FDA Briefing Document

Joint Meeting of Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee

January 15, 2020 (AM Session)

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. The new drug application (NDA) 213426 for tramadol 44mg and celecoxib 56mg tablet, which contains a fixed dose combination of an opioid and an NSAID for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate, has been brought to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

FOOD AND DRUG ADMINISTRATION

Center for Drug Evaluation and Research

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety & Risk Management Advisory Committee

January 15, 2020

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Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP) Director Memorandum

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIOLOGY, ADDICTION MEDICINE AND PAIN MEDICINE

M E M O R A N D U M

DATE: January 15, 2020

FROM: Naomi Lowy, MD
Deputy Director (Acting)
Division of Anesthesiology, Addiction Medicine and Pain Medicine
Office of Neuroscience, CDER, FDA

TO: Chair, Members and Invited Guests
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)
Drug Safety and Risk Management Advisory Committee (DSaRM)

RE: Overview of the January 15, 2020, AADPAC/DSaRM Meeting to Discuss NDA 213426

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1 Division Memorandum

At this half-day, joint meeting of AADPAC and DSaRM, we will be discussing an application from Esteve Pharmaceuticals for E-58425 (tramadol hydrochloride (HCl) 44 mg and celecoxib 56 mg), a fixed-dose combination drug product. 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. The Applicant's goal was to develop a formulation of two analgesics of different classes such that the recommended dose of each component of the drug is less than the recommended dose of each component when taken individually for management of acute pain.

The product contains tramadol, an opioid with abuse potential, and has not been formulated with any excipients to impart abuse-deterrent characteristics. As an opioid-containing product, the considerations described in the Agency's draft guidance Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework, Guidance for Industry (June 2019) are relevant to the benefit-risk assessment of E-58425.

This Briefing Document summarizes data related to both benefit and risk of E-58425. A Phase 3 factorial study demonstrated that each component of E-58425 contributes to the efficacy of the product and provides evidence that supports a finding of analgesic efficacy for E-58425. From a safety perspective, there are no data to support a conclusion that E-58425 has any advantage or disadvantage compared to other approved analgesic drugs. During this meeting, to help inform your thinking, you will hear a review of recent epidemiologic data on use, misuse, and abuse of tramadol.

If approved, E-58425 will add an alternative option to the existing armamentarium for the treatment of acute pain severe enough to require an opioid.

The Comprehensive Addiction and Recovery Act of 2016, Section 106, requires FDA to refer new drug applications for opioids to an advisory committee before approval. As we review this new drug application of an opioid analgesic combined with a non-steroidal anti-inflammatory drug, we are interested in your thoughts, concerns, and recommendations. You will specifically be asked whether you have concerns about the impact of this product on public health. You will also be asked if you believe the benefits outweigh the risks for the proposed indication. Your advice and recommendations will be essential in assisting us with addressing this application. We are grateful that you have agreed to join us for this important discussion and look forward to seeing you at the meeting.

2 Discussion Topics

Considering the abuse potential of E-58425, and its proposed use for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate, please discuss any concerns you have regarding the impact of this product, if approved, on public health.

Discuss whether the benefits outweigh the risks for the proposed indication. Discuss any additional data that are needed for this application to be approved.

3 Background

Esteve Pharmaceuticals S.A. has developed E-58425, celecoxib and tramadol tablet, as a fixed-dose drug-drug combination product for the proposed indication of management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. One 100-mg tablet of celecoxib and tramadol contains 56 mg of celecoxib and 44 mg of tramadol hydrochloride, with a molecular ratio of 1:1 and a weight ratio of 1.27:1 for celecoxib and tramadol. The proposed dosing regimen is two tablets (112 mg of celecoxib and 88 mg of tramadol) every 12 hours as needed for pain relief. The Applicant's product is referred to as E-58425 throughout the document.

The Applicant submitted a 505(b)(2) application that relies in part on FDA's findings of safety and efficacy for Celebrex® (celecoxib) and Ultram® (tramadol hydrochloride or tramadol) as

individual components. Celecoxib and tramadol are analgesic medications with different mechanisms of action. Celecoxib is a cyclooxygenase-2 (COX-2) selective inhibitor in the class of nonsteroidal anti-inflammatory drugs (NSAIDs). Tramadol is a μ-opioid agonist and a norepinephrine and serotonin re-uptake inhibitor. Celecoxib products and tramadol products have been widely marketed and used for treatment of pain since their respective approvals. At the time of this review, there are no approved products containing combinations of tramadol and celecoxib in or outside the United States.

Celecoxib was initially approved on December 31, 1998, under the brand name Celebrex (NDA 20998). Celebrex is a COX-2 selective inhibitor in the NSAID class. COX-2 inhibitors have fewer gastrointestinal adverse effects compared with other NSAIDs. Celebrex is supplied as 50 mg, 100 mg, 200 mg, and 400 mg capsules for oral use. Celebrex is indicated for osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis in patients 2 years and older, ankylosing spondylitis, acute pain, and primary dysmenorrhea. The labeled dosage for Celebrex is as below:

For management of Acute Pain and Treatment of Primary Dysmenorrhea, the dosage is 400 mg initially, followed by an additional 200-mg dose if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily as needed.

Celecoxib is not available in combination with any other analgesic medication. A combination of amlodipine and celecoxib was approved on May 31, 2018, under the trade name Consensi® for patients for whom treatment with amlodipine for hypertension and celecoxib for osteoarthritis are appropriate (NDA 210045, amlodipine/celecoxib 2.5 mg/200 mg, 5 mg/200 mg, or 10 mg/200 mg). There are multiple combination products containing NSAIDs (other than celecoxib) and opioids in different strengths such as hydrocodone bitartrate/ibuprofen 2.5 mg/200 mg to 10 mg/200 mg, oxycodone/aspirin 4.8 mg/325 mg, oxycodone/ibuprