure calls involving misuse were comparable, ranging from 12.2-14.4%.

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Table 12. Number of intentional drug exposure calls, by exposure type: U.S., NPDS 2014-2018

Exposure Type	Tramadol n (%)	Other Opioids n (%)			
		Codeine	Hydrocodone	Morphine	Oxycodone
All	33,857	12,571	60,799	7,502	42,543
Intentional*					
Abuse	2,673 (7.9)	1,478 (11.8)	5,704 (9.4)	1,380 (18.4)	7,327 (17.2)
Misuse	4,127 (12.2)	1,812 (14.4)	7,525 (12.4)	957 (12.8)	5,449 (12.8)
Suspected Suicide	25,320 (74.8)	8,641 (68.7)	43,981 (72.3)	4,461 (59.5)	26,559 (62.4)
Unknown**	1,737 (5.1)	640 (5.1)	3,589 (5.9)	704 (9.4)	3,208 (7.5)

NPDS: National Poison Data System

*Includes abuse, misuse, suicide, and unknown

**Intentional unknown defined as exposures that are deemed to be intentional although the specific motive is undetermined.

- c. Cases of misuse/abuse by route of use: for tramadol, codeine, and hydrocodone, most misuse/abuse, single-substance exposure calls occurred via the oral route (98.5-99.6%). In addition, most misuse/abuse, single-substance calls for morphine and oxycodone products, respectively occurred via oral route (82.8-88.8%), while injection of morphine products was 12.8% and the inhalation/nasal route for oxycodone products was 7.3% (**Table 13**).

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Table 13. Percentage of misuse/abuse, single-substance abuse exposure calls reporting specific exposure routes for tramadol and selected other opioids[^]: U.S., NPDS, 2014-2018

Route	Tramadol (n*=3,929)	Other Opioids			
		Codeine (n*=1,803)	Hydrocodone (n*= 6,057)	Morphine (n*=1,045)	Oxycodone (n*=5,710)
Oral** n (%)	3,892 (99.1)	1,796 (99.6)	5,963 (98.5)	865 (82.8)	5,071 (88.8)
Inhalation/nasal n (%)	28 (0.7)	1 (0.1)	84 (1.4)	36 (3.4)	419 (7.3)
Injection n (%)	9 (0.2)	4 (0.2)	24 (0.4)	134 (12.8)	221 (3.9)
Other*** n (%)	4 (0.1)	2 (0.1)	7 (0.1)	7 (0.7)	18 (0.3)
Unknown n (%)	9 (0.2)	2 (0.1)	6 (0.1)	19 (1.8)	48 (0.8)

[^]Routes are represented as percentage of exposure calls reporting a specific route over misuse/abuse, single-substance exposure calls for the opioid. A single-substance exposure call may be associated with more than one exposure route, thus the sum for total route of exposure may be greater than the sum for total number of single-substance exposure calls, thus the total % for each column may exceed 100%

NPDS: National Poison Data System

*Number of misuse/abuse exposure calls

**Oral included aspiration/with ingestion.

*** "Other" includes exposure routes categorized as bite/sting, dermal, ocular, otic, vaginal, rectal, and/or other

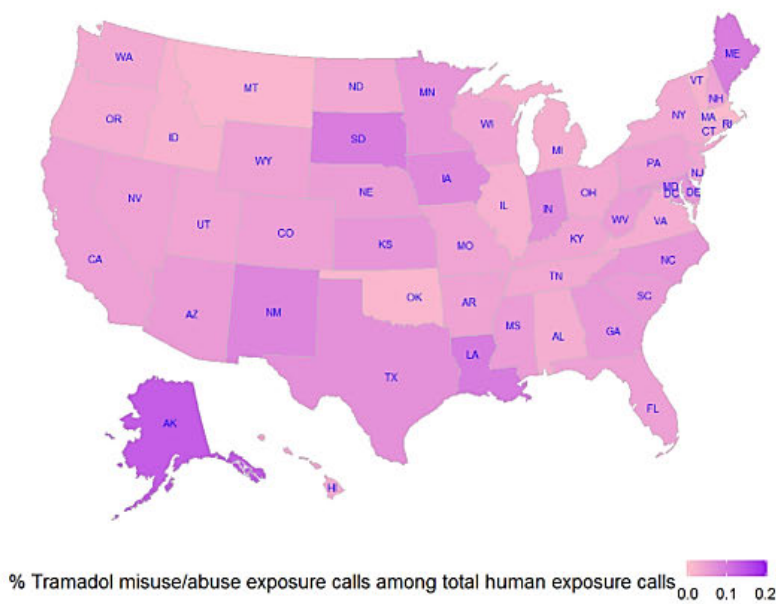
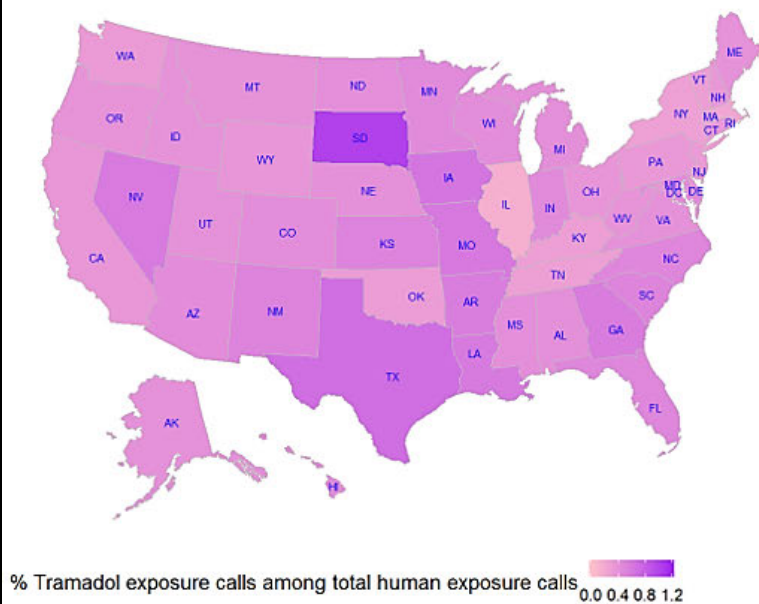
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3.5 Map of tramadol misuse/abuse exposure call percentages by State

The data in the map show the geographic distribution in the U.S. at the state level of exposure calls involving tramadol products, and exposure calls involving misuse/abuse of tramadol products in 2018 (**Figures 5A-B**). **Figure 5A** shows the estimated, state-specific rates of exposure calls involving tramadol for any reason among total human exposure calls, and **Figure 5B** shows the estimated, state-specific rate tramadol misuse/abuse exposure calls among total human exposure calls. Overall, the estimated rates for exposure calls involving tramadol, as well as misuse/abuse exposure calls involving tramadol varied widely across different states. States with apparently higher rates are identified by darker color on the maps. For example, South Dakota had the highest estimated rate of exposure calls involving tramadol products (1.02% of all human exposure calls). In addition, Alaska had the highest estimated rates of exposure calls involving misuse/abuse of tramadol products (0.13% of all human exposure calls), followed by Louisiana, Maine, and South Dakota, respectively (0.09% of all human exposure calls).

Figure 5A. % Tramadol exposure calls among total human exposure calls: U.S. NPDS, 2018

Figure 5B. % Tramadol misuse/abuse exposure calls among total human exposure calls: U.S. NPDS, 2018



NPDS: National Poison Data System

3.4 RADARS® TCP

From 2017 through 2018, the total number of respondents who completed the assessments of individuals with opioid use disorders (OUD) entering the treatment programs participating in the RADARS® surveillance program was 17,844. Of those, 10,339 respondents (57.9%) reported past-month abuse of a prescription opioid. Past-month abuse of tramadol was reported by 1,321 respondents, accounting for 7.4% (95% CI: 7.0-7.8%) of respondents who completed the assessment (**Table 14**). Past-month abuse of three other selected opioid analgesics was more common: oxycodone was most prevalent, followed by hydrocodone, and morphine, accounting for 29.2%, 22.5%, and 12.5% of respondents who completed the assessment, respectively.

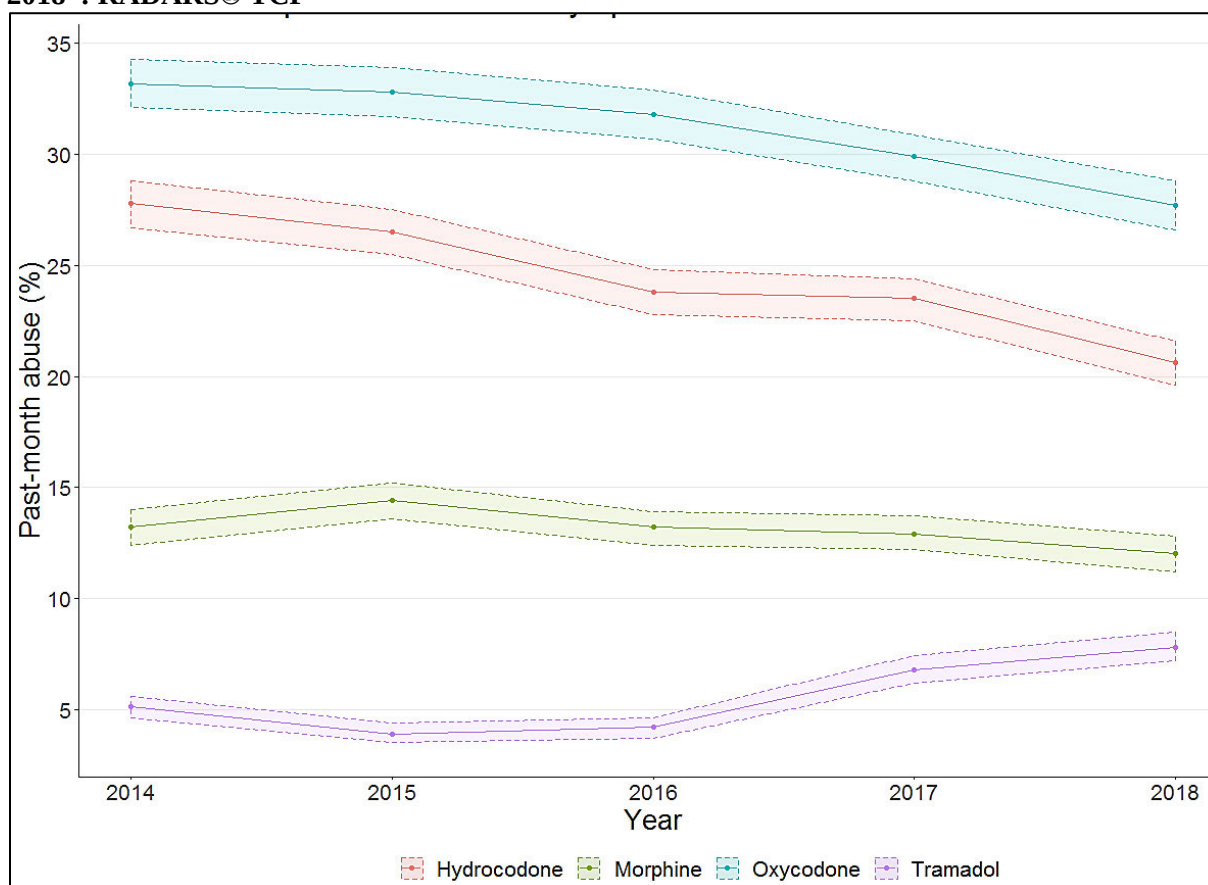
Of those who completed the survey and reported routes of abuse, swallowing was the most commonly reported route of abuse of tramadol (76%) and comparator opioid analgesics. Oxycodone (37.7%), hydrocodone (21.6%), and morphine (21.4%) were commonly snorted opioids. Chewing was also commonly reported as a route of abuse of hydrocodone (21.4%), oxycodone (16.9%), and tramadol (14.2%). Injecting was more commonly associated with abuse of morphine (36.1%) and oxycodone (16.4%) (**Table 14**). Of note, we did not include data on codeine because codeine was not included on the questionnaire during the entire surveillance period.

Table 14. Percent respondents with past-month abuse and by route* of administration: RADARS® TCP, U.S., 2017-2018

Opioids of Interest	Past-Month abuse, Unadjusted		Swallowed %	Chewed %	Smoked %	Snorted %	Injected %	Dissolved** %
	N	% Respondents (95% CI)						
Tramadol	1,321	7.4 (7.0-7.8)	76.0	14.2	1.4	9.6	3.2	5.8
Hydrocodone	4,020	22.5 (21.9-23.1)	69.9	21.4	2.0	21.6	3.1	5.8
Morphine	2,229	12.5 (12.0-13.0)	40.1	11.5	2.1	21.4	36.1	6.3
Oxycodone	5,211	29.2 (28.5-29.9)	57.2	16.9	5.4	37.7	16.4	7.3
RADARS®: Researched Abuse, Diversion, and Addiction-Related Surveillance; TCP: Treatment Center Program; CI: confidence interval *Respondents may report multiple opioids and multiple routes per opioid. Percentage of respondents represents the number of respondents who endorsed past-month abuse of a product divided by the total number of respondents. RADARS staff excluded from this analysis any data that they had flagged as <i>careless response</i> . **Dissolved was defined as “dissolved in mouth”.								

From 2014 through 2018, 35,660 respondents completed the assessments at treatment centers that contributed data for at least 75% of calendar quarters, after excluding careless responses. Of those, 19,772 respondents (55.4%) reported past-month abuse of a prescription opioid. **Figure 6** shows a 52.9% increase in the percent of respondents reporting past-month abuse of tramadol from 5.1% (95% CI: 4.6-5.6%) in 2014 to 7.8% (95% CI: 7.2-8.5%) in 2018 (**Figure 6**). Compared with 2017, the percent of respondents endorsing tramadol abuse increased by 15.4% in 2018. During this time, the percent of respondents endorsing tramadol abuse increased by 15.4% in 2018. During this time, the percent of respondents reporting past-month misuse/abuse of hydrocodone and oxycodone declined, while the percent reporting morphine was steady. Codeine was first reported in 2018. Therefore, we did not report it in the figure. We found similar trends when examining data from OTP and SKIP separately, and from all treatment sites that conducted assessments from 2014 through 2018. More information is provided in **Appendix D1**.

Figure 6. Percent respondents endorsing past-month abuse of specific opioids, by year, 2014-2018*: RADARS® TCP



RADARS®: Researched Abuse, Diversion, and Addiction-Related Surveillance; TCP: Treatment Center Program The dashed lines represent the 95% confidence interval.

*Among sites participating in 75% or more of calendar quarters in the study period and excluding careless responses

3.5 NAVIPPRO™

From 2017 through 2018, there were 105,166 NAVIPPRO™ ASI-MV assessments in individuals entering or being assessed for substance abuse treatment participating in the NAVIPPRO™ treatment center surveillance program. Of those, 24,477 (23.3%) endorsed misuse/abuse of a prescription opioid. During this period, past-month abuse of tramadol was reported in 1,553 respondents, accounting for 1.5% (95% CI:1.4-1.6%) of respondents who completed the assessment (**Table 15**). Past-month abuse of hydrocodone (8.3%; 95%CI: 8.1-8.5%) and oxycodone (8.2%; 95%CI: 8.0-8.3%) was more prevalent than tramadol abuse. The percent of respondents reporting past-month abuse of morphine was similar to tramadol.

Swallowed whole was the most commonly reported route of abuse of tramadol (1,300 out of 1,553, 83.7%), hydrocodone, and oxycodone (**Table 15**). Snorting was common among respondents reporting abuse of hydrocodone (27.5%) and oxycodone (44.1%). Injecting was more commonly reported with abuse of morphine (46.3%) and oxycodone (18.3%) (**Table 15**).

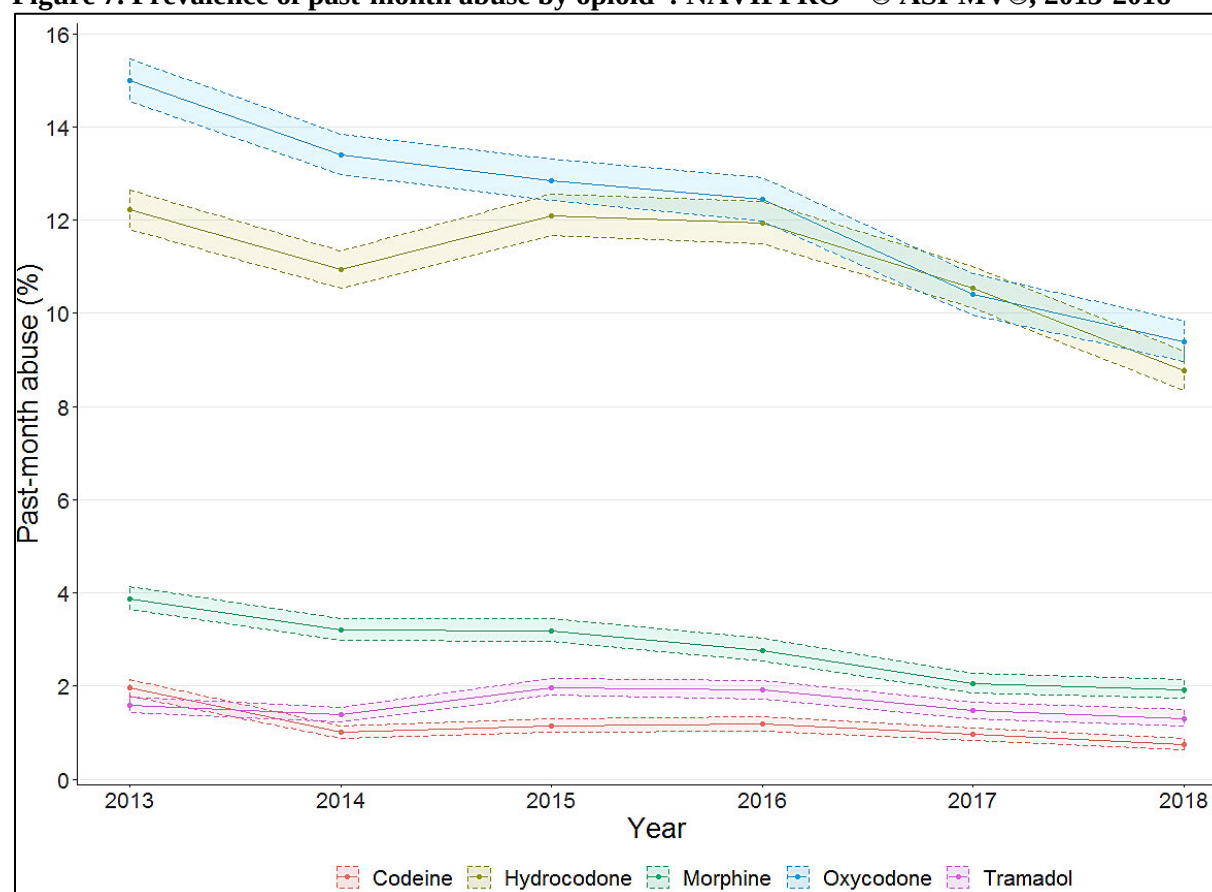
Table 15. Percent of past-month abuse by route of administration*: NAVIPPRO™ ASI-MV®, 2017-2018

Opioid Molecule	Past-Month Abuse, Unadjusted		Swallowed Whole		Chewed		Snorted		Injected	
	N	% Respondents (95% CI)	N	%	N	%	N	%	N	%
Tramadol	1,553	1.5 (1.4-1.6)	1,300	83.7	136	8.8	128	8.2	22	1.4
Codeine	993	0.9 (0.9-1.0)	—	—	—	—	—	—	—	—
Hydrocodone	8,719	8.3 (8.1-8.5)	7,028	80.6	1,796	20.6	2,393	27.5	182	2.1
Morphine	1,609	1.5 (1.5-1.6)	627	39.0	165	10.3	382	23.7	745	46.3
Oxycodone	8,575	8.2(8.0-8.3)	5,633	65.7	1,470	17.1	3,779	44.1	1,566	18.3
NAVIPPRO: National Addictions Vigilance Intervention and Prevention Program; ASI-MV: Addiction Severity Index-Multimedia Version; CI: confidence interval *Percent reporting that route among people reporting abuse of the specific opioid molecule. Participants could select multiple routes, and so percentages do not sum to 100%. '—' indicates data not available.										

From 2013 through 2018, the total number of respondents who completed the assessments was 122,664. Of these, 32,473 respondents (26.5%) endorsed past-month abuse of prescription opioids. **Figure 7** shows trends in past-month misuse/abuse by opioid from 2013 through 2018 among consistent treatment sites reporting at least one assessment per quarter.

The prevalence of tramadol abuse decreased from 1.59% (95% CI: 1.44-1.76) in 2013 to 1.31% (95% CI: 1.15-1.49) in 2018, a 10.9% decrease. Also, all comparators' respective prevalence of abuse declined. We found similar overall trends in the sub-group of assessments that reported abuse of at least one prescription opioid, and when examining data from all treatment sites that conducted assessments from 2013 through 2018. More information is provided in **Appendix E1**.

Figure 7. Prevalence of past-month abuse by opioid*: NAVIPPRO™ ASI-MV®, 2013-2018



NAVIPPRO: National Addictions Vigilance Intervention and Prevention Program; ASI-MV: Addiction Severity Index-Multimedia Version.

The dashed lines represent the 95% confidence interval.

*Among consistent treatment sites reporting at least one assessment per quarter.

3.6 NEISS-CADES

Based on approximately 3,800 NEISS-CADES surveillance cases, there were over 127,000 estimated ED visits annually in the U.S. attributed to non-medical use of any prescription opioid analgesic per year, from 2016-2017. During this period, there were 628 cases of people presenting to the ED for adverse events involving tramadol-containing products. Based on 138 cases involving non-medical use of tramadol, as defined in Section 2.7, there were an estimated 4,250 ED visits each year during 2016-2017 for non-medical use of tramadol-containing products. (**Table 16A**).

Table 16A. National estimates of emergency department (ED) visits from use of tramadol-containing products and comparator opioid analgesics, by intent of drug use: NEISS-CADES, 2016-2017^a

Intent of Drug Use by Drug Product	Number of Cases (n)	Average Annual National Estimate N (%) of ED Visits Involving Each Specified Drug by Intent
Non-medical Use^d		
Tramadol ^b	138	4,250 (20.1%)
Codeine ^c	80	2,448 (22.7%)
Hydrocodone ^b	376	14,901 (31.7%)
Morphine ^b	212	7,814 (43.2%)
Oxycodone ^b	1,478	49,609 (49.5%)
Self-harm		
Tramadol ^b	167	5,687 (26.9%)
Codeine ^c	52	1,437* (13.3%)
Hydrocodone ^b	263	9,478 (20.2%)
Morphine ^b	52	2,103 (11.6%)
Oxycodone ^b	394	13,707 (13.7%)
All other cases^e		
Tramadol ^b	323	11,206 (53.0%)
Codeine ^c	188	6,888 (63.9%)
Hydrocodone ^b	540	22,647 (48.2%)
Morphine ^b	220	8,175 (45.2%)
Oxycodone ^b	1,069	36,997 (36.9%)
CI: Confidence Interval; ED: Emergency Department ^aCases and national estimates of ED visits for drug-related adverse events were based on data from the National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, a national stratified probability sample of approximately 60 hospitals with a minimum of 6 beds and a 24-hour ED in the United States and its territories. The NEISS-CADES project, which has been described in detail elsewhere, is a joint effort of the Centers for Disease Control and Prevention, the US Consumer Product Safety Commission, and the US Food and Drug Administration (1-4). In brief, trained data abstractors located at each participating hospital review clinical records of every ED visit to identify clinician-diagnosed drug-related adverse events, to report up to 4 medications implicated in each adverse event, and to record narrative descriptions of the incident. ^bExcludes opioid-containing cough and cold products. ^cIncludes opioid-containing cough and cold products. ^dIncludes pharmaceutical abuse, therapeutic misuse (use other than as directed by a clinician), and opioid overdoses without indication of intent. ^eIncludes adverse effects, allergic reactions, medication errors, and unsupervised pediatric ingestions; Excludes cases of assault. *Estimate has a coefficient of variation >30% and may be statistically unstable.		

In addition, among ED visits attributed to non-medical use of any prescription opioid analgesic, excluding cough and cold products, an estimated 3.3% (95% CI: 2.4-4.2) involved tramadol. Among ED visits attributable to non-medical use of any prescription opioid, 39.0% involved oxycodone (95% CI: 32.7-45.3), 11.7% involved hydrocodone (95% CI: 6.1-17.3), and 6.1% involved morphine (95% CI: 4.0-8.3) (Table 16B).

Table 16B. National estimates of ED visits involving use of tramadol-containing products and comparator opioid analgesics, as percentages of visits involving any prescription opioids, by intent of drug use: NEISS-CADES, 2016-2017^a

Intent of Drug Use by Drug Product	Average Annual National Estimate	
	Percent (%) of ED Visits Involving Any Prescription Opioids, by Intent of Use ^{d,e}	95% CI
Non-medical Use^f		
Tramadol ^b	3.3	2.4-4.2
Codeine ^c	1.9	1.0-2.8
Hydrocodone ^b	11.7	6.1-17.3
Morphine ^b	6.1	4.0-8.3
Oxycodone ^b	39.0	32.7-45.3
Self-harm		
Tramadol ^b	15.8	11.7-19.8
Codeine ^c	4.0*	1.1-6.9*
Hydrocodone ^b	26.3	19.8-32.8
Morphine ^b	5.8	4.3-7.4
Oxycodone ^b	38.0	30.7-45.3
All other cases^g		
Tramadol ^b	10.8	9.4-12.2
Codeine ^c	6.5	4.6-8.4
Hydrocodone ^b	21.8	15.7-27.9
Morphine ^b	7.9	6.2-9.5
Oxycodone ^b	35.6	29.3-42.0
CI: Confidence Interval; ED: Emergency Department ^a National estimates of ED visits for drug-related adverse events were based on data from the National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, a national stratified probability sample of approximately 60 hospitals with a minimum of 6 beds and a 24-hour ED in the United States and its territories. The NEISS-CADES project, which has been described in detail elsewhere, is a joint effort of the Centers for Disease Control and Prevention, the US Consumer Product Safety Commission, and the US Food and Drug Administration (1-4). In brief, trained data abstractors located at each participating hospital review clinical records of every ED visit to identify		

clinician-diagnosed drug-related adverse events, to report up to 4 medications implicated in each adverse event, and to record narrative descriptions of the incident.

^bExcludes opioid-containing cough and cold products.

^cIncludes opioid-containing cough and cold products.

^dFor tramadol, hydrocodone, morphine, and oxycodone products, average annual estimates were based on estimated annual ED visits attributed to any prescription opioid analgesic from 2016 through 2017 (non-medical use: 127,177; self-harm: 36,057; all other visits, excluding assault: 103,786).

^eFor codeine products, average annual estimates were based on estimated annual ED visits attributed to any prescription opioid analgesic or opioid-containing cough and cold product from 2016 through 2017 (non-medical use: 127,683; self-harm: 36,126; all other visits, excluding assault: 105,698).

^fIncludes pharmaceutical abuse, therapeutic misuse (use other than as directed by a clinician), and opioid overdoses without indication of intent.

^gIncludes adverse effects, allergic reactions, medication errors, and unsupervised pediatric ingestions; Excludes cases of assault.

*Estimate has a coefficient of variation >30% and may be statistically unstable.

Among surveillance cases of ED visits involving non-medical use of tramadol (n=138), the most common adverse event manifestation was altered mental status (n=58). Of these, 10 cases specifically documented convulsions. In many cases of altered mental status after non-medical use of tramadol, the patient had consumed multiple concurrent substances (e.g., alcohol).

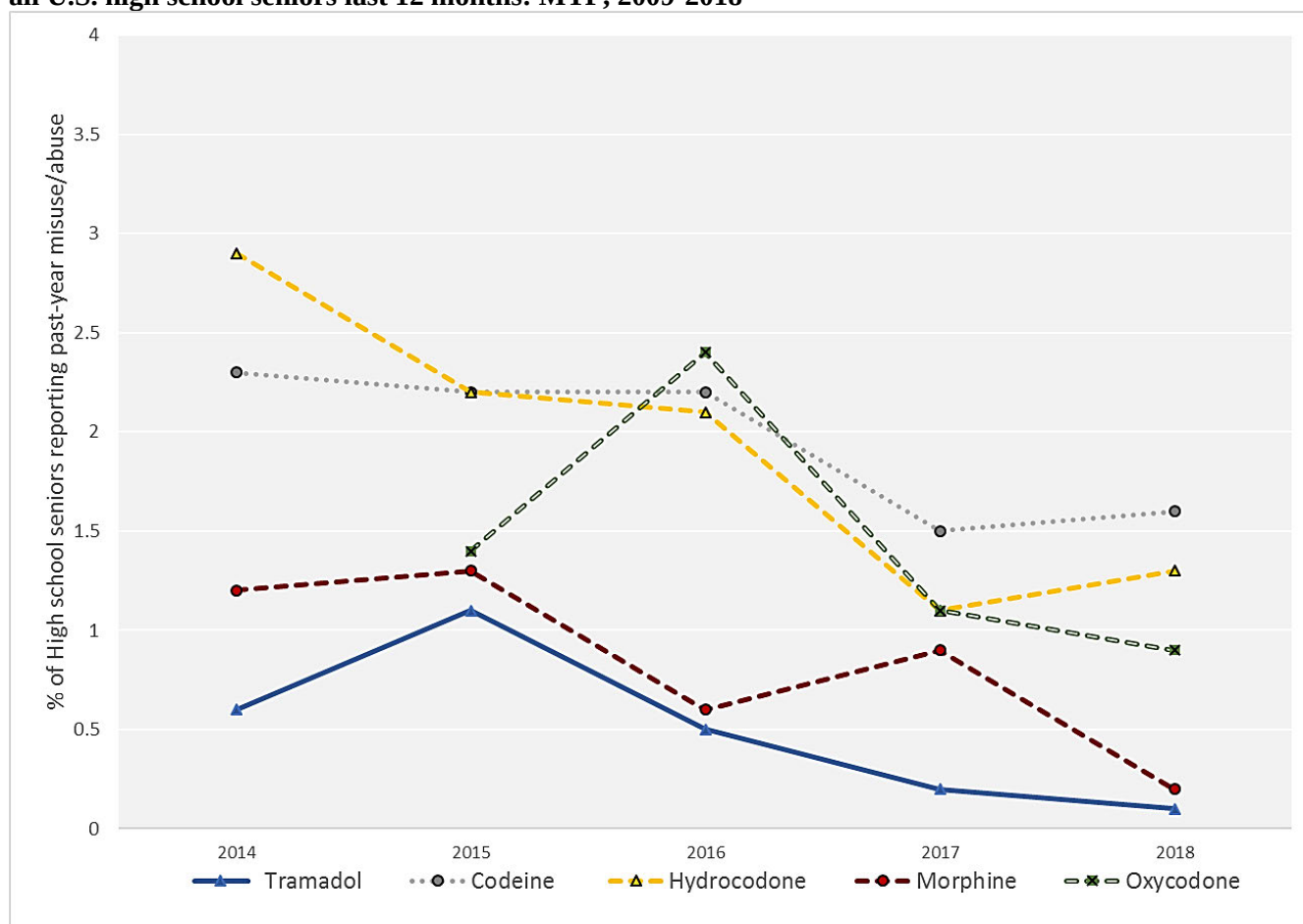
Based on 58 cases, altered mental status was documented in an estimated 1,899 (44.7%) ED visits annually involving non-medical use of tramadol. In addition, cardiac arrest, unresponsiveness, or respiratory failure/distress (n=20) and psychiatric or other central nervous system effects (n=9) were also commonly documented in cases of non-medical tramadol use (**Appendix F, Table F2**). However, we did not calculate average annual national estimates of ED visits for these adverse event manifestations, since there were <20 cases, and/or the total estimate was <1,200 (i.e., estimates are statistically unstable).

3.7 MTF

The estimated annual prevalence of misuse/abuse of tramadol and selected OAs (i.e., “*narcotics other than heroin without a doctor’s orders*”) are presented in **Figure 8**.

Across the 10-year period, the percentages of high school seniors reporting past-year misuse/abuse of tramadol and comparator OAs appeared to decline. The data suggested that, among high school seniors, the percentage who abused/misused tramadol products in the last 12 months was generally lower than for comparators. In 2018, the estimated annual prevalence of misuse/abuse for tramadol (0.1%) was similar to that of morphine (0.2%). There was no significant change between 2017 and 2018 for tramadol and comparators. **Appendix G** provides information in table format.

Figure 8. Trends in annual prevalence of tramadol and other selected opioids misuse/abuse for all U.S. high school seniors last 12 months: MTF, 2009-2018

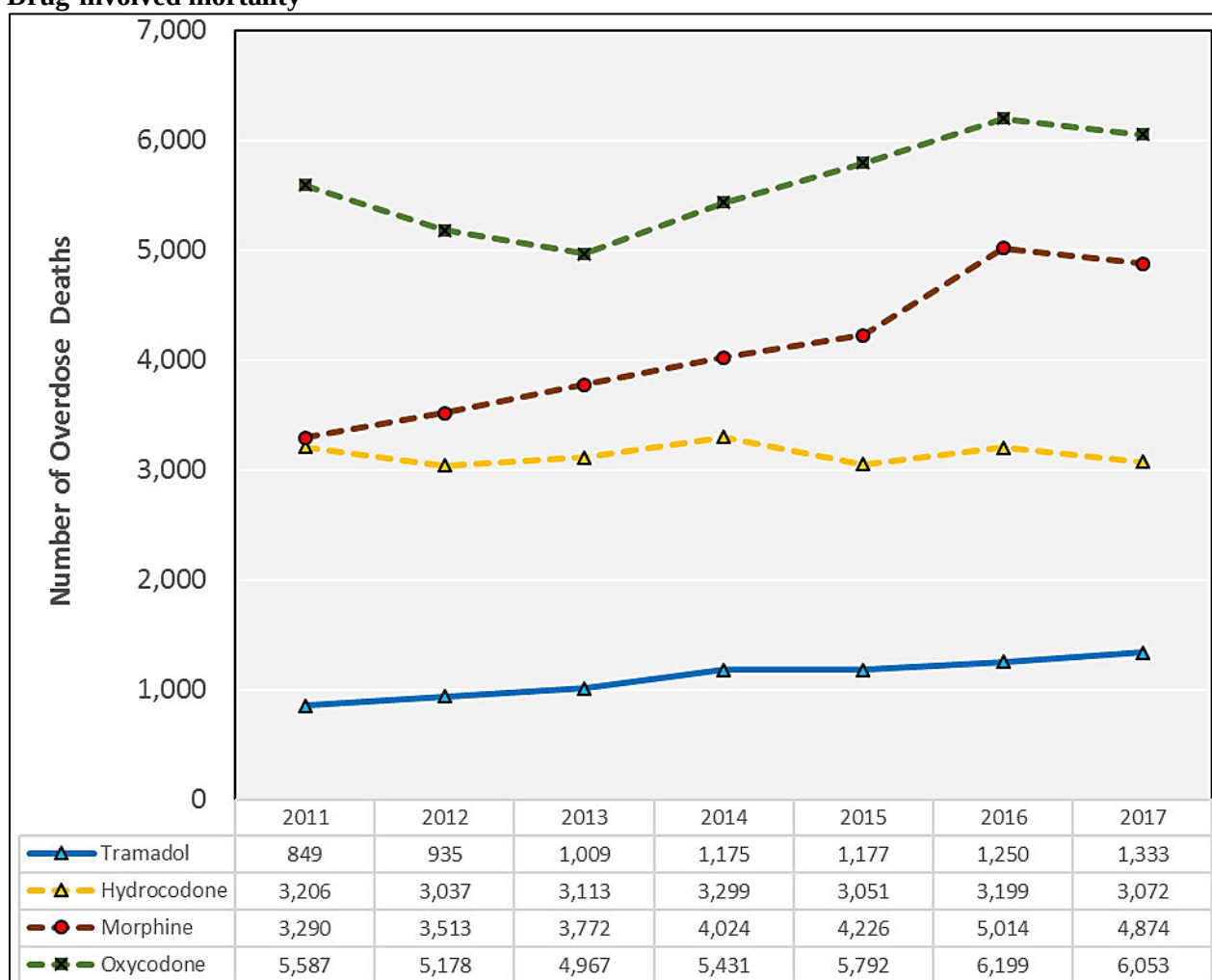


Source: The Monitoring the Future (MTF) study, the University of Michigan. Table C-4 Specific Narcotics Other than Heroin: Trends in Annual Prevalence of Use for All Seniors.
http://www.monitoringthefuture.org/pubs/monographs/mtf-vol1_2018.pdf.

3.8 NVSS-M AND DIM

Recent published reports of analyses of NVSS-M and DIM linked databases^{3,23} found that in the U.S., 2011-2017, there were 7,728 overdose deaths involving tramadol, 21,977 involving hydrocodone, 28,713 involving morphine, and 39,207 involving oxycodone (**Figure 9 and Appendix H2**). Tramadol-involved overdose deaths increased approximately 57%, from 849 in 2011 to 1,333 in 2017 (**Figure 9**). Overdose deaths involving morphine and oxycodone, respectively, also increased over the study period, with a decline in the most recent year of data (2017), while overdose deaths involving hydrocodone decreased slightly over the study period.

Figure 9. Select opioid-involved drug overdose deaths by year, U.S., 2011-2017*: NVSS-M and Drug-involved mortality



The National Vital Statistics System-Mortality (NVSS-M); Notes: *Codeine was not reported in the study. Drug overdose deaths are identified using International Classification of Diseases, Tenth Revision (ICD-10) underlying cause-of-death codes X40-X44, X60-X64, X85, and Y10-Y14. Deaths may involve other drugs in addition to the referent drug (i.e., the one listed). Deaths involving more than one drug (e.g., a death involving both heroin and cocaine) are counted in both totals. Caution should be used when comparing numbers across years. The reporting of at least one specific drug or drug class in the literal text, as identified using ICD-10 multiple cause-of-death codes T36-T50.8, improved from 75% of drug overdose deaths in 2011 to 85% of drug overdose deaths in 2016.

*Adapted from: Hedegaard H, Bastian BA, Trinidad JP, Spencer M, Warner M. 1) Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2011-2016. Natl Vital Stat Rep. 2018 Dec;67(9):1-14 and 2) Regional Differences in the Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2017. Natl Vital Stat Rep. 2019 Oct;68(12):1-15

4. DISCUSSION

4.1 SUMMARY AND INTERPRETATION OF FINDINGS

4.1.1 Drug utilization

Utilization patterns based on prescriptions dispensed for tramadol-containing products and other opioid analgesics from the retail pharmacy setting were provided as contextual background for the upcoming advisory committee meeting for NDA 213426. Retail prescription utilization of tramadol-containing products increased by 64% from 2009 through 2014 but has been declining every year from 2015 through 2018 (22%). Our analyses showed that tramadol-containing products accounted for 19% of the total 169 million OA prescriptions dispensed from retail pharmacies in 2018. There was an increasing trend in SE tramadol IR as a percentage of the total opioid analgesic prescriptions from 14% in 2012 to 19% in 2018. SE tramadol products were the second most commonly dispensed OA after hydrocodone/acetaminophen in 2018.

Compared to SE tramadol, combination tramadol/acetaminophen use was relatively low, representing 3% of the total tramadol market in 2018. SE Tramadol IR represented the most utilized form of tramadol, representing an estimated 95% of total use of tramadol. Tramadol-containing products were most frequently utilized by patients 40 years and above. Primary care physicians wrote approximately one-third of the total tramadol-containing product prescriptions dispensed through retail pharmacies in 2018.

There have been several regulatory actions with regards to tramadol in recent years. In July of 2014, the Drug Enforcement Administration (DEA) classified tramadol as a schedule IV substance.² The FDA also released safety communications restricting the use of tramadol in children and breastfeeding mothers in 2015 and 2018.³

Based on U.S. office-based physician survey data, the most common diagnoses associated with the use of tramadol-containing products were primarily the diseases of the musculoskeletal system and connective tissue, such as back pain, in 2018. A review of concurrent use(s) of tramadol-containing products showed that tramadol was mainly mentioned as being used alone or in combination with ibuprofen, meloxicam and naproxen from the NSAID class of medications. Of note, dentists are not included in the sample of U.S. office-based physician surveys.

Findings from this review should be interpreted within the context of the known limitations of the databases used. Dispensed prescription estimates are nationally projected based on a sample of prescription claims from U.S. retail pharmacies. Summarization of these projected estimates across time periods and/or products may lead to differences in prescription count due to rounding attributable to the projection methodology utilized. This analysis focused on data from the retail pharmacy setting where tramadol is primarily utilized. Thus, the prescription estimates reported in this review can only be generalized to the retail setting of care and may not be applicable to other settings in which tramadol may be prescribed or dispensed, such as mail-order/specialty pharmacies or hospitals and various other clinical settings where patients receive health care. The office-based physician surveys

² U.S. Drug Enforcement Administration (2014). Rules-2014. Schedules of Controlled Substances: Placement of Tramadol into Schedule IV. Accessed October 16, 2019. https://www.deadiversion.usdoj.gov/fed_regs/rules/2014/fr0702.htm.

³ U. S. Food and Drug Administration (2017). Drug Safety Communications. FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. Accessed October 16, 2019. <https://www.fda.gov/media/104268/download>.

database provides reported drug use mentions and diagnoses information to provide insight into prescriber intent. Although physician survey data provide insight into the prescriber's intent, they are not directly linked to dispensed prescriptions. Given these limitations, survey results may not be representative of national trends.

4.1.2 Scale of misuse/abuse of OAs

In 2018, approximately 10 million people, 3.6% of the U.S. population, had misused or abused opioid analgesics in the past year, as estimated by the NSDUH survey. The estimated number of people reporting any past-year misuse/abuse of opioid analgesics declined by 10.2% from 2017 to 2018, a statistically significant decrease. In addition, there were over 127,000 ED visits annually in 2016-2017 attributed to non-medical use of any prescription opioid analgesic, estimated from NEISS-CADES data. Of the opioid analgesics we examined, hydrocodone and oxycodone were most commonly misused/abused across data sources, while tramadol's position relative to codeine and morphine depended on the data source.

4.1.3 Relative frequency of misuse/abuse of tramadol and comparator OAs

Most data sources suggested a decrease in misuse/abuse of tramadol and comparator opioid analgesics during the study period. In contrast, data from people presenting for opioid or substance use disorder treatment showed mixed results. Specifically, data from NAVIPPRO™ ASI-MV showed a decline in past-month abuse of tramadol and comparator opioid analgesics from 2013-2018. However, data from RADARS® TCP showed an increase in past-month abuse of tramadol from 2014-2018, increased from 5.1% to 7.8% of surveys, while comparator opioid analgesics declined.

It is unclear why RADARS® TCP showed this increasing trend of tramadol abuse, and more research and confirmation is needed. One hypothesis is that data from RADARS® TCP are from people with more advanced opioid use disorder, compared with NAVIPPRO which has a more heterogeneous population of people being assessed or treated for various substance use disorders. Tramadol may be relatively easier to obtain since there are fewer restrictions on its prescribing relative to schedule II opioids, and tramadol may be trending toward an increasing percentage of total opioid analgesic outpatient prescriptions, as suggested by the results of the drug utilization analysis. However, the available data are insufficient to draw a conclusion, especially since the increased availability would be expected to increase misuse and abuse across all data sources.

4.1.4 Routes of abuse for tramadol and comparator OAs

Across different data sources and populations, the oral route was the most commonly reported for misuse/abuse involving tramadol and comparator opioid analgesics. For instance, in poison center data, almost all exposures (99.1%) occurred via the oral route. Consistently, we found comparable proportions of individuals endorsing tramadol abuse via the oral route in treatment center data.

4.1.5 Morbidity and mortality involving tramadol and comparator OAs

Tramadol was involved in an estimated 3.3% of ED visits attributed to non-medical use of any prescription opioid analgesic from 2016-2017, as estimated from NEISS-CADES. The most common category of adverse event attributed to non-medical use of tramadol was altered mental status. Among poison center calls for misuse/abuse of tramadol, 2014-2018, moderate adverse effect, which is non-life-threatening, was the most common category of related medical outcome.

Finally, mortality data from NVSS-M/DIM for the period 2011-2017 suggested that tramadol-involved overdose deaths increased. Overdose deaths involving morphine and oxycodone, respectively, also increased over the study period, with a decline in the most recent year of data (2017), while overdose

deaths involving hydrocodone decreased slightly over the study period. It was not clear whether the observed increase in overdose deaths involving tramadol is due to changes in use and abuse, or to other factors. For example, improved documentation of death certificates or increased surveillance after tramadol was placed in Schedule IV may have driven the increase in death certificates mentioning tramadol involved in the overdose. Another source of uncertainty is that the overdose deaths involving tramadol may have involved multiple opioids, including fentanyl.

4.2 DATA AND METHODS CONSIDERATIONS

4.2.1 NSDUH and MTF

Although NSDUH and MTF provide national estimates of drug misuse and abuse, individuals with advanced substance use disorders may be underrepresented, particularly if they become homeless, incarcerated, or enter a residential treatment facility (for NSDUH) or they have dropped out of high school before graduation (for MTF). Also, these survey results are subject to the inherent limitations of self-reported data, such as non-response bias, misclassification, and recall bias. In addition, their definitions capture a broad range of behaviors, including misuse for therapeutic purposes as well as use of the drug to gain a high or euphoric effect. Finally, the surveys do not collect data on route of administration.

4.2.2 AAPCC NPDS

While the NPDS contains virtually all calls to U.S. PCCs, it does not contain all cases of misuse/abuse that warrant medical attention, because not every case generates a call to a PCC. It is uncertain what fraction of events result in a poison center call, and to what extent this fraction varies over time. The most severe events, resulting in out-of-hospital overdose death, may be unlikely to generate a call to a PCC.²⁴ Therefore, AAPCC NPDS may disproportionately fail to capture cases involving drugs with the highest risk of such fatal overdoses. Calls related to misuse/abuse of tramadol and other selected opioids may be affected by the overall decline in calls to U.S. PCCs in recent years^{11,25}, and by changes in the awareness of the risks and effects of these drugs by medical personnel and the public. Finally, follow-up and medical outcomes are not available for all calls.

4.2.3 RADARS® TCP and NAVIPPRO™ ASI-MV®

Both data sources use convenience samples of people entering or being assessed for substance use disorder treatment. Therefore, information about self-reported specific products and routes of abuse may reflect individuals with more advanced substance use disorders or who are at high risk of prescription opioid abuse, and may not be generalizable to the general population. Moreover, other factors, for example, judicial referral policies and available funding for substance use disorders treatment may affect the probability that an individual who is abusing or addicted to prescription opioids is assessed for treatment and included in the sample. Also, the geographic distribution of the sample, as well as in the characteristics of the participating treatment programs may vary over time and affect observed trends in abuse rates. In addition, data are subject to various types of misclassification (e.g., incorrect identification of use of an opioid).

4.2.4 NEISS-CADES

The main limitation of this data source is that cases of adverse events involving non-therapeutic medication use (e.g., non-medical use and self-harm) were collected starting in 2016, yielding only 2 years of data at the time of this review. It is also important to note the potential for under-estimation of non-medical use of a specific prescription drug, such as tramadol. Non-medical use is typically a covert activity, and therefore medical personnel may not ascertain the full details of the pharmaceutical exposure when a person presents to the ED. The NEISS-CADES sample includes 60 participating

hospitals; national estimates may be statistically unstable or have wide confidence intervals for less frequent events (e.g., for some individual substances or clinical manifestations).

4.2.5 NVSS-M and DIM

The DIM dataset relies on drug mentions in the death certificate literal text to identify cases. Opioid-involved deaths can only be identified when these substances are specifically mentioned on death certificates, thus these findings may underestimate the number of opioid-involved deaths. There were also changes in the percentage of drug overdose deaths with a specific drug mentioned in the literal text over the course of the study period. The percentage of drug overdose deaths with codes T36–T50.8 increased from 75% in 2011 to 85% in 2016; however the study authors obtained similar results after adjusting for this increase in detection.²³

5. CONCLUSIONS

In conclusion, more than 95% of tramadol prescriptions were SE tramadol IR. Tramadol was mainly mentioned as being used for the management of diseases of the musculoskeletal system and connective tissue, such as back pain. The number of dispensed SE tramadol IR prescriptions gradually declined after the rescheduling in 2014. However, there was an increasing trend in tramadol as a percentage of the total opioid analgesic prescriptions in recent years. In addition, results from national surveys and poison center calls suggest that abuse and misuse of tramadol and comparator opioid analgesics have been declining among the general U.S. population in recent years. Tramadol was less frequently implicated in prescription opioid misuse, abuse, and related outcomes than were hydrocodone and oxycodone, while results were mixed for tramadol's position relative to codeine and morphine. Notably, tramadol abuse may have increased among people with opioid use disorder. Also, tramadol-involved overdose deaths increased from 2011 to 2017. It is uncertain whether the observed increase is due to changes in use and abuse, increased surveillance, improved documentation, or other factors.

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7. APPENDICES

7.1 APPENDIX A. DRUG USE TABLES

Table 1. Estimated number of prescriptions dispensed (TRxs) for top 20 opioid analgesics from U.S. outpatient retail pharmacies, 2009-2018

	Year									
	2009		2010		2011		2012		2013	
	TRxs	%	TRxs	%	TRxs	%	TRxs	%	TRxs	%
Total Opioid Prescriptions	249,938,576	100.0%	256,933,227	100.0%	257,827,651	100.0%	260,432,746	100.0%	251,753,771	100.0%
Hydrocodone/Acetaminophen	121,275,845	48 5%	124,240,708	48 4%	128,731,399	49 9%	128,671,889	49 4%	121,788,457	48 4%
Tramadol	22,739,933	9 1%	25,031,058	9 7%	30,373,078	11 8%	35,379,388	13 6%	37,709,881	15 0%
Oxycodone/Acetaminophen	34,024,456	13 6%	35,537,081	13 8%	36,444,479	14 1%	35,662,987	13 7%	33,666,315	13 4%
Oxycodone	14,361,327	5 7%	17,857,214	7 0%	19,258,577	7 5%	19,256,761	7 4%	19,378,727	7 7%
Codeine/Acetaminophen	13,275,099	5 3%	12,679,115	4 9%	13,158,106	5 1%	12,113,290	4 7%	10,870,622	4 3%
Morphine	6,649,031	2 7%	7,074,186	2 8%	7,725,399	3 0%	8,043,386	3 1%	8,157,283	3 2%
Fentanyl	5,072,043	2 0%	5,079,056	2 0%	5,144,706	2 0%	5,062,397	1 9%	5,018,309	2 0%
Hydromorphone	2,408,981	1 0%	2,622,249	1 0%	3,008,609	1 2%	3,256,928	1 3%	3,271,343	1 3%
Methadone	3,863,991	1 5%	3,935,176	1 5%	3,938,607	1 5%	3,725,332	1 4%	3,484,537	1 4%
Tramadol/Acetaminophen	2,636,537	1 1%	2,358,192	0 9%	2,643,923	1 0%	2,389,582	0 9%	2,116,851	0 8%
Buprenorphine	--	--	--	--	266,332	0 1%	431,793	0 2%	497,697	0 2%
Tapentadol	133,239	0 1%	534,145	0 2%	958,288	0 4%	1,027,503	0 4%	857,811	0 3%
Hydrocodone/Ibuprofen	2,284,448	0 9%	2,246,153	0 9%	2,200,305	0 9%	2,083,892	0 8%	1,868,431	0 7%
Oxymorphone	747,804	0 3%	967,721	0 4%	1,436,513	0 6%	1,103,288	0 4%	1,087,857	0 4%
Codeine/Butalbital/Caffeine/Acetaminophen	459,373	0 2%	470,043	0 2%	495,073	0 2%	502,576	0 2%	496,592	0 2%
Hydrocodone	--	--	--	--	--	--	--	--	--	--
Codeine/Butalbital/Caffeine/Aspirin	652,136	0 3%	595,647	0 2%	556,289	0 2%	491,420	0 2%	437,346	0 2%
Butorphanol	379,743	0 2%	354,119	0 1%	325,083	0 1%	292,574	0 1%	270,133	0 1%
Meperidine	668,496	0 3%	615,363	0 2%	563,482	0 2%	479,709	0 2%	397,705	0 2%
Morphine/Naltrexone	14,106	<0.1%	145,597	0 1%	35,081	<0.1%	5	<0.1%	1	<0.1%
All Other OA	18,291,988	7 3%	14,590,404	5 7%	564,322	0 2%	458,046	0 2%	377,873	0 2%

	Year									
	2014		2015		2016		2017		2018	
	TRxs	%	TRxs	%	TRxs	%	TRxs	%	TRxs	%
Total Opioid Analgesics	244,463,305	100.0%	227,785,440	100.0%	215,970,206	100.0%	192,670,584	100.0%	168,842,024	100.0%
Hydrocodone/Acetaminophen	111,799,887	45 7%	91,278,023	40 1%	84,042,577	38 9%	74,154,779	38 5%	63,572,429	37 7%
Tramadol	39,849,633	16 3%	38,955,855	17 1%	38,102,568	17 6%	34,658,293	18 0%	31,657,256	18 7%
Oxycodone/Acetaminophen	33,331,864	13 6%	34,566,007	15 2%	32,798,891	15 2%	29,051,057	15 1%	25,015,442	14 8%
Oxycodone	20,671,709	8 5%	21,740,503	9 5%	21,789,172	10 1%	20,507,003	10 6%	19,029,654	11 3%
Codeine/Acetaminophen	11,284,947	4 6%	14,926,493	6 6%	14,360,809	6 6%	12,651,706	6 6%	11,110,556	6 6%
Morphine	8,268,144	3 4%	8,329,295	3 7%	8,129,505	3 8%	7,449,411	3 9%	6,746,168	4 0%
Fentanyl	4,977,439	2 0%	4,882,242	2 1%	4,502,576	2 1%	3,724,634	1 9%	2,963,377	1 8%
Hydromorphone	3,216,603	1 3%	3,171,856	1 4%	2,928,772	1 4%	2,568,022	1 3%	2,209,116	1 3%
Methadone	3,242,281	1 3%	2,846,882	1 2%	2,591,013	1 2%	2,241,870	1 2%	1,918,665	1 1%
Tramadol/Acetaminophen	1,863,739	0 8%	1,630,228	0 7%	1,381,929	0 6%	1,133,565	0 6%	945,452	0 6%
Buprenorphine	613,086	0 3%	643,634	0 3%	696,025	0 3%	654,859	0 3%	673,148	0 4%
Tapentadol	782,089	0 3%	778,518	0 3%	831,183	0 4%	740,349	0 4%	583,695	0 3%
Hydrocodone/Ibuprofen	1,597,567	0 7%	1,069,122	0 5%	856,478	0 4%	641,606	0 3%	468,920	0 3%
Oxymorphone	1,173,046	0 5%	1,180,788	0 5%	1,156,518	0 5%	835,542	0 4%	441,953	0 3%
Codeine/Butalbital/Caffeine/Acetaminophen	504,948	0 2%	498,959	0 2%	462,851	0 2%	409,147	0 2%	359,482	0 2%
Hydrocodone	35,093	0 0%	149,957	0 1%	240,748	0 1%	274,804	0 1%	275,302	0 2%
Codeine/Butalbital/Caffeine/Aspirin	382,313	0 2%	343,119	0 2%	304,643	0 1%	258,989	0 1%	226,853	0 1%
Butorphanol	249,804	0 1%	223,207	0 1%	209,091	0 1%	185,476	0 1%	165,978	0 1%
Meperidine	333,454	0 1%	275,659	0 1%	240,970	0 1%	190,125	0 1%	145,691	0 1%
Morphine/Naltrexone	--	--	27,775	<0.1%	110,865	0 1%	131,620	0 1%	140,685	0 1%
All Other OA	285,659	0.1%	267,318	0.1%	233,022	0.1%	207,727	0.1%	192,202	0.1%

Source: IQVIA National Prescription Audit™. 2019. Data extracted October 2019. File: USC02200 Launch MVP_1_Oct-03-2019.xlsx.

Of note, there are changes in the underlying data and methodology of the proprietary database IQVIA NPA to account for a dynamic pharmaceutical market, including a change to manage prescription claims that are voided or reversed. Prescription volumes dispensed from the retail pharmacies have been historically adjusted back to January 2017. Data prior to January 2017 have not been adjusted to the new methodology. In 2018, an estimated 2% of total prescription claims for opioid analgesics dispensed from U.S. retail pharmacies appear to have been voided or reversed.

Table 2. Estimated number of units (tablets, capsules; EUTRx) of Top 20 opioid analgesics dispensed from U.S. retail pharmacies, 2009-2018

	Year									
	2009		2010		2011		2012		2013	
	EUTRx	%	EUTRx	%	EUTRx	%	EUTRx	%	EUTRx	%
Total of Extended Units	15,693,610,464	100.0%	16,617,426,098	100.0%	17,086,533,698	100.0%	17,279,208,003	100.0%	16,758,908,853	100.0%
Hydrocodone/Acetaminophen	6,901,991,346	44 0%	7,247,794,778	43 6%	7,649,331,240	44 8%	7,687,616,005	44 5%	7,372,189,123	44 0%
Tramadol	1,735,039,774	11 1%	1,924,580,449	11 6%	2,310,738,119	13 5%	2,724,100,214	15 8%	2,909,229,820	17 4%
Oxycodone/Acetaminophen	2,128,481,313	13 6%	2,258,182,656	13 6%	2,350,143,440	13 8%	2,295,738,734	13 3%	2,164,268,830	12 9%
Oxycodone	1,349,011,486	8 6%	1,746,761,220	10 5%	1,947,085,506	11 4%	1,897,793,703	11 0%	1,845,928,191	11 0%
Codeine/Acetaminophen	741,484,690	4 7%	709,554,869	4 3%	719,536,033	4 2%	638,232,568	3 7%	543,809,316	3 2%
Morphine	504,188,447	3 2%	539,754,055	3 2%	587,965,089	3 4%	604,359,470	3 5%	601,876,572	3 6%
Methadone	621,215,224	4 0%	626,301,120	3 8%	614,857,283	3 6%	563,940,760	3 3%	504,324,507	3 0%
Hydromorphone	206,121,388	1 3%	222,431,422	1 3%	254,695,459	1 5%	276,382,787	1 6%	272,024,910	1 6%
Tramadol/Acetaminophen	181,872,143	1 2%	162,926,859	1 0%	179,816,793	1 1%	162,894,743	0 9%	145,495,297	0 9%
Tapentadol	9,745,171	0 1%	38,037,166	0 2%	64,406,693	0 4%	69,966,432	0 4%	64,138,800	0 4%
Fentanyl	70,153,426	0 4%	67,874,606	0 4%	67,281,250	0 4%	63,495,824	0 4%	62,646,789	0 4%
Oxymorphone	53,655,669	0 3%	69,148,409	0 4%	103,926,535	0 6%	78,293,631	0 5%	77,598,580	0 5%
Hydrocodone/Ibuprofen	108,547,161	0 7%	108,505,573	0 7%	107,605,338	0 6%	101,892,218	0 6%	92,185,051	0 6%
Codeine/Butalbital/Caffeine/Acetaminophen	26,221,184	0 2%	27,016,844	0 2%	28,535,661	0 2%	28,544,074	0 2%	28,192,869	0 2%
Codeine/Butalbital/Caffeine/Aspirin	38,077,777	0 2%	35,297,279	0 2%	33,659,643	0 2%	30,173,735	0 2%	26,904,426	0 2%
Hydrocodone	--	--	--	--	--	--	--	--	--	--
Buprenorphine	--	--	--	--	1,063,280	<0.1%	1,740,164	<0.1%	2,016,762	<0.1%
Morphine/Naltrexone	727,063	<0.1%	7,621,406	0 0%	1,849,914	<0.1%	319	<0.1%	60	<0.1%
Meperidine	28,023,339	0 2%	25,746,965	0 2%	23,438,595	0 1%	19,643,201	0 1%	16,104,095	0 1%
Codeine	8,178,369	0 1%	9,263,239	0 1%	9,423,215	0 1%	8,351,032	<0.1%	7,641,637	<0.1%
All Other OA	980,875,494	6 3%	790,628,183	4 8%	31,174,612	0 2%	26,048,389	0 2%	22,333,218	0 1%

	Year									
	2014		2015		2016		2017		2018	
	EUTRx	%	EUTRx	%	EUTRx	%	EUTRx	%	EUTRx	%
Total of Extended Units	16,257,973,764	100.0%	15,307,357,326	100.0%	14,529,690,603	100.0%	12,871,198,518	100.0%	10,986,934,416	100.0%
Hydrocodone/Acetaminophen	6,822,465,610	42 0%	5,866,934,507	38 3%	5,415,706,934	37 3%	4,761,252,849	37 0%	4,013,622,997	36 5%
Tramadol	3,041,294,306	18 7%	2,918,687,771	19 1%	2,836,720,170	19 5%	2,538,580,250	19 7%	2,210,593,470	20 1%
Oxycodone/Acetaminophen	2,123,205,691	13 1%	2,182,888,194	14 3%	2,120,424,150	14 6%	1,904,376,751	14 8%	1,632,381,951	14 9%
Oxycodone	1,909,710,878	11 7%	1,979,785,083	12 9%	1,964,093,765	13 5%	1,798,816,647	14 0%	1,582,508,896	14 4%
Codeine/Acetaminophen	543,799,311	3 3%	672,016,543	4 4%	631,644,117	4 3%	536,776,040	4 2%	444,880,376	4 0%
Morphine	598,194,475	3 7%	588,845,637	3 8%	560,667,514	3 9%	499,041,235	3 9%	436,486,965	4 0%
Methadone	448,631,224	2 8%	378,862,157	2 5%	330,837,979	2 3%	270,709,238	2 1%	216,634,179	2 0%
Hydromorphone	265,503,241	1 6%	258,906,437	1 7%	241,071,276	1 7%	208,300,044	1 6%	173,632,771	1 6%
Tramadol/Acetaminophen	127,645,318	0 8%	108,952,742	0 7%	91,804,284	0 6%	73,552,356	0 6%	57,305,024	0 5%
Tapentadol	59,274,655	0 4%	58,520,791	0 4%	60,869,454	0 4%	53,483,342	0 4%	42,516,607	0 4%
Fentanyl	62,327,536	0 4%	60,905,992	0 4%	54,420,351	0 4%	43,506,381	0 3%	33,401,273	0 3%
Oxymorphone	82,246,861	0 5%	81,535,101	0 5%	78,625,208	0 5%	56,853,799	0 4%	30,889,153	0 3%
Hydrocodone/Ibuprofen	80,009,024	0 5%	57,941,277	0 4%	47,311,809	0 3%	36,530,560	0 3%	27,269,531	0 2%
Codeine/Butalbital/Caffeine/Acetaminophen	28,261,070	0 2%	27,761,746	0 2%	25,999,865	0 2%	23,107,568	0 2%	20,110,751	0 2%
Codeine/Butalbital/Caffeine/Aspirin	23,497,293	0 1%	21,340,530	0 1%	19,287,464	0 1%	16,506,395	0 1%	14,040,798	0 1%
Hydrocodone	1,971,428	<0.1%	6,179,148	<0.1%	9,261,790	0 1%	10,361,257	0 1%	10,676,788	0 1%
Buprenorphine	2,482,332	<0.1%	2,608,698	<0.1%	5,324,680	0 0%	6,810,659	0 1%	10,628,383	0 1%
Morphine/Naltrexone	--	<0.1%	1,265,159	<0.1%	5,142,027	0 0%	6,155,215	<0.1%	6,609,744	0 1%
Meperidine	13,439,874	0 1%	11,024,579	<0.1%	9,582,261	0 1%	7,340,502	0 1%	5,355,759	<0.1%
Codeine	7,165,950	<0.1%	6,865,251	<0.1%	6,530,811	<0.1%	5,798,829	<0.1%	5,123,529	<0.1%
All Other OA	16,847,687	0 1%	15,529,983	<0.1%	14,364,694	0 1%	13,338,601	0 1%	12,265,471	0 1%

Source: IQVIA National Prescription Audit™. 2019. Data extracted October 2019. File: USC02200 Launch MVP_1_Oct-03-2019.xlsx

Of note, there are changes in the underlying data and methodology of the proprietary database IQVIA NPA to account for a dynamic pharmaceutical market, including a change to manage prescription claims that are voided or reversed. Prescription volumes dispensed from the retail pharmacies have been historically adjusted back to January 2017. Data prior to January 2017 have not been adjusted to the new methodology. In 2018, an estimated 2% of total prescription claims for opioid analgesics dispensed from U.S. retail pharmacies appear to have been voided or reversed.

Table 3. Estimated number of prescriptions dispensed (TRxs) for tramadol-containing immediate-release (IR) and extended-release (ER) products from US retail pharmacies, 2014-2018

	Year									
	2014		2015		2016		2017		2018	
	TRxs	%	TRxs	%	TRxs	%	TRxs	%	TRxs	%
Total Dispensed Tramadol-Containing Prescriptions	41,713,372	100.0%	40,586,083	100.0%	39,484,497	100.0%	35,791,858	100.0%	32,602,708	100.0%
Single Entity (SE) Tramadol	39,849,633	95.5%	38,955,855	96.0%	38,102,568	96.5%	34,658,293	96.8%	31,657,256	97.1%
Tramadol IR	39,122,552	98.2%	38,250,588	98.2%	37,426,659	98.2%	34,066,754	98.3%	31,097,128	98.2%
Tramadol ER	727,081	1.8%	705,267	1.8%	675,909	1.8%	591,539	1.7%	560,128	1.8%
Combination Tramadol/Acetaminophen	1,863,739	4.5%	1,630,228	4.0%	1,381,929	3.5%	1,133,565	3.2%	945,452	2.9%

Source: IQVIA National Prescription Audit™. 2019. Data extracted October 2019. File: NPA 2019-1557 Tramadol IR&ER 2014-2018. 10-30-19.xlsx

Of note, there are changes in the underlying data and methodology of the proprietary database IQVIA NPA to account for a dynamic pharmaceutical market, including a change to manage prescription claims that are voided or reversed. Prescription volumes dispensed from the retail pharmacies have been historically adjusted back to January 2017. Data prior to January 2017 have not been adjusted to the new methodology. In 2018, an estimated 2% of total prescription claims for opioid analgesics dispensed from U.S. retail pharmacies appear to have been voided or reversed.

Table 4. Estimated number of prescriptions* (TRxs) dispensed for tramadol-containing immediate-release (IR) and extended-release (ER) products from U.S. retail pharmacies stratified by patient age, 2018.**

	TRxs	%
Total Tramadol-Containing Prescriptions	32,017,041	100%
Single Ingredient Tramadol	31,077,692	97%
Tramadol IR	30,525,289	98%
0-19 years	14,683	1%
20-39 years	4,132,782	14%
40-59 years	10,650,439	35%
60-74 years	10,131,514	33%
75+ years	5,323,470	17%
Unspecified Age	52,980	<0.1%
Tramadol ER	552,116	2%
0-19 years	27	<0.1%
20-39 years	55,308	10%
40-59 years	241,918	44%
60-74 years	193,911	35%
75+ years	59,396	11%
Unspecified Age	785	<0.1%
Combination Tramadol/Acetaminophen IR	939,349	3%
0-19 years	60	1%
20-39 years	116,674	12%
40-59 years	260,328	28%
60-74 years	308,916	33%
75+ years	237,651	25%
Unspecified Age	1,700	0%
Unknown	287	<0.1%

Source: IQVIA National Prescription Audit™. 2019. Data extracted October 2019. File: NPA 2019-1557 Tramadol by Age. No Vet Oct-31-19.xlsx

*Data exclude prescriptions written by veterinarians

**Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 20-39 years include patients less than 40 years of age (39 years and 11 months)

Table 5. Estimated number of prescriptions dispensed (TRxs) for tramadol-containing products, stratified by top ten prescriber specialties, from U.S. retail pharmacies, 2018

	TRxs	%
Total Tramadol-Containing Prescriptions	32,602,708	100.0%
FP/GP/IM	12,195,696	37.4%
NP/PA	6,600,699	20.3%
Osteopathic Medicine	3,359,317	10.3%
Orthopedic Surgery	1,633,101	5.0%
Emergency Medicine	1,010,511	3.1%
Rheumatology	997,932	3.1%
Anesthesiology	786,403	2.4%
Dentistry	661,509	2.0%
Physical Medicine and Rehab	640,161	2.0%
Veterinary Medicine	550,256	1.7%
All Other Specialties	4,167,123	12.8%

Source: IQVIA National Prescription Audit™. 2019. Data extracted September 2019. File: NPA Tramadol by Specialty.9-16-19.xlsx

*FP/GP/IM-family practice, general practice and internal medicine, NP/PA- nurse practitioners/physician assistants

Table 6. Estimated number (in thousands (000)) of drug use mentions with the use of tramadol-containing products in association with a diagnosis* (ICD-10-CM) as reported by U.S. office-based physician surveys, 2018

	Uses (000)	%	95% CI (000)
Total Tramadol Use Mentions	12,535	100%	11,834 - 13,236
SE Tramadol IR	12,217	98%	11,525 - 12,909
M00-M99 Diseases of the musculoskeletal system and connective tissue	6,297	52%	5,800 - 6,794
M54 Dorsalgia	2,575	41%	2,257 - 2,893
M75 Shoulder lesions	497	8%	357 - 637
M25 Other joint disorder, not elsewhere classified	435	7%	305 - 566
M17 Osteoarthritis of knee	399	6%	274 - 524
M79 Oth and unsp soft tissue disorders, not elsewhere classified	335	5%	220 - 450
All Others	2,056	33%	1,772 - 2,340
S00-T88 Injury, poisoning and certain external cause consequences	2,251	18%	1,954 - 2,549
S93 Disloc & sprain of joints & ligaments at ankl, ft & toe lev	305	14%	195 - 414
S33 Disloc & sprain of joints & ligaments of lumbar spin & pelv	189	8%	103 - 275
S83 Dislocation and sprain of joints and ligaments of knee	187	8%	101 - 273
S52 Fracture of forearm	152	7%	75 - 230
S23 Dislocation and sprain of joints and ligaments of thorax	108	5%	43 - 173
All Others	1,310	58%	1,084 - 1,537
Z00-Z99 Factors influencing health status and health services	875	7%	690 - 1,060
Z09 Encntr for f/u exam aft trtmt for cond oth than malig neoplsm	347	40%	230 - 463
Z08 Encntr for follow-up exam after trtmt for malignant neoplasm	160	18%	81 - 240
Z47 Orthopedic aftercare	105	12%	41 - 169
Z96 Presence of other functional implants	89	10%	30 - 148
Z90 Acquired absence of organs, not elsewhere classified	87	10%	29 - 146
All Others	87	10%	29 - 146
C00-D49 Neoplasms	618	5%	462 - 774
C50 Malignant neoplasm of breast	243	39%	145 - 341
D25 Leiomyoma of uterus	202	33%	113 - 291
C44 Other and unspecified malignant neoplasm of skin	91	15%	32 - 151
C49 Malignant neoplasm of other connective and soft tissue	32	5%	<0.5 - 67
C07 Malignant neoplasm of parotid gland	29	5%	<0.5 - 63
All Others	21	3%	<0.5 - 50
G00-G99 Diseases of the nervous system	539	4%	394 - 685
G89 Pain, not elsewhere classified	211	39%	120 - 302
G56 Mononeuropathies of upper limb	102	19%	39 - 165
G90 Disorders of autonomic nervous system	63	12%	13 - 112
G43 Migraine	32	6%	<0.5 - 68
G58 Other mononeuropathies	23	4%	<0.5 - 53
All Others	108	20%	43 - 173
All Others	1,637	13%	1,383 - 1,890
SE Tramadol ER	163	1%	83 - 242
M00-M99 Diseases of the musculoskeletal system and connective tissue	163	100%	83 - 242
Tramadol/acetaminophen	155	1%	77 - 233
M00-M99 Diseases of the musculoskeletal system and connective tissue	82	53%	25 - 138
R00-R99 Symptoms, signs and abnormal clinical and lab findings, nec	28	18%	<0.5 - 61
S00-T88 Injury, poisoning and certain external cause consequences	27	17%	<0.5 - 59
Z00-Z99 Factors influencing health status and health services	19	12%	<0.5 - 46

Source: Syneos Health Research & Insights LLC., TreatmentAnswers™ 2019. Data extracted September 2019. PDDA_2019-1557_tramadol_product_chap_Dx_09-18-19.xls

*Diagnosis data are not directly linked to dispensed prescriptions but are obtained from surveys of a sample of 3,200 office-based physicians reporting on patient activity during one day per month. Syneos recommends caution interpreting results where projected drug use mentions fall below 100,000 because the sample size may be very small with correspondingly large confidence intervals and may not provide reliable national estimates of use.

Table 7 Estimated concurrent mentions (in thousands (000)) of the use of tramadol-containing products stratified by the top 10 other molecules as reported by U.S. office-based physician surveys, 2018

	Occur (000)	%	95% CI (000)
SE Tramadol IR	12,521	97%	11,818 - 13,224
Used Alone	6,740	54%	6,224 - 7,256
Ibuprofen	1,019	8%	819 - 1,220
Meloxicam	526	4%	382 - 670
Cyclobenzaprine hydrochloride	506	4%	364 - 647
Gabapentin	410	3%	283 - 538
Methylprednisolone acetate	335	3%	220 - 450
Famotidine/ibuprofen	335	3%	220 - 449
Naproxen sodium	265	2%	163 - 368
Acetaminophen	227	2%	132 - 321
Clindamycin hydrochloride	149	1%	72 - 226
Celecoxib	37	<1%	<0.5 - 75
All Others	3,375	27%	3,010 - 3,740
SE Tramadol ER	169	1%	87 - 250
Used Alone	71	42%	18 - 123
Hydrocodone/Acetaminophen	27	16%	<0.5 - 59
Oxycodone/Acetaminophen	25	15%	<0.5 - 57
Tramadol IR	23	14%	<0.5 - 53
Diclofenac sodium	17	10%	<0.5 - 43
Lidocaine	6	4%	<0.5 - 22
Celecoxib	5	3%	<0.5 - 18
Metaxalone	5	3%	<0.5 - 18
Oxycodone hydrochloride	5	3%	<0.5 - 18
Tramadol/Acetaminophen	201	2%	112 - 290
Used Alone	70	35%	17 - 122
Methocarbamol	27	13%	<0.5 - 59
Naproxen	27	13%	<0.5 - 59
Lidocaine	27	13%	<0.5 - 59
Fluticasone propionate	19	9%	<0.5 - 46
Azelastine hydrochloride	19	9%	<0.5 - 46
Aspirin	19	9%	<0.5 - 46
Tadalafil	19	9%	<0.5 - 46
Diclofenac sodium	15	7%	<0.5 - 39
Gabapentin	15	7%	<0.5 - 39
All Others	10	5%	<0.5 - 31

Source: Syneos Health Research & Insights LLC., TreatmentAnswers™ 2019. Data extracted October 2019. PDDA_2019-1557_Concurrency tramadol_celebrex_10-11-19.xls

Data are obtained from surveys of a sample of 3,200 office-based physicians reporting on patient activity during one day per month. Syneos recommends caution interpreting results where projected drug mentions fall below 100,000 because the sample size may be very small with correspondingly large confidence intervals and may not provide reliable national estimates of use.

Appendix A1. Database Description

IQVIA National Sales Perspectives™ (NSP)

The IQVIA National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches (number of single items such as vials, syringes, etc. contained in a shipping package), extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

The manufacturer sales distribution data do not provide an estimate of direct patient use; rather, they provide a national estimate of units sold from the manufacturer to various retail and non-retail settings of care. The amount of product purchased by these settings of care may be a possible surrogate for use if we assume that facilities purchase drugs in quantities reflective of actual patient use.

IQVIA National Prescription Audit™ (NPA)

The IQVIA National Prescription Audit (NPA) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit provide a national level estimate of the drug activity from retail pharmacies. NPA receives over 3.7 billion prescription claims per year, captured from a sample of the universe of approximately 58,900 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 92% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part D prescriptions. Data are also collected from approximately 60 – 86% (varies by class and geography) of mail service pharmacies and approximately 75 – 83% of long-term care pharmacies. Data are available on-line for 72-rolling months with a lag of 1 month.

Due to the changing pharmaceutical marketplace, IQVIA has implemented changes to its prescription database to manage prescription voids, reversals, and abandonments that span multiple weeks. Beginning in January 2019, IQVIA has projected published prescription volumes dispensed from the retail pharmacies based on sold date, instead of date of adjudication (i.e., fill date). Projected estimates have been adjusted and restated in the database back to January 2017; data prior to 2017 remain unadjusted. As a result, a trend break occurs between 2016 and 2017 prescription volumes dispensed from the retail pharmacies; any changes over time must be interpreted in the context of the changes in the underlying data and methodology.

Dispensed prescription estimates are nationally projected based on a sample of prescriptions claims from mail-order/specialty and retail pharmacies. Summarization of these projected estimates across time periods and/or settings of care may lead to differences in prescription count due to rounding attributable to the projection methodology utilized. No statistical tests were performed on these estimates to determine statistically significant changes over time. Therefore, all changes over time should be considered approximate and may be due to random error.

Syneos Health Research & Insights LLC., TreatmentAnswers™ with Pain Panel

Syneos Health Research & Insights, LLC., TreatmentAnswers™ is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit, and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

7.3 APPENDIX B. NSDUH

Appendix B1. NSDUH product categories and descriptions

Drug Product Category*	Category Description
Tramadol	Ultram®, Ultram® ER, Ultracet®, generic tramadol, generic extended-release tramadol, or other similar products
Codeine	Tylenol® with codeine 3 or 4, generic codeine pills, or other similar products
Hydrocodone	Vicodin®, Lortab®, Norco®, Zohydro® ER, generic hydrocodone, or other similar products
Morphine	Avinza®, Kadian®, MS Contin®, generic morphine, generic extended-release morphine, or other similar products
Oxycodone	OxyContin®, Percocet®, Percodan®, Roxicodone®, generic oxycodone, or other similar products
*Over-the-counter drugs are not included. Source: Center for Behavioral Health Statistics and Quality. (2018). 2017 National Survey on Drug Use and Health (NSDUH): Methodological summary and definitions. Rockville, MD: Substance Abuse and Mental Health Services Administration	

Appendix B2. National projections for any use and misuse/abuse of tramadol products and comparator opioid analgesics among persons aged 12 or older: number in thousands, U.S., national survey on drug use and health, 2015-2018

Drug product	2015	2016	2017	2018
Any Prescription Pain Reliever				
Any use in past year, n (% of total population)	97,499 ^b (36.4)	91,846 (34.1)	90,799 ^e (33.4)	86,548 (31.6)
Misuse in past year, n (% of total population)	12,462 ^a (4.7)	11,517 (4.3)	11,077 ^e (4.1)	9,948 (3.6)
Misuse in past year, n (% of past-year any use)	12,462 ^a (12.8)	11,517 (12.5)	11,077 ^e (12.2)	9,948 (11.5)
Tramadol				
Any use in past year, n (% of total population)	18,573 (6.9)	18,931 (7.0)	18,485 (6.8)	17,982 (6.6)
Misuse in past year, n (% of total population)	1,794 (0.7)	1,591 (0.6)	1,753 (0.6)	1,455 (0.5)
Misuse in past year, n (% of past-year any use)	1,794 (9.7)	1,591 (8.4)	1,753 (9.5)	1,455 (8.1)
Codeine				
Any use in past year, n (% of total population)	NA	26,544 (9.9)	26,870 (9.9) ^e	25,413 (9.3)
Misuse in past year, n (% of total population)	NA	2,767 (1.0)	2,832 (1.0) ^e	2,393 (0.9)
Misuse in past year, n (% of past-year any use)	NA	2,767 (10.4)	2,832 (10.5) ^e	2,393 (9.4)
Hydrocodone				
Any use in past year, n (% of total population)	58,261 ^b (21.8)	54,807 (20.3) ^d	51,979 (19.1) ^e	47,731 (17.4)
Misuse in past year, n (% of total population)	7,193 (2.7)	6,924 (2.6) ^c	6,262 (2.3) ^e	5,502 (2.0)
Misuse in past year, n (% of past-year any use)	7,193 (12.3)	6,924 (12.6) ^c	6,262 (12.0) ^e	5,502 (11.5)
Morphine				
Any use in past year, n (% of total population)	7,205 (2.7)	6,828 (2.5)	6,231 (2.3)	6,161 (2.3)
Misuse in past year, n (% of total population)	697 (0.3)	536 (0.2)	501 (0.2)	486 (0.2)
Misuse in past year, n (% of past-year any use)	697 (9.7)	536 (7.9)	501 (8.0)	486 (7.9)
Oxycodone				
Any use in past year, n (% of total population)	27,873 (10.4)	27,622 (10.3)	26,720 (9.8)	26,392 (9.6)
Misuse in past year, n (% of total population)	4,258 (1.6)	3,905 (1.4)	3,735 (1.4)	3,374 (1.2)
Misuse in past year, n (% of past-year any use)	4,258 (15.3)	3,905 (14.1)	3,735 (14.0)	3,374 (12.8)

n: Numbers in Thousands

^a The difference between this estimate and the 2016 estimate is statistically significant at the .05 level. Rounding may make the estimates appear identical.

^b The difference between this estimate and the 2016 estimate is statistically significant at the .01 level. Rounding may make the estimates appear identical.

^c The difference between this estimate and the 2017 estimate is statistically significant at the .05 level. Rounding may make the estimates appear identical.

^d The difference between this estimate and the 2017 estimate is statistically significant at the .01 level. Rounding may make the estimates appear identical.

^e The difference between this estimate and the 2018 estimate is statistically significant at the .05 level. Rounding may make the estimates appear identical.

Note: Tramadol products included Ultram®, Ultram® ER, Ultracet®, generic tramadol, generic extended-release tramadol, or other similar products.

Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2017 and 2018 Detailed Tables. Tables 1.98A and 1.98B <https://www.samhsa.gov/data/nsduh/reports-detailed-tables-2018-NSDUHhttps://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2018R2/NSDUHDetTabsSect1pe2018.htm>; SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2016 and 2017 Detailed Tables. Tables 1.97A and 1.97B <https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2017/NSDUHDetailedTabs2017.htm#tab1-97A>; SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2014 and 2015. Detailed Tables. Tables 1.139A and 1.139B <https://www.samhsa.gov/data/report/results-2015-national-survey-drug-use-and-health-detailed-tables>

7.4 APPENDIX C. AAPCC NPDS

(b) (4)



Appendix C2. AAPCC NPDS variable definitions

REASON:

Unintentional: An unintentional exposure results from an unforeseen or unplanned event. For example, a child gaining access to a toxic substance, when it is obvious the child did not realize the danger of the action, is an unintentional exposure. The following eight coding options are available for unintentional exposures. (Includes sub-categories: *General; Environmental; Occupational; Therapeutic Error; Misuse; Bite/Sting, Food Poisoning; Unknown*)

Intentional: A purposeful action results in an exposure. The following four categories relate to intentional exposures. (Includes sub-categories: *Suspected Suicide; Misuse; Abuse; Unknown*)

Intentional exposure reasons	Definition
Suspected Suicide	“An exposure resulting in the inappropriate use of a substance for self-harm or self-destruction or manipulative reasons”
Abuse	“An exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect or some other psychotropic effect”, including recreational use of a substance for any effect
Misuse	“An exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect”
Unknown	“Exposures that are deemed to be intentional although the specific motive is undetermined”
Source: American Association of Poison Control Centers. National Poison Data System (NPDS) Data Dictionary. Version 2016.07.11. July 11, 2016	

Adverse Reaction: This category is used to monitor adverse reactions (experiences) to a variety of products, including drugs, foods, cosmetics and industrial or household chemicals. (Includes sub-categories: *Drug; Food; Other*)

Other/Unknown: This category is used when the reason for the exposure cannot be determined or if no other category is appropriate. (Includes sub-categories: *Contaminant/Tampering; Malicious; Withdrawal; Unknown*)

MEDICAL OUTCOME:

No Effect: The patient developed no symptoms (clinical effects) as a result of the exposure. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long enough after the exposure that the poison center is reasonably certain no effects will occur.

Minor Effect: The patient exhibited some symptoms as a result of the exposure, but they were minimally bothersome to the patient. The symptoms usually resolve rapidly and often involve skin or mucous membrane manifestations. The patient has returned to a pre-exposure state of well-being and has no residual disability or disfigurement. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long enough after the exposure that there is

reasonable certainty that the clinical effect(s) will not worsen. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the residual symptoms are anticipated to be long-term and of minimal clinical significance.

Moderate Effect: The patient exhibited symptoms as a result of the exposure which are more pronounced, more prolonged or more of a systemic nature than minor symptoms. Usually some form of treatment is or would have been indicated. Symptoms were not life-threatening, and the patient has returned to a pre-exposure state of well-being with no residual disability or disfigurement. Follow-up is required to make this determination unless the initial regional poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty that the clinical effect(s) will not get worse. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the residual symptoms are anticipated to be long-term and of minimal clinical significance.

Major Effect: The patient has exhibited symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement. Follow-up is required to make this determination unless the initial poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty the clinical effect(s) will not get worse. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the symptoms are anticipated to be long-term or permanent.

Death: The patient died as a result of the exposure or as a direct complication of the exposure where the complication was unlikely to have occurred had the toxic exposure not preceded the complication. Only include those deaths which are probably or undoubtedly related to the exposure. A fatality verification is required. Also include deaths in which the exposure was a contributing factor in the death. For deaths determined to be unrelated to the exposure (those in which the most clinically significant clinical effects are coded as unrelated) the outcome is coded as “Unrelated effect” (the exposure was probably not responsible for the effect[s]).

Other – Includes sub-categories:

Case not followed to a known outcome: In some circumstances it is not appropriate or possible to follow a patient to a reasonably certain medical outcome. In these instances, choose one of the following:

Not followed, judged as nontoxic exposure: The patient was not followed, per clinical judgment the exposure was likely to be nontoxic because the agent involved was nontoxic. The amount implicated in the exposure was insignificant (nontoxic), and/or the route of exposure was unlikely to result in a clinical effect. If this response is selected, there must be reasonable certainty that the patient will not experience any clinical effect from the exposure. Cases that refused follow-up if the exposure was judged as nontoxic may also be included.

Not followed, minimal clinical effects possible: The patient was not followed because, per clinical judgment, the exposure was likely to result in only minimal toxicity of a trivial nature. If this response is selected, the poison center must be reasonably certain, in a worst-case scenario, that the patient will experience no more than a minor effect. Cases that refused follow-up if the exposure would possibly result in minimal clinical effects and would cause no more than a minor effect may also be included. *Appendix C2 continued on next page...*

Appendix C2, continued...

Unable to follow, judged as a potentially toxic exposure: The patient was lost to follow-up (or the poison center neglected to provide follow-up) and per clinical judgment the exposure was significant and may have resulted in toxic manifestations with A MODERATE, MAJOR OR DEATH OUTCOME.

Exposure not responsible for the effect: This category is provided for those patients who exhibit clinical effects, which in the final analysis are determined unrelated to a toxic problem.

Unrelated Effect: Based upon all the information available, the exposure was probably not responsible for the effect(s). If this response is selected, all coded clinical effects must be coded as “unrelated”.

7.5 APPENDIX D. RADARS® TCP

Appendix D1. RADARS® TCP: Percent respondents with past-month abuse by year, 2014-2018*

Opioid Product	2014	2015	2016	2017	2018
	Percent Estimate (%), 95% CI	Percent Estimate (%), 95% CI	Percent Estimate (%), 95% CI	Percent Estimate (%), 95% CI	Percent Estimate (%), 95% CI
All Tramadol	5.1 (4.6-5.6)	3.9 (3.5-4.4)	4.2 (3.7-4.6)	6.8 (6.2-7.4)	7.8 (7.2-8.5)
All Codeine	—	—	—	—	1.0 (0.8-1.3)
All Hydrocodone	27.8 (26.7-28.8)	26.5 (25.5-27.5)	23.8 (22.8-24.8)	23.5 (22.5-24.4)	20.6 (19.6-21.6)
All Morphine	13.2 (12.4-14.0)	14.4 (13.6-15.2)	13.2 (12.4-13.9)	12.9 (12.2-13.7)	12.0 (11.2-12.8)
All Oxycodone	33.2 (32.1-34.3)	32.8 (31.7-33.9)	31.8 (30.7-32.9)	29.9 (28.8-30.9)	27.7 (26.6-28.8)
RADARS®: Researched Abuse, Diversion, and Addiction-Related Surveillance; TCP: Treatment *Among sites participating in 75% or more of calendar quarters in the study period and excluding careless responses; CI: confidence interval. ' — ' indicates data not available.					

7.6 APPENDIX E. NAVIPRO™

Appendix E1. NAVIPPRO™® ASI-MV®, 2013-2018; Prevalence of past-month abuse by opioid*

Opioid product	2013	2014	2015	2016	2017	2018
	Percent Estimate (%), 95% CI	Percent Estimate (%), 95% CI	Percent Estimate (%), 95% CI	Percent Estimate (%), 95% CI	Percent Estimate (%), 95% CI	Percent Estimate (%), 95% CI
Any tramadol	1.6 (1.4-1.8)	1.4 (1.2-1.5)	2.0 (1.8-2.2)	1.9 (1.7-2.1)	1.5 (1.3-1.7)	1.31 (1.2-1.5)
Any codeine	2.0 (1.8-2.2)	1.0 (0.9-1.2)	1.2 (1.0-1.3)	1.2 (1.0-1.3)	1.0 (0.8-1.1)	0.7 (0.6-0.9)
Any hydrocodone	12.2 (11.8-12.7)	10.9 (10.6-11.4)	12.1 (11.7-12.6)	11.9 (11.5-12.4)	10.5 (10.1-11.0)	8.8 (8.3-9.2)
Any morphine	3.9 (3.6-4.1)	3.2 (3.0-3.4)	3.2 (3.0-3.4)	2.8 (2.6-3.0)	2.1 (1.9-2.3)	1.9 (1.7-2.1)
Any oxycodone	15.0 (14.6-15.5)	13.4 (13.0-13.9)	12.9 (12.4-13.3)	12.4 (12.0-12.9)	10.4 (10.0-10.9)	9.4 (9.0-9.8)
NAVIPPRO: National Addictions Vigilance Intervention and Prevention Program; ASI-MV: Addiction Severity Index-Multimedia Version						
*restricted to sites reporting results from at least one assessment per quarter 2013-2018; CI: confidence interval.						

7.7 APPENDIX F. NEISS-CADES

Table F1. Definitions for Intent of Drug Use

Intent of drug use	Definition
Non-medical	Nonmedical use includes pharmaceutical abuse, therapeutic misuse, and overdoses without indication of intent. Abuse cases involve documented clinician diagnosis of abuse or documented recreational use (e.g., “to get high”). Therapeutic misuse cases involved documented therapeutic intent, but use was not as directed (e.g., taking someone else's prescription medication for pain, intentionally taking larger doses than prescribed). Cases of overdose without indication of intent lack documentation of therapeutic intent, abuse, or self-harm (e.g., patients found unresponsive by paramedics and patients unable or unwilling to provide description of circumstances or intent).
All other cases	Therapeutic use includes adverse effects, allergic reactions, medication errors, and unsupervised ingestions by children
Self-harm	Self-harm includes administration of pharmaceuticals to injure or kill oneself
National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance (NEISS-CADES) Source: Geller AI, Dowell D, Lovegrove MC, McAninch JK, Goring SK, Rose KO, Weidle NJ, Budnitz DS. U.S. Emergency Department Visits Resulting From Nonmedical Use of Pharmaceuticals, 2016. Am J Prev Med. 2019 May;56(5):639-647. doi: 10.1016/j.amepre.2018.12.009. Epub 2019 Mar 6.	

Table F2. National estimates of ED visits for non-medical use of tramadol-containing products, by adverse event manifestation, 2016-2017^a

National estimates of ED visits for non-medical use of tramadol-containing products ^b , by adverse event manifestation, 2016-2017 ^a				
Adverse Event Manifestation ^d	Non-Medical Use of Tramadol-containing Products ^c			
	Number of Cases (n)	Average Annual National Estimate ^e		
		(N)	%	95% CI
Cardiac Arrest/Unresponsive/Respiratory Failure/Distress	20	--	--	--
Severe Allergic Reaction	0	--	--	--
Altered Mental Status	58	1,899	44.7	33.8-55.6
Convulsion ^f	10			
Injection-related Infection/Reaction	0	--	--	--
Fall/Injury	1	--	--	--
Presyncope/Syncope/Dyspnea	5	--	--	--
Psychiatric or Other Central Nervous System Effect	9	--	--	--
Cardiovascular Effect	0	--	--	--
Mild-to-Moderate Allergic Reaction	1	--	--	--
Gastrointestinal Effect	5	--	---	--
Other/Unspecified Effect	39	1,094	25.7	15.9-35.6
Total	138	4,250	100.0	
CI: Confidence interval; ED: Emergency Department ^aCases and national estimates of ED visits for drug-related adverse events were based on data from the National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, a national stratified probability sample of approximately 60 hospitals with a minimum of 6 beds and a 24-hour ED in the United States and its territories. The NEISS-CADES project, which has been described in detail elsewhere, is a joint effort of the Centers for Disease Control and Prevention, the US Consumer Product Safety Commission, and the US Food and Drug Administration (1-4). In brief, trained data abstractors located at each participating hospital review clinical records of every ED visit to identify clinician-diagnosed drug-related adverse events, to report up to 4 medications implicated in each adverse event, and to record narrative descriptions of the incident. ^bIncludes pharmaceutical abuse, therapeutic misuse (use other than as directed by a clinician), and opioid overdoses without indication of intent. ^cEstimates based on <20 cases or total estimates <1,200 are considered statistically unstable and are not shown (--). ^dAdverse event manifestations were categorized in a mutually exclusive and hierarchical manner based on severity (e.g., a case involving a patient who had depressed consciousness and had a fall would be classified as altered mental status based on the depressed consciousness). ^eAverage annual estimates were based on total non-medical use visits attributed to tramadol-containing products, from 2016 through 2017. ^f1 additional case involving Cardiac Arrest/Unresponsive/Respiratory Failure/Distress also documented convulsions.				

7.8 APPENDIX G. MTF

Table G. Trends in annual prevalence of tramadol and other selected opioids misuse/abuse for all U.S. high school seniors last 12 months

Percentage of all U.S. high school seniors using tramadol and other selected opioids indicated in last 12 months											
	2009 (%)	2010 (%)	2011 (%)	2012 (%)	2013 (%)	2014 (%)	2015 (%)	2016 (%)	2017 (%)	2018 (%)	Change (2017 vs 2018)
Drug Product											
Tramadol products											
<i>Tramadol</i>	—	—	—	—	0.8	0.6	1.1	0.5	0.2	0.1	0.0
<i>Ultram</i>	0.1	0.5	0.3	0.4	0.3	0	0	0.1	0	0	-0.1
Codeine	4.0	3.4	3.4	3.5	2.6	2.3	2.2	2.2	1.5	1.6	+0.1
Hydrocodone	—	—	—	—	2.9	2.9	2.2	2.1	1.1	1.3	+0.2
<i>Vicodin</i>	4.6	4.6	4.3	4.3	2.6	1.9	1.8	1.3	0.5	0.5	0.0
Morphine	1.5	1.6	1.4	1.7	1.2	1.2	1.3	0.6	0.9	0.2	-0.7 ^s
Oxycodone	—	—	—	—	—	—	1.4	2.4	1.1	0.9	-0.1
Notes: Level of significance of difference between the two most recent classes: $s = .05$; '—' indicates data not available. Any apparent inconsistency between the change estimate and the prevalence estimates for the two most recent years is due to rounding											

Source: The Monitoring the Future (MTF) study, the University of Michigan. Table C-4 Specific Narcotics Other than Heroin: Trends in Annual Prevalence of Use for All Seniors, http://www.monitoringthefuture.org/pubs/monographs/mtf-vol1_2018.pdf.

7.9 APPENDIX H. DIM

Appendix H1. Description of the Drug-Involved Mortality Data extraction

The drug-involved mortality data combine the cause-of-death, demographic, and geographic information from the National Vital Statistics System – Mortality files, with drug-involved mortality information extracted from the death certificate literal text. The method used to extract information on drug-involved mortality has been described previously by Trinidad et al.²² In brief, the programs were designed to search the literal text from three fields of the death certificate, including:

- The chain of events leading to death (from Part I)
- Other significant conditions that contributed to the death (from Part II)
- How the injury occurred (in the case of deaths due to injuries [from Box 43]).

The literal text information had been processed to allow for the identification of cases of drug-involved mortality, i.e., mortality cases having at least one literal text mention of a drug, drug class, or exposure not otherwise specified, excluding mentions where information in the literal text suggests that the drug was not involved in the death. For example, the drug “METHICILLIN” in the phrase “METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS INFECTION” does not suggest drug involvement in mortality, but rather a type of bacterial infection. Similarly, the phrase “NOT DRUG RELATED” clearly indicates that a death did not involve drugs.

Appendix H2. Tramadol and other selected opioids involving drug overdose deaths by year 2011-2017*

Opioid product	Number of Deaths per Year							Percent change* 2016-2017, %	Total*
	2011	2012	2013	2014	2015	2016	2017		
Tramadol	849	935	1,009	1,175	1,177	1,250	1,333	6.6	7,728
Codeine	—	—	—	—	—	—	—	—	—
Hydrocodone	3,206	3,037	3,113	3,299	3,051	3,199	3,072	-4.0	21,977
Morphine	3,290	3,513	3,772	4,024	4,226	5,014	4,874	-2.8	28,713
Oxycodone	5,587	5,178	4,967	5,431	5,792	6,199	6,053	-2.4	39,207

‘—’ indicates data not available.

NOTES: Drug overdose deaths are identified using International Classification of Diseases, Tenth Revision (ICD-10) underlying cause-of-death codes X40–X44, X60–X64, X85, and Y10–Y14. Deaths may involve other drugs in addition to the referent drug (i.e., the one listed). Deaths involving more than one drug (e.g., a death involving both heroin and cocaine) are counted in both totals. Caution should be used when comparing numbers across years. The reporting of at least one specific drug or drug class in the literal text, as identified using ICD-10 multiple cause-of-death codes T36–T50.8, improved from 75% of drug overdose deaths in 2011 to 85% of drug overdose deaths in 2016.

*Adapted from: Hedegaard H, Bastian BA, Trinidad JP, Spencer M, Warner M. 1) Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2011-2016. Natl Vital Stat Rep. 2018 Dec;67(9):1-14 and 2) Regional Differences in the Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2017. Natl Vital Stat Rep. 2019 Oct;68(12):1-15

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/s/

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MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: February 28, 2020

To: Rigoberto Roca, MD., Director (Acting)
Division of Anesthesiology, Addiction Medicine and Pain Medicine

Through: Dominic Chiapperino, PhD, Director
Silvia Calderon, PhD, Senior Pharmacologist
Chad J Reissig, PhD, Supervisory Pharmacologist
Controlled Substance Staff

From: Shalini Bansil, MD, Medical Officer
Controlled Substance Staff

Subject: **Product name:** Celecoxib and Tramadol, Tablets **Trade Name:** (b) (4)
Dosages, formulations, routes: 200 mg oral tablets every 12 hours as needed.
NDA number: 213426
IND Number: 128177
Indication: Management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.
Sponsor: Esteve Pharmaceuticals, S.A.
PDUFA Goal Date: March 15, 2020.

Materials Reviewed: All abuse-related data in Original NDA submission dated May 15, 2019 and subsequent amendments

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I. SUMMARY

1. Background

This memorandum responds to a consult request by the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP), dated May 21, 2019, to evaluate abuse-related preclinical and clinical data submitted by Esteve Pharmaceuticals, S.A. (Sponsor) under NDA 213426 and IND 128177 for Celecoxib and Tramadol tablets (Trade Name (b) (4)). Celecoxib and Tramadol tablets are indicated for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

The Sponsor, has developed Celecoxib and Tramadol Tablets also referred to as co-crystal E-58425, Saco-4, 4248, or MR308 for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Celecoxib and Tramadol tablets are formulated as an immediate release tablet for oral administration containing a co-crystal of rac-tramadol HCl (racemic tramadol hydrochloride, also referred to as the cis-diastereoisomer of tramadol) and celecoxib. This 505(b)(2) application will rely on the Agency's previous findings on tramadol and celecoxib as monotherapies as well as original studies performed by the Sponsor for approval. The reference drug products are Ultram® for tramadol HCl and Celebrex® for celecoxib. No products containing combinations of tramadol and celecoxib are marketed anywhere in the world.

Tramadol is a Schedule IV substance under the Controlled Substances Act (CSA) and celecoxib is not scheduled under the CSA.

The Sponsor proposes to maintain Celecoxib and Tramadol Tablets under Schedule IV of the CSA.

2. Conclusions

- The Sponsor proposes to maintain Celecoxib and Tramadol Tablets under Schedule IV of the CSA.
- . The pharmacokinetics of tramadol appear to be not significantly altered by celecoxib in the cocrystal formulation
- .
- The abuse-related adverse event (AE) profile during clinical development of E-58425 does not suggest an increase in abuse-related AEs with E-58425 compared to tramadol.
- We agree with the Sponsor that Celecoxib and Tramadol Tablets should be maintained under Schedule IV of the CSA.

3. Recommendations:

Drug Scheduling: CSS agrees with the Sponsor that Celecoxib and Tramadol Tablets should be maintained under Schedule IV of the CSA.

Drug label: CSS recommends the following changes to the Sponsor's label, where additions are indicated in **bold underlined text** and deletions have been ~~stricken through~~:

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

(b) (4) contains tramadol, a Schedule IV controlled substance. (b) (4)

9.2 Abuse

(b) (4) contains tramadol, a substance with a high potential for abuse similar to other opioids and can be abused and is subject to misuse, addiction, and criminal diversion [see *Warnings and Precautions* (5.1)].

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful, or potentially harmful, consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

“Drug seeking” behavior is very common in persons with substance use disorders. Drug seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated “loss” of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Health care providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

(b) (4) like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of (b) (4)

(b) (4) is for oral use only. Abuse of (b) (4) poses a risk of overdose and death. The risk is increased with concurrent abuse of (b) (4) with alcohol and other central nervous system depressants.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence

(b) (4)

(b) (4) Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Do not abruptly discontinue (b) (4) **in a patient physically dependent on opioids** (b) (4)

Rapid tapering of (b) (4) **in a patient physically dependent on opioids may lead to serious withdrawal symptoms, uncontrolled pain and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.**

When discontinuing (b) (4) **gradually taper the dosage using a patient-specific plan that considers the following: the dose of** (b) (4) **the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for a long duration at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper [see Dosage and Administration (b) (4)], Warnings and Precautions (5. (b) (4))].** If (b) (4) is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [see Use in Specific Populations (8.1)].

II. DISCUSSION

1. Chemistry

1.1 Substance and Product Information

One 100 mg tablet of Celecoxib and Tramadol, Tablets contains 44 mg of rac-tramadol HCl and 56 mg of celecoxib as the active pharmaceutical ingredients (APIs). The final dose regimen is 2 tablets (2 x 100 mg) of Celecoxib and Tramadol every 12 hours. Celecoxib and Tramadol tablets are formulated as an immediate release tablet for oral administration containing a co-crystal of rac-tramadol HCl and celecoxib. The drug substance of Celecoxib and Tramadol tablets is a co-crystal composed of two APIs: rac-tramadol HCl (racemic tramadol hydrochloride, also referred to as +/- tramadol hydrochloride) and celecoxib, at the co-crystal intrinsic 1:1 molecular ratio, equivalent to 1:1.27 weight ratio between rac-tramadol HCl and celecoxib. No other components are present in the co-crystal structure.

Co-crystals are defined as solids that are crystalline materials composed of two or more molecules in the same crystal lattice. Co-crystals are usually composed of an API with a neutral guest compound (also referred to as a coformer) in the crystal lattice, such that its components are in a neutral state and interact via non-ionic interactions. Celecoxib and Tramadol, Tablets are composed of an API-API combination without additional inactive coformers.

The (+) enantiomer of tramadol binds to the μ -opioid receptor and preferentially inhibits serotonin reuptake, whereas the (-) enantiomer inhibits norepinephrine reuptake. Celecoxib is an NSAID that inhibits prostaglandin synthesis primarily via selective inhibition of cyclooxygenase 2 (COX-2) which results in an analgesic, anti-inflammatory, and antipyretic activity.

According to the Sponsor, Co-crystal E-58425 is a white, crystalline solid, with a melting point of 164.4 °C. It is freely soluble in methanol, absolute ethanol and dimethylsulfoxide. It is sparingly soluble in acetone, slightly soluble in ethyl acetate, very slightly soluble in 1N NaOH and practically insoluble in isopropanol, water and 1N HCl. Its molecular weight is 681.21.

The Sponsor states that the molecular structure of co-crystal E-58425 results in changes in the physicochemical properties of each therapeutic moiety and confers significantly different dissolution profiles of tramadol and celecoxib when compared to the individual dissolution profiles of tramadol HCl and celecoxib. The intrinsic dissolution rate of tramadol HCl is slowed down while that of celecoxib is accelerated. These differences in dissolution profiles of each therapeutic moiety in Celecoxib and Tramadol, Tablets translates into changes in human pharmacokinetics of tramadol and celecoxib.

2. Nonclinical Pharmacology

The nonclinical development program relies on information from the Agency's evaluation of the two NDAs for tramadol (Ultram®) and celecoxib (Celebrex®) as well as additional studies with Celecoxib and Tramadol tablets. The Sponsor states that for Celecoxib and Tramadol tablets, there is no scientific evidence or medical reasons to support that the abuse potential of Celecoxib and Tramadol tablets should be higher than the established risk profile of tramadol alone. This is supported by the pharmacokinetic characteristics of tramadol produced by the Celecoxib and Tramadol tablets. Abuse has not been reported with celecoxib, nor has an increase of adverse events or potentiation of adverse events with Celecoxib and Tramadol tablets compared to tramadol alone. Therefore, nonclinical abuse liability studies have not been conducted.

CSS agrees with the Sponsor that nonclinical abuse liability studies are not necessary to assess the abuse potential of Celecoxib and Tramadol tablets since the abuse-related adverse event profile (see Section 4) of Celecoxib and Tramadol tablets is similar to tramadol alone.

3. Clinical Pharmacology

ESTEVE-SUSA-101: A Single Dose 4-Way Crossover Bioavailability Study of Tramadol HCl and Celecoxib Following the Administration of Co-Crystal E-58425 Versus the Drug Products Taken Individually or Concomitantly in Healthy Male and Female Volunteers / Fasting State. Phase I

The main objective of this study was to determine the pharmacokinetic profile of the formulated co-crystal E-58425 compared with the individual reference products (Ultram® and Celebrex®) and their combination (co-administration) under fasting conditions. The secondary objective was to evaluate the safety of co-crystal E-58425 following a single dose administration.

This was a single center, randomized, single dose, open-label, 4-period, 4-sequence, crossover comparative bioavailability study under fasting conditions on 36 healthy male and female subjects. The rate and extent of absorption of celecoxib, tramadol, and O-desmethyl tramadol were measured and compared following a single dose of Treatment-1 (2 x E-58425 100 mg tablets [Co-crystal E-58425 100 mg (44 mg tramadol HCl: 56 mg celecoxib) tablets], Treatment-2 (2 x Ultram® 50 mg capsule), Treatment-3 (1 x Celebrex® 100 mg capsule) and Treatment-4 (2 x Ultram® 50 mg capsule and 1 x Celebrex® 100 mg capsule). The dose administered of tramadol from co-crystal E-58425 (Treatment-1) corresponds to 88 mg and was compared to a 100 mg dose of Ultram®, administered alone (Treatment-2) or to a 100 mg dose of Ultram® and a 100 mg dose of Celebrex® taken concomitantly (Treatment-4).

The administration of 88 mg of tramadol from the formulated co-crystal E-58425 tablets (Treatment-1) resulted in a reduced peak plasma concentration and exposure to tramadol in comparison to 100 mg of tramadol taken alone (Ultram®: Treatment-2) or taken concomitantly with celecoxib (Ultram® plus Celebrex®: Treatment-4). Similar results were found for tramadol active metabolite, O-desmethyl tramadol.

The administration of 112 mg of celecoxib from the formulated co-crystal E-58425 tablets (Treatment-1) resulted in a celecoxib reduced peak plasma concentration and reduced extent of exposure in comparison to 100 mg of celecoxib taken alone (Celebrex®: Treatment-3). In contrast, the co-crystal E-58425 formulation resulted in a greater celecoxib peak plasma concentration and similar AUCs in comparison to 100 mg of celecoxib taken concomitantly with tramadol (Celebrex® and Ultram®: Treatment-4).

In summary, pharmacokinetic studies demonstrate that administration of tramadol and celecoxib as a cocrystal formulation results in lower exposure to tramadol when compared to plasma levels reached upon administration of comparable doses of tramadol alone or in combination with celecoxib. A lower exposure of tramadol would have been predicted as 88 mg of tramadol were compared to 100 mg of tramadol alone or in combination; however, the pharmacokinetics of tramadol appear to be not significantly altered by celecoxib in the cocrystal formulation.

4. Clinical Studies

4.1 Human Abuse Potential Studies

The Sponsor did not conduct human abuse potential studies to assess the abuse potential of Celecoxib and Tramadol, Tablets. This is acceptable since this is a 505(b)(2) application referencing drug products Ultram® for tramadol HCl and Celebrex® for celecoxib and the abuse-related adverse event profile of Celecoxib and Tramadol, Tablets is similar to tramadol (Section 4.2).

4.2 Adverse Event Profile Through all Phases of Development

The Sponsor has conducted five Phase 1, one Phase 2 and one Phase 3 clinical studies. The completed clinical development program of Celecoxib and Tramadol, Tablets relies on information from the Agency's evaluation of the two NDAs for tramadol and celecoxib as well as: one Phase 1 study conducted in the USA using USA comparators of tramadol and celecoxib, three single-dose Phase 1 studies, and one single- and multi-dose Phase 1 clinical trial conducted in Canada using EU comparators. In addition, one Phase 2 dose-finding clinical trial performed on postsurgical pain after oral surgical procedures and a Phase 3 confirmatory study on a post-surgical acute pain model (bunionectomy with osteotomy) conducted in the USA to establish efficacy were performed. An independent third-party company, Mundipharma Research Ltd (MRL), has conducted one Phase 1 and two Phase 3 studies with Celecoxib and Tramadol tablets outside the USA (Europe and Canada), under the code name MR308. These studies have been included in the NDA.

All adverse events (AEs), including abuse-related AEs were coded to a Medical Dictionary for Regulatory Activities (MedDRA) and the MedDRA system organ class (SOC) and preferred term (PT). The following is a description of and analysis of abuse-related AEs found during different phases of clinical development.

Phase 1 Studies: The Sponsor conducted Phase 1 studies in which AEs, including abuse-related AEs were evaluated.

ESTEVE-SACO4-104: This was a single dose study (Co-Crystal E-58425 200 mg) administered to healthy subjects in the fed or fasting state. Abuse-related AEs are displayed in **Table 1**

Table 1: Abuse-related AEs ESTEVE-SACO-104 n (%)

	E-58425 200 mg/ Fed N=36	E-58425 200 mg/Fasted N=35
Somnolence	7 (19.4)	9 (25.7)
Feeling abnormal	0	1 (2.9)
Euphoric mood	0	1 (2.9)

The Sponsor conducted four Phase 1 studies comparing Co-Crystal E-58425 to tramadol, celecoxib or a combination of tramadol and celecoxib. These studies were conducted in the US or Canada

ESTEVE-SUSA-101: This was a single dose study in healthy subjects. Abuse-related AEs are displayed in **Table 2**

Table 2: Abuse-related AEs ESTEVE-SUSA-101 n (%)

	E-58425 200 mg N=34	Tramadol 100mg N=32	Celebrex 100 mg N=34	Tramadol 100mg + Celebrex 100 mg N=33
Somnolence	1 (2.9)	0	0	1 (3.0)

ESTEVE-SACO4-102: This was a single dose study in healthy subjects. Abuse-related AEs are displayed in **Table 3**.

Table 3: Abuse-related AEs ESTEVE-SACO4-102 n (%)

	E-58425 200 mg N=34	Tramadol 100mg N=35	Celebrex 100 mg N=35	Tramadol 100mg + Celebrex 100 mg N=36
Somnolence	8 (23.5)	10 (28.6)	5 (14.3)	10 (27.8)
Feeling abnormal	0	1(2.9)	0	1(2.8)
Euphoric mood	1 (2.9)	2 (5.7)	0	0

ESTEVE-SACO4-103: This was a single dose study in healthy subjects. Abuse-related AEs are displayed in **Table 4**.

Table 4: Abuse-related AEs ESTEVE-SACO4-103 n (%)

	E-58425 200 mg N=9 (formulation 1)	E-58425 200 mg N=12 (formulation 2)	Tramadol 100mg + Celebrex 100 mg N=9
Somnolence	1 (11.1)	0	2 (22.2)
Disturbance in attention	0	1 (8.3)	0

ESTEVE-SACO4-105: This was a multiple dose study in healthy subjects who were treated for 7 days. Abuse-related AEs are displayed in **Table 5**.

Table 5: Abuse-related AEs ESTEVE-SACO4-105 n (%)

	E-58425 200 mg bid N=29	Tramadol 100mg bid N=30	Celebrex 100 mg bid N=28	Tramadol 100mg + Celebrex 100 mg bid N=28
Somnolence	5 (17.2)	7 (23.3)	6 (21.4)	8 (28.6)
Psychomotor hyperactivity	0	0	0	1 (3.6)

Feeling abnormal	0	1(3.3)	0	0
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Conclusions Phase1 Studies: Somnolence was the only consistent abuse-related AE that occurred in subjects treated with E-58425 and this occurred to a similar extent with tramadol (about 20% of subjects). Euphoric mood was reported in 0-3% of subjects on E-58425 and 0-5.7% subjects on tramadol. Thus, the AE profile does not suggest an increase in abuse-related AEs with E-58425 compared to tramadol.

Phase 2 and 3 studies

A randomized, double-blind, controlled with active treatment (tramadol 100 mg) and placebo, parallel groups, Phase II clinical trial to establish the effective dose between 4 strengths of E-58425 for moderate to severe dental pain. ESTEVE-SAC04-201

The primary objective of this study was to establish the effective dose between 4 strengths of E 58425 for moderate to severe pain. This was a phase II, double-blind, randomized, placebo and active controlled, parallel group study in patients with moderate to severe dental pain after extraction of two or more impacted third molars requiring bone removal. Patients who reached a pain intensity ≥ 50 mm VAS were eligible for the study and randomly assigned to one of six treatments including four different doses of E-58425 (50, 100, 150, and 200 mg), the reference therapy tramadol 2x50 mg, and placebo. A total of 334 subjects were enrolled. A single dose was administered following impacted third molar extraction. Somnolence occurred in 1 subject (1.8%) in the 150 mg E 58425 group. No other abuse-related AEs were reported.

A Randomized, Double-blind, Active- (Tramadol and Celecoxib) and Placebo-controlled, Parallel Groups, Phase 3 Clinical Trial to Establish the Efficacy of Co-crystal E-58425 for the Management of Moderate to Severe Post-surgical Pain after Bunionectomy ESTEVE-SUSA-301.

The primary objective of this study was to establish the analgesic efficacy of co-crystal E-58425 compared to tramadol and to celecoxib for the management of moderate to severe post-operative pain for 48 hours after bunionectomy. This was a phase 3, randomized, double-blind, active- and placebo-controlled, parallel-group, multicenter clinical trial with co-crystal E-58425 compared to tramadol, to celecoxib, and to placebo. Male and female subjects at least 18 years old, scheduled to undergo primary unilateral first metatarsal osteotomy with internal fixation with no additional collateral procedure, were eligible. Study medications were administered 4 times daily for a maximum of 2 days. Subjects were admitted to the study center on the morning of the scheduled surgery (Day -1), remained at the study center until postoperative Day 3 (a total of 3 nights at the study center) A total of 637 subjects participated in the study which contained the following arms:

Arm 1: E58425 200 mg bid

Arm 2: Tramadol 50 mg qid

Arm 3 Celecoxib 100 mg bid

Arm 4: Placebo

The abuse-related adverse events are displayed in **Table 6**.

Table 6: Abuse related adverse events Esteve-SUSA-301 (n= number of subjects with AE)

	Co-Crystal E58425 (N = 183)			Tramadol (N = 183)			Celecoxib (N = 182)			Placebo (N = 89)		
PT	Events	n	%	Events	n	%	Events	n	%	Events	n	%
Anxiety	1	1	0.55	1	1	0.55	0	0	0	0	0	0
Euphoric mood	0	0	0	1	1	0.55	0	0	0	0	0	0
Feeling abnormal	0	0	0	0	0	0	1	1	0.55	0	0	0
Feeling jittery	2	2	1.09	0	0	0	0	0	0	0	0	0
Hyperhidrosis	3	3	1.64	5	5	2.73	2	2	1.1	3	3	3.37
Irritability	0	0	0	1	1	0.55	0	0	0	0	0	0
Restlessness	0	0	0	1	1	0.55	0	0	0	0	0	0
Sedation	0	0	0	1	1	0.55	0	0	0	0	0	0
Somnolence	16	15	8.2	10	10	5.46	4	4	2.2	3	3	3.37

There are additional studies that have been performed by an independent third-party company, Mundipharma Research Ltd (MRL). MRL has conducted two phase 3 studies MR308-3501 (Stardom 01) and MR308-3502 (Stardom 02, completed, but final report not yet available) and one phase 1 study (MR308-1501) outside the USA (Europe and Canada). The name MR308 has been used to identify the co-crystal E-58425 in different studies performed outside the US.

In MR308-1501 somnolence (6.7%) and hyperhidrosis (6.7%) were reported in subjects on MR308.

Table 7 displays the abuse-related AEs in MR308-3501. A higher percentage of patients on tramadol alone had ‘disturbance in attention’ and ‘confusional state’ compared to those on MR308 but this may be related to higher doses of total tramadol dose in the tramadol only arm.

Table 7: Abuse-related AEs MR308-3501 n (%)

	MR308 100mg Total daily tramadol dose 88mg N=164	MR308 150mg Total daily tramadol dose 132 mg N=159	MR308 200mg Total daily tramadol dose 176 mg N=160	Tramadol 100mg Total daily tramadol dose 400 mg N=160	Placebo N=83
Disturbance in attention	27 (16.5)	25 (15.7)	39 (24.4)	51 (31.9)	16 (19.3)
Somnolence	75 (45.7)	83 (52.2)	105 (65.6)	101 (63.1)	31 (37.3)
Anxiety	1 (0.6)	1 (0.6)	0	0	1 (1.2)

Confusional state	11 (6.7)	9 (5.7)	17 (10.6)	30 (18.8)	8 (9.6)
Hyperhidrosis	4 (2.4)	1 (0.6)	1 (0.6)	4 (2.5)	0

Conclusions Phase 2 and 3 studies: The Phase 2 and 3 studies reported low rates of abuse related AEs (less than 1%) except for ‘somnolence,’ ‘disturbance in attention,’ and ‘confusional state.’ Rates of these AEs were similar between tramadol alone and E58425. These AEs in the absence of euphoria and sedation, do not suggest abuse potential. Euphoria was reported in 1-5% of subjects taking Ultram (Ultram PI).

4.3 Safety Profile

Conclusions Phase1 Studies: Somnolence was the only consistent abuse-related AE that occurred in subjects treated with E-58425 and this occurred to a similar extent with tramadol (about 20% of subjects). Euphoric mood was reported in 0-3% of subjects on E-58425 and 0-5.7% subjects on tramadol. Thus, the AE profile does not suggest an increase in abuse-related AEs with E-58425 compared to tramadol.

Conclusions Phase 2 and 3 studies: The Phase 2 and 3 studies reported low rates of abuse related AEs (less than 1%) except for ‘somnolence,’ ‘disturbance in attention,’ and ‘confusional state.’ Rates of these AEs were similar between tramadol alone and E58425. These AEs in the absence of euphoria and sedation, do not suggest abuse potential.

4.4 Evidence of Abuse, Misuse and Diversion in Clinical Trials

Evidence of abuse, misuse, or diversion could not be assessed in the controlled environment in which the studies were carried out. (Phase 1 studies and studies in patients that remained in-hospital during the treatment administration period).

4.5 Tolerance and Physical Dependence Studies in Humans

Withdrawal and rebound was not adequately assessed in the clinical development program because Celecoxib and Tramadol Tablets were not administered for more than 7 days in any clinical study. The risk of dependence and withdrawal is described in the Sponsor’s proposed label.

5. Regulatory Issues and Assessment

This 505(b)(2) application showed a similar abuse-related AE profile for Celecoxib and Tramadol Tablets and tramadol alone. Thus we agree with the Sponsor that Celecoxib and Tramadol Tablets should be maintained in Schedule IV of the CSA. The label is discussed in the Recommendations section.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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Division of Pediatric and Maternal Health Memorandum

Date: February 19, 2020 **Date Consulted:** September 4, 2019

From: Christos Mastroyannis, M.D.,
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Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, M.D., MS,
Team Leader, Maternal Health
Division of Pediatric and Maternal Health

To: Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

Drug: (b) (4) (Tramadol Hydrochloride 44 mg/ Celecoxib 56 mg)

Class: Opioid agents/NSAIDS

NDA: 213426

Applicant: Esteve Pharmaceuticals

Subject: Labeling review of an initial NDA application to be compliant with PLLR

Indication: (b) (4) is a co-crystal (tramadol hydrochloride (an opioid agonist, and inhibitor of norepinephrine and serotonin re-uptake) and celecoxib (selective cyclooxygenase-2 inhibitor)). Indicated for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Materials Reviewed:

- DPMH consult request dated September 4, 2019, DARRTS Reference ID 4486274
- DPMH labeling review of Amlodipine and Celecoxib dated May 7, 2018, in DARRTS, Reference ID: 4258383 by Christos Mastroyannis, M.D.
- DPMH labeling review for Ultram, Ultracet, Ultram ER, Rybix ODT, Conzip (2010) (tramadol) dated October 13, 2015, in DARRTS, Reference ID: 3829377 by Miriam Dinatale, D.O.
- DPMH response to TSI 1418, for “Updating lactation labeling to reflect risk to nursing child from a nursing mother who is an ultra-rapid metabolizer of CYP2D6 substrates for tramadol”, dated February 14, 2017, in DARRTS, Reference ID: 4055175 by Miriam Dinatale, D.O.
- DPMH NSAIDs PLLR template, dated March 12, 2015, in DARRTS, Reference ID: 3715387, by Melissa Tassinari Ph.D., DABT.
- Immediate release (IR) opioid labeling template safety labeling language.¹

Consult Question:

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Division of Pediatric and Maternal Health (DPMH) to provide recommendations on the content and format for the Pregnancy and Lactation subsections of the (b) (4) labeling, as per Pregnancy and Lactation Labeling Rule (PLLR).

BACKGROUND

On May 15, 2019, Esteve Pharmaceuticals, submitted a 505 (b)(2) New Drug Application (NDA) for (b) (4) (NDA 213426) for the proposed indication for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. (b) (4) is a co-crystal (rac-tramadol hydrochloride (an opioid agonist, and inhibitor of norepinephrine and serotonin re-uptake) and celecoxib (selective cyclooxygenase-2 inhibitor). The listed products relied upon are: Ultram, Ultram ER, and Celebrex – NDAs 020281, 021692, and 020998.

The reader is referred to DPMH previous labeling reviews mentioned above for Ultram and Celecoxib, and for the NSAIDs PLLR template. On March 22, 2016, FDA also published an example of immediate release (IR) opioid labeling template required for safety labeling language (see Appendix 1).

Review of published clinical data (review publications and case report studies) and existing labelings for Celebrex and Ultram provided by the applicant, and publications identified by DPMH, did not identify any new safety concerns related to tramadol HCl or celecoxib use during pregnancy or lactation, or related to their effects on human fertility.

CONCLUSIONS

DPMH participated in internal team meetings and has provided labeling recommendations consistent with PLLR format and safety labeling language for both the NSAIDs and opioid drug

¹ <https://www.fda.gov/media/96712/download>

classes. DPMH refers to the final NDA action for final labeling.

LABELING RECOMMENDATIONS

HIGHLIGHTS

BOXED WARNING

Prolonged use of (b) (4) during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.7)

-----USE IN SPECIFIC POPULATIONS-----

- **Pregnancy:** (b) (4)
- **Lactation:** Not recommended (8.2).
- **Infertility:** NSAIDs are associated with reversible infertility. Consider withdrawal of (b) (4) in women who have difficulties conceiving (8.3).

FULL PRESCRIBING INFORMATION

Boxed Warning

NEONATAL OPIOID WITHDRAWAL SYNDROME

Prolonged use of (b) (4) during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Warnings and Precautions* (b) (4)].

5 WARNINGS AND PRECAUTIONS

(b) (4) Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children

Lactating Women

Tramadol is subject to the same polymorphic metabolism as codeine, with ultra-rapid metabolizers of CYP2D6 substrates being potentially exposed to life-threatening levels of O-desmethyltramadol (M1). At least one death was reported in a nursing infant who was exposed

to high levels of morphine in breast milk because the mother was an ultra-rapid metabolizer of codeine. A baby nursing from an ultra-rapid metabolizer mother taking (b) (4) could potentially be exposed to high levels of M1, and experience life-threatening respiratory depression. For this reason, breastfeeding is not recommended during treatment with (b) (4) [see Use in Specific Populations (8.2)].

5.5 Neonatal Opioid Withdrawal Syndrome

Tramadol

Prolonged use of tramadol during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see Use in Specific Populations (8.1), (b) (4)].

5.27 Premature Closure of Fetal Ductus Arteriosus

Celecoxib

(b) (4) Avoid use of NSAIDs, including (b) (4)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on use of (b) (4) in pregnant women. In an animal reproduction study, oral administration of celecoxib and tramadol co-crystal to pregnant rabbits during the period of organogenesis, resulted in embryo-fetal deaths and an increase of incidence of vertebral defects at approximately (b) (4) and 0.11 times the dose of celecoxib and tramadol, respectively, at the maximum recommended human dose (MRHD) of TRADENAME at 400 mg/day (224 mg celecoxib/176 mg tramadol) (see Data).

Tramadol

(b) (4)
Available data with tramadol use in pregnant women are insufficient to inform a drug-associated risk for major birth defects, miscarriage, or adverse maternal outcomes. There are adverse outcomes reported with fetal exposure to opioid analgesics (see Clinical Considerations). In animal reproduction studies, tramadol administration during organogenesis decreased fetal weights and reduced ossification in mice, rats, and rabbits at 3.2, 1.4, and 8.2 times the tramadol dose of 176 mg at the maximum recommended human daily dose (MRHD) of TRADENAME. In a pre- and post-natal

development study, tramadol decreased pup body weight and increased pup mortality at 2.7 and 4.3 times the MRHD, respectively (*see Data*).

Celecoxib

Use of NSAIDs, including celecoxib, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including celecoxib, in pregnant women starting at 30 weeks of gestation (third trimester).

The available published data and case reports did not identify a risk of major birth defects, miscarriage or adverse maternal outcomes with celecoxib use during pregnancy. Published literature reports that use of NSAIDs, including celecoxib, during the third trimesters of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimester of pregnancy are inconclusive (*see Clinical Considerations, Data*). In animal reproduction studies, embryo-fetal deaths and an increase in diaphragmatic hernias were observed in rats administered celecoxib daily during the period of organogenesis at oral doses approximately 13 times the celecoxib dose of 224 mg at the maximum recommended human dose of TRADENAME. In addition, structural abnormalities (e.g., septal defects, ribs fused, sternebrae fused and sternebrae misshapen) were observed in rabbits given daily oral doses of celecoxib during the period of organogenesis at approximately 4 times the MRHD. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as celecoxib, resulted in increased pre- and post-implantation loss (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Tramadol:

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in respiratory depression and physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing, and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms and signs of neonatal opioid withdrawal syndrome and manage accordingly [see Warnings and Precautions (5.5)].

Neonatal seizures, neonatal withdrawal syndrome, fetal death and stillbirth have been reported with tramadol hydrochloride during postmarketing.

Celecoxib:

Avoid use of NSAID's in pregnant women in the third trimester because NSAIDs, including celecoxib, can cause premature closure of the fetal ductus arteriosus (see Data).

Labor or Delivery

Tramadol:

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid induced respiratory depression in the neonate. (b) (4) is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate.

Opioid analgesics, including (b) (4) can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women given tramadol during labor.

The effect of (b) (4), if any, on the later growth, development, and functional maturation of the child is unknown.

Celecoxib

There are no studies on the effects of (b) (4) during labor or delivery. In animal studies, NSAIDS, including celecoxib, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data

Human Data

Celecoxib:

Published literature has concluded that the use of NSAIDs during the third trimester of pregnancy may cause constriction of the patent ductus arteriosus and premature closure of the fetal ductus arteriosus.

Animal Data

Treatment of pregnant rabbits during organogenesis with celecoxib and tramadol co-crystal resulted in an increase in the incidence of scoliosis and other vertebral defects (including absent thoracic hemicentrum/a and neural arch(es) and fused thoracic vertebral centra and/or neural

arch(es)) at an oral dose of 100 mg/kg/day (56 mg celecoxib/44 mg tramadol/kg/day; approximately (b) (4) and 0.11 times the MRHD on the basis of celecoxib and tramadol, respectively, on an AUC basis), which is a dose that also caused maternal toxicity (decreased body weight gain). In addition, a slight increase of post-implantation loss in rabbits at 100 mg/kg/day. The No Observed Adverse Effect Level (NOAEL) for embryofetal toxicity was 55 mg/kg/day (approximately 3.3 and 0.02 times the MRHD of celecoxib and tramadol, respectively, on an AUC basis).

Tramadol:

Tramadol has been shown to be embryotoxic and fetotoxic in mice, (120 mg/kg), rats (25 mg/kg) and rabbits (75 mg/kg) at maternally toxic dosages but was not teratogenic at these dose levels. These doses on a mg/m² basis are 3.2, 1.4, and 8.2 times the maximum recommended human daily dosage (MRHD) of tramadol (176 mg) for mouse, rat and rabbit, respectively. No drug-related teratogenic effects were observed in progeny of mice (up to 140 mg/kg), rats (up to 80 mg/kg) or rabbits (up to 300 mg/kg) treated with tramadol by various routes. Embryo and fetal toxicity consisted primarily of decreased fetal weights, decreased skeletal ossification and increased supernumerary ribs at maternally toxic dose levels. Transient delays in developmental or behavioral parameters were also seen in pups from rat dams allowed to deliver. Embryo and fetal lethality were reported only in one rabbit study at 300 mg/kg, a dose that would cause extreme maternal toxicity in the rabbit. The dosages listed for mouse, rat and rabbit are 3.9, 4.3, and 33.1 times the MRHD of tramadol (176 mg), respectively.

Tramadol was evaluated in pre-and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg (2.7 times the MRHD) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (4.3 times the MRHD of tramadol).

Celecoxib:

Celecoxib at oral doses $\geq$ 150 mg/kg/day (approximately 4 times the level of celecoxib of 224 mg at the maximum recommended human dose (MRHD) of TRADENAME based on AUC), caused an increased incidence of ventricular septal defects, a rare event, and fetal alterations, such as ribs fused, sternbrae fused and sternbrae misshapen when rabbits were treated throughout organogenesis. A dose-dependent increase in diaphragmatic hernias was observed when rats were given celecoxib at oral doses $\geq$ 30 mg/kg/day (approximately 13 times the MRHD based on AUC) throughout organogenesis. In rats, exposure to celecoxib during early embryonic development resulted in pre-implantation and post-implantation losses at oral doses $\geq$ 50 mg/kg/day (approximately 13 times the MRHD based on AUC).

Celecoxib produced no evidence of delayed labor or parturition at oral doses up to 100 mg/kg in rats (approximately 15 times the MRHD based on AUC).

8.2 Lactation

Risk Summary

Tramadol:

(b) (4) is not recommended for obstetrical preoperative medication or for post-delivery analgesia in lactating women because its safety in infants and newborns has not been studied.

Tramadol and its metabolite, O-desmethyltramadol (M1), are present in human milk. There is no information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. The M1 metabolite is more potent than tramadol in mu opioid receptor binding [see Clinical Pharmacology (12.1)]. Published studies have reported tramadol and M1 in colostrum with administration of tramadol to breastfeeding mothers in the early post-partum period. Women who are ultra-rapid metabolizers of tramadol may have higher than expected serum levels of M1, potentially leading to higher levels of M1 in breast milk that can be dangerous in their breastfed infants. In women with normal tramadol metabolism, the amount of tramadol secreted into human milk is low and dose-dependent. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with (b) (4) (see Data) [see Warnings and Precautions (b) (4)].

Celecoxib:

Limited Data from 3 published reports that included a total of 12 breastfeeding women calculated the average daily infant dose of celecoxib as 10–40 mcg/kg/day, less than 1% of the weight-based therapeutic dose for a two-year old-child. A report of two breastfed infants 17 and 22 months of age did not show any adverse events with maternal use of celecoxib (*see Data*).

Clinical Considerations

Tramadol:

If infants are exposed to (b) (4) through breast milk, they should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breastfeeding is stopped.

Data

Tramadol:

Following a single IV 100 mg dose of tramadol, the cumulative excretion in breast milk within 16 hours post dose was 100 mcg of tramadol (0.1% of the maternal dose) and 27 mcg of M1.

Celecoxib:

A clinical lactation study in 6 volunteers administered a single oral dose of 200 mg celecoxib [median maternal celecoxib dose of 3.3 mg/kg (range of 2.3-3.7)] at 6.5 to 15 months postpartum (mean 11 months) and in the final stage of weaning showed that the median total amount of celecoxib present in milk was 0.011 mg (range 0.004-0.042) or 0.04% (range 0.01-0.15) of the maternal single dose (weight adjusted). The estimated daily infant dose was 0.013 mg/kg/day (range 0.011-0.021), which is 0.13 to 0.33% of the clinically used celecoxib dose for pediatric patients.

A clinical lactation study in 3 breastfeeding mothers who had been taking 200 mg celecoxib orally once daily for many weeks and who were at steady state (group 1) and 2 breastfeeding mothers administered a single 200-mg oral dose of celecoxib (group 2) averaging 12 months post-partum (range 3-22 months). The mean average concentration of celecoxib in milk during the 8-hour interval following administration of celecoxib for all five mothers was 66 mcg/L

(95% CI: 41-89). The estimated mean absolute infant dose was 9.8 mcg/kg/day (95% CI: 6.2-13.4), which is 0.1 to 0.25% of the dose clinically used for pediatric patients. Comparison of this to the weight-normalized maternal dose yields an estimated mean relative infant dose of 0.30% (95% CI: 0.19-0.39).

8.3 Females and Males of Reproductive Potential

Infertility

Tramadol:

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see *Adverse Reactions* (6.2), *Clinical Pharmacology* (12.2),

Celecoxib:

Females Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including celecoxib, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including celecoxib, in women who have difficulties conceiving or who are undergoing investigation of infertility.

17 PATIENT COUNSELING INFORMATION

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of (b) (4) during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated and that the patient should inform their healthcare provider if they have used opioids at any time during their pregnancy, especially near the time of birth. [see *Warnings and Precautions* (5.7); *Use in Specific Populations* (8.1)].

Embryo-Fetal Toxicity

Advise female patients of reproductive potential that (b) (4) may cause fetal harm [see *Use in Specific Populations* (8.1)].

Advise pregnant women to avoid use of (b) (4) starting at 30 weeks of gestation because of the risk of the premature closing of the fetal ductus arteriosus [see *Warnings and Precautions* (5.27) and *Use in Specific Populations* (8.1)].

Advise women of reproductive potential to inform the healthcare provider of a known or suspected pregnancy [see *Use in Specific Populations* (8.1)].

Lactation

Advise women that breastfeeding is not recommended during treatment with (b) (4) [see *Warnings and Precautions* (5.4); *Use in Specific Populations* (8.2)].

Infertility

Advise patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible [see *Use in Specific Populations* (8.3)].

Advise females of reproductive potential who desire pregnancy that NSAIDs, including (b) (4) may be associated with a reversible delay in ovulation [see *Use in Specific Populations* (8.3)].

Appendix 1

March 22, 2016, Required Safety Labeling Language for Immediate-Release Opioids¹

The following mocked up labeling is an example of how the required safety labeling changes may be implemented and does not represent a complete package insert. This example is for a single-entity, solid oral dosage form. The language may vary for different products.

ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME Addiction, Abuse, and Misuse [TRADENAME] exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing [TRADENAME] and monitor all patients regularly for the development of these behaviors or conditions [see Warnings and Precautions (5.X)]. Life-Threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression may occur with use of [TRADENAME]. Monitor for respiratory depression, especially during initiation of [TRADENAME] or following a dose increase [see Warnings and Precautions (5.X)]. Accidental Ingestion Accidental ingestion of even one dose of [TRADENAME], especially by children, can result in a fatal overdose of [active moiety] [see Warnings and Precautions (5.X)].

Neonatal Opioid Withdrawal Syndrome Prolonged use of [TRADENAME] during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see Warnings and Precautions (5.X)].

1. INDICATIONS AND USAGE [TRADENAME] is indicated for the management of [insert product-specific indication] pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Limitations of Use Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses [see Warnings and Precautions (5.X)], reserve [TRADENAME] for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see Warnings and Precautions (5.X)]. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with [TRADENAME] and adjust the dosage accordingly [see Warnings and Precautions (5.X)].

2.2 Initial Dosage Use of [TRADENAME] as the First Opioid Analgesic Initiate treatment with [TRADENAME] in a dosing range of X to X mg every X to X hours as needed for pain. Conversion from Other Opioids to [TRADENAME] There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dosage of [TRADENAME]. It is safer to underestimate a patient's 24-hour [TRADENAME] dosage than to overestimate the 24-hour [TRADENAME] dosage and manage an adverse reaction due to overdose. Conversion from [TRADENAME] to Extended-Release [active moiety] The relative bioavailability of [TRADENAME] compared to extended-release [active moiety] is unknown, so conversion to extended-release [dosage form] must be accompanied by close observation for signs of excessive sedation and respiratory depression.

2.X Titration and Maintenance of Therapy Individually titrate [TRADENAME] to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving [TRADENAME] to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse [see Warnings and Precautions (5.X)]. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the [TRADENAME] dosage. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions. 2.X Discontinuation of [TRADENAME] When a patient who has been taking [TRADENAME] regularly and may be physically dependent no longer requires therapy with [TRADENAME], use a gradual downward titration of the dosage to prevent signs and symptoms of withdrawal. Do not stop [TRADENAME] abruptly [see Warnings and Precautions (5.X), Drug Abuse and Dependence (9.3)]. [TRADENAME] is contraindicated in patients with:

- Significant respiratory depression [see Warnings and Precautions (5.X)]
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see Warnings and Precautions (5.X)]

5 WARNINGS AND PRECAUTIONS 5.X Addiction, Abuse, and Misuse [TRADENAME] contains [active moiety], a Schedule [XX] controlled substance. As an opioid, [TRADENAME] exposes users to the risks of addiction, abuse, and misuse [see Drug Abuse and Dependence (9)]. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed [TRADENAME]. Addiction can occur at recommended dosages and if the drug is misused or abused. Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing [TRADENAME], and monitor all patients receiving [TRADENAME] for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as [TRADENAME] but use in such patients necessitates intensive counseling about the risks and proper use of [TRADENAME] along with intensive monitoring for signs of addiction, abuse, and misuse. Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing

or dispensing [TRADENAME]. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [see Patient Counseling Information (17)]. Contact local state professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.X Life-Threatening Respiratory Depression Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [see Overdosage (10)]. Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of [TRADENAME], the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of [TRADENAME]. To reduce the risk of respiratory depression, proper dosing and titration of [TRADENAME] are essential [see Dosage and Administration (2.X)]. Overestimating the [TRADENAME] dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of [TRADENAME], especially by children, can result in respiratory depression and death due to an overdose of [active moiety].

5.X Neonatal Opioid Withdrawal Syndrome Prolonged use of [TRADENAME] during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see Use in Specific Populations (8.1), Patient Counseling Information].

5.X Risks due to Interactions with Central Nervous System Depressants Hypotension, profound sedation, respiratory depression, coma, and death may result if [TRADENAME] is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids). When considering the use of [TRADENAME] in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol or illicit drugs that can cause CNS depression. If the decision to begin [TRADENAME] is made, start with a lower dosage of [TRADENAME], monitor patients for signs of respiratory depression, sedation, and hypotension, and consider using a lower dose of the concomitant CNS depressant. [see Drug Interactions (7)].

5.X Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients The use of [TRADENAME] in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated. Patients with Chronic Pulmonary Disease: [TRADENAME]-treated patients

with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of [TRADENAME] [see Warnings and Precautions (5.X)]. Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [see Warnings and Precautions (5.X)]. Monitor such patients closely, particularly when initiating and titrating [TRADENAME] and when [TRADENAME] is given concomitantly with other drugs that depress respiration [see Warnings and Precautions (5.X)]. Alternatively, consider the use of non-opioid analgesics in these patients.

5.X Adrenal Insufficiency Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse [see Warnings and Precautions (5.X)]
- Life-Threatening Respiratory Depression [see Warnings and Precautions (5.X)]
- Neonatal Opioid Withdrawal Syndrome [see Warnings and Precautions (5.X)]
- Interactions with CNS Depressants [see Warnings and Precautions (5.X)]
- Adrenal Insufficiency [see Warnings and Precautions (5.X)]

6.2 Postmarketing Experience serotonin syndrome, adrenal insufficiency Androgen deficiency: Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

7 DRUG INTERACTIONS Table X includes clinically significant drug interactions with [TRADENAME]. (In the table below, include relevant cross-references to section 12)
Table X: Clinically Significant Drug Interactions with [TRADENAME]
Central Nervous System (CNS) Depressants

Clinical Impact: Due to additive pharmacologic effect, the concomitant use of CNS depressants can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.

Intervention: Consider dose reduction of one or both drugs. Monitor patients for signs of respiratory depression, sedation, and hypotension [see Warnings and Precautions (5.X)].

Examples: Alcohol, benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids.

Serotonergic Drugs

Clinical Impact: The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.

Intervention: If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue [TRADE NAME] if serotonin syndrome is suspected.

Examples: Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT₃ receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly [see Warnings and Precautions (5.X)].

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. [TRADE NAME] is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including [TRADE NAME], can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

8.2 Lactation

Risk Summary

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for [TRADENAME] and any potential adverse effects on the breastfed infant from [TRADENAME] or from the underlying maternal condition.

Clinical Considerations

Infants exposed to [TRADENAME] through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [*see Adverse Reactions (6.2)*].

17 PATIENT COUNSELING INFORMATION

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform patients that prolonged use of [TRADENAME] during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [*see Warnings and Precautions (5.x), Use in Specific Populations (8.1)*].

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that [TRADENAME] can (or may) cause fetal harm and to inform the prescriber of a known or suspected pregnancy [*see Use in Specific Populations (8.1)*].

Lactation

Advise nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs [*see Use in Specific Populations (8.2)*].

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/s/

CHRISTOS MASTROYANNIS
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02/20/2020 07:05:04 PM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: January 31, 2020

To: Sepideh Haghpanah, Clinical Reviewer
Division of Anesthesia, Addiction Medicine and Pain Medicine (DAAP)

Jaimin Patel, Regulatory Project Manager, (DAAP)

Lisa Basham, Associate Director for Labeling, (DAAP)

From: L. Sheneé Toombs, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP labeling comments for (b) (4) (celecoxib and tramadol hydrochloride) Tablets, for oral use, C-IV

NDA/BLA: NDA 213246

In response to DAAP's consult request dated July 1, 2019, OPDP has reviewed the proposed product labeling (PI) for the original NDA/BLA submission for (b) (4) (celecoxib and tramadol hydrochloride) Tablets, for oral use, C-IV

PI and PPI/Medication Guide/IFU: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAAP on January 17, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI/Medication Guide/IFU were sent under separate cover on January 31, 2020.

Thank you for your consult. If you have any questions, please contact Sheneé Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: January 31, 2020

To: Jaimin Patel, PharmD
**Division of Anesthesiology, Addiction, Medicine, and
Pain Medicine (DAAP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Morgan Walker, PharmD, MBA, CPH
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
LaToya Sheneé Toombs, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): (b) (4) (celecoxib and tramadol)

Dosage Form and Route: Tablets, for oral use, C-IV

Application Type/Number: NDA 213426

Applicant: Esteve

1 INTRODUCTION

On May 15, 2019, Esteve submitted for the Agency's review an original New Drug Application (NDA) 213426 for (b) (4) (tramadol and celecoxib) Tablets. The proposed indication is for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesiology, Addiction, Medicine, and Pain Medicine (DAAP) on July 1, 2019, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for (b) (4) (tramadol and celecoxib) Tablets.

2 MATERIAL REVIEWED

- Draft (b) (4) (tramadol and celecoxib) Tablets MG received on May 15, 2019 and received by DMPP and OPDP on January 17, 2020.
- Draft (b) (4) (tramadol and celecoxib) Tablets Prescribing Information (PI) received on May 15, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 17, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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01/31/2020 11:59:46 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 13, 2019
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 213426
Product Name and Strength:	celecoxib and tramadol hydrochloride tablet, 44 mg and 56 mg
Applicant/Sponsor Name:	Esteve Pharmaceuticals, SA
OSE RCM #:	2019-1058-1
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on December 10, 2019 for celecoxib and tramadol hydrochloride tablets. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container labels and carton labeling for celecoxib and tramadol hydrochloride (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Johnson, C. Label and Labeling Review for celecoxib and tramadol hydrochloride (NDA 213426). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 10. RCM No.: 2019-1058.

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CAMERON D JOHNSON
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Clinical Inspection Summary

Date	November 22, 2019
From	John Lee, M.D., Medical Officer Phillip Kronstein, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Jaimin Patel, Pharm.D., Regulatory Project Manager Sepideh Haghpahan, M.D., Medical Officer Pamela Horn, M.D., Clinical Team Leader Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application	NDA 213426
Applicant	Esteve Pharmaceuticals, S.A.
Drug	Celecoxib and Tramadol Tablets (b) (4)
NME / Original NDA	No
Review Status	Standard
Proposed Indication	Management of acute pain in adults (severe enough for opioids)
Consultation Date	July 10, 2019
CIS Goal Date	November 22, 2019
Action Goal Date	March 13, 2019
PDUFA Due Date	March 15, 2019

I. OVERALL ASSESSMENT OF INSPECTIONAL FINDINGS AND RECOMMENDATIONS

Two clinical investigator (**CI**) sites were inspected for Study ESTEVE-SUSA-301. For both CI sites, no significant good clinical practice (**GCP**) deficiencies were observed and a Form FDA 483 was not issued.

Based on the inspections of these two CI sites, study conduct appeared GCP-compliant, including sponsor oversight. All audited data were verifiable against source records and case report forms (**CRFs**). The data from the inspected CI sites appear reliable as reported in the NDA.

II. BACKGROUND

This 505(b)(2) NDA 213426 for (b) (4) (celecoxib and tramadol, co-crystal E-58425) relies on the previous findings of safety and efficacy for Ultram® (tramadol) and Celebrex® (celecoxib) as the two reference listed drugs (**RLDs**) as well as on new original study results to support the proposed indication: management of acute pain in adults severe enough to require an opioid analgesic for which alternative analgesics are inadequate. To support the NDA review, two (of six) clinical investigator (**CI**) sites in the major pivotal study ESTEVE-SUSA-301 were inspected to audit data quality and study conduct compliant with good clinical practice (**GCP**).

ESTEVE-SUSA-301: *A Randomized, Double-blind, Active- (Tramadol and Celecoxib) and Placebo-controlled, Parallel Groups, Phase 3 Clinical Trial to Establish the Efficacy of Co-crystal E-58425 for the Management of Moderate to Severe Post-surgical Pain after Bunionectomy*

This double-blind randomized controlled trial (**DBRCT**) was conducted in 2017 over 8 months in 637 subjects undergoing bunionectomy, enrolled/randomized at 6 study sites into one of four study arms in 1/2/2/2 ratio, respectively (number of subjects): placebo (89), celecoxib (181), tramadol (183), and test/co-crystal (184). The primary study objective was to demonstrate the analgesic efficacy of co-crystal E-58425 relative to tramadol and to celecoxib (separately) in managing moderate/severe post-operative pain, using: Numerical Pain Rating Scale (**NPRS**) as the pain measurement instrument, pain intensity (**PI**) as the primary endpoint (measurement) variable, and the sum of PI differences (index minus baseline) over the first 48 post-operative hours (**SPID-48**) as the primary analysis variable. Subjects were selected as follows:

- Adults (age ≥ 18 years) scheduled to undergo primary unilateral first metatarsal osteotomy with internal fixation, with no additional collateral procedure
- Must not have received any medication and must not have (had) any condition that could interfere with or confound the results of the study
- Must have a score between ≥ 5 and ≤ 9 on NPRS at rest, as a result of turning off the popliteal sciatic block

Subject randomization was stratified by baseline pain score, i.e., moderate (NPRS 5-6) or severe (NPRS 7-9). Study medications were administered four times daily for a

maximum of two days. Rescue medication was permitted: acetaminophen 1 g intravenous (IV) every 4-6 hours up to 4 g/24 hours or oxycodone hydrochloride 5 mg (immediate release tablet) every 4-6 hours up to 30 mg/24 hours.

III. INSPECTION RESULTS: ESTEVE-SUSA-301

1. Joseph Gimbel, M.D.

110 subjects were screened, 101 were enrolled, and 98 completed the study. Two subjects withdrew consent and one subject was discontinued for lack of efficacy and adverse events (AEs) of lower back pain, nausea/vomiting, and constipation.

Case records were reviewed in detail for 25 subjects completing study. Major NDA data listings were verified against on-site source records and CRFs: subject randomization, primary and secondary efficacy endpoints, AEs, protocol deviations, and subject discontinuation.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared GCP-compliant, including sponsor oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs.

2. Peter Winkle, M.D.

320 subjects were pre-screened by telephone (passive receipt of phone calls in response to advertisement), 100 were enrolled, and 100 completed the study.

Case records were reviewed in detail for 10 enrolled subjects. Major NDA data listings were verified against on-site source records and CRFs: subject randomization, primary and secondary efficacy endpoints, AEs, protocol deviations, and subject discontinuation.

No significant deficiencies were observed and a Form FDA 483 was not issued. Study conduct appeared GCP-compliant, including sponsor oversight of study conduct. All audited NDA data were adequately verifiable against source records and CRFs.

The Establishment Inspection Report (EIR) has not been received from the field office. The results reported in this Clinical Inspection Summary (CIS) is based on preliminary communication with the field investigator. An addendum to this CIS will be forwarded to the review division if any new significant information is received; otherwise, OSI's written post-inspection correspondence letter to the inspected entity (to be copied to review division) indicates completion of inspection and EIR review with confirmation of the findings as reported in this CIS.

{See appended electronic signature page}

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 10, 2019
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 213426
Product Name and Strength:	celecoxib and tramadol hydrochloride tablet, 44 mg and 56 mg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Esteve Pharmaceuticals, SA
FDA Received Date:	August 2, 2019
OSE RCM #:	2019-1058
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

As part of the approval process for celecoxib and tramadol hydrochloride tablet, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the proposed celecoxib and tramadol hydrochloride prescribing information (PI), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), container labels and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	The proposed proprietary name, (b) (4) is used throughout the	The proposed proprietary name, (b) (4), was found unacceptable by DMEPA under IND 128177 on	Remove the proposed proprietary name, (b) (4) throughout the PI. Until a new name is found to be

Table 2. Identified Issues and Recommendations for Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	Prescribing Information (PI).	September 3, 2019 due to potential confusion with another name that is also under review.	conditionally acceptable, the placeholder, "TRADENAME" may be used.
2.	The strength presentation and established names are inconsistently displayed throughout the Prescribing Information. For example, the strength is presented as "100 mg" in the Dosage and Administration, Dosage Forms and Strengths, and How Supplied and Handling sections of the Full Prescribing Information (FPI). Also, the tramadol established name is listed first in the Dosage Forms and Strengths section of the Highlights.	We note that in the 74-Day filing letter, Esteve was informed that the appropriate strength presentation should be "56 mg celecoxib and 44 mg tramadol hydrochloride".	The Office of Pharmaceutical Quality (OPQ) has determined the appropriate strength presentation for this product. Therefore, revise the strength presentation to "56 mg celecoxib and 44 mg tramadol hydrochloride" where appropriate throughout the PI.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The proposed indication for this product is the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. In section 2.2 Recommended Dosage, the frequency of administration is	This product is intended to be used "as needed" for pain as described in the Highlights.  (b) (4) 	Revise the frequency of administration to include "as needed" (i.e. every 12 hours as needed for pain).

Table 2. Identified Issues and Recommendations for Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	included (b) (4)		
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The NDC (National Drug Code) is denoted by a placeholder, XXXXX-XXX-XX.	The similarity of NDC's on container labels and carton labeling may lead to selection and dispensing errors. The package code portion (last 1-2 digits) is used to identify the container size. ^a	We have provided a recommendation for Esteve in the table below to submit NDC's for all the container labels and carton labeling and to ensure that the package code portion is different and non-sequential (e.g. -64, -70 vs. -64, -65) between 30 tablet and 90 tablet package sizes. Once Esteve addresses our recommendation below, they should also revise the PI accordingly and resubmit for review.

Table 3. Identified Issues and Recommendations for Esteve Pharmaceuticals, SA (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The proposed proprietary name, (b) (4) is used throughout the	We reference our September 9, 2019 Proprietary Name Request Unacceptable letter for IND 128177 informing you that	Remove the proposed proprietary name, (b) (4) from all labels and labeling. You may replace it with "TRADENAME" placeholder

^a Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

Table 3. Identified Issues and Recommendations for Esteve Pharmaceuticals, SA (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	container labels and carton labeling.	the proprietary name, (b) (4) was found unacceptable due to potential for confusion with another product that is also under review.	until a new name is found to be conditionally acceptable.
2.	The established name is not at least half the size of the proprietary name.	The established name is required to be at least half the size of the proprietary name per 21 CFR 201.10(g)(2).	Revise the established name to be in accordance with 21 CFR 201.10(g)(2).
3.	The NDC (National Drug Code) is denoted by a placeholder, XXXXX-XXX-XX.	The similarity of NDC's on container labels and carton labeling may lead to selection and dispensing errors. The package code portion (last 1-2 digits) is used to identify the container size. ^b	Please submit NDC's for all the container labels and carton labeling. Please ensure that the package code portion is different and non-sequential (e.g. -64, -70 vs. -64, -65) between the 30 tablet container label/carton labeling and the 90 tablet container label/carton labeling.
4.	The side panel contains the statement "For dosage and other prescribing information, see package insert."	This statement is inconsistent with the Prescribing Information.	To ensure consistency with the Prescribing Information, revise the statement to read "Recommended Dosage: See prescribing information."
Carton Labeling			
1.	The carton labeling contains a (b) (4)	The use of inconsistent terminology on container	Revise the carton labeling from (b) (4) to "Lot".

^b Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

Table 3. Identified Issues and Recommendations for Esteve Pharmaceuticals, SA (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4) statement while the container labels contain a “Lot #” statement.	labels and carton labeling may lead to confusion.	

4 CONCLUSION

Our evaluation of the proposed celecoxib and tramadol hydrochloride prescribing Information (PI), container labels and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Esteve Pharmaceuticals, SA so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for celecoxib and tramadol hydrochloride that Esteve Pharmaceuticals, SA submitted on August 2, 2019.

Table 4. Relevant Product Information for celecoxib and tramadol hydrochloride	
Initial Approval Date	N/A
Active Ingredient	Celecoxib and tramadol hydrochloride
Indication	Management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate
Route of Administration	oral
Dosage Form	tablet
Strength	56 mg celecoxib and 44 mg tramadol hydrochloride
Dose and Frequency	2 tablets every 12 hours as needed for pain
How Supplied/ Container Closure	Bottles containing 30 tablets or 90 tablets
Storage	Controlled room temperature

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 27, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, tramadol and celecoxib. Our search did not identify any previous reviews.

APPENDIX C. – N/A

APPENDIX D. – N/A

APPENDIX E. – N/A

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following celecoxib and tramadol hydrochloride labels and labeling submitted by Esteve Pharmaceuticals, SA on August 2, 2019.

- Container label(s)
- Carton labeling
- Prescribing Information (Image not shown) but can be accessed in EDR via:
 - o <\\cdsesub1\evsprod\nda213426\0007\m1\us\114-labeling\114a-draft-label\draft-labeling-text.docx>

F.2 Label and Labeling Images

Container label(s)



^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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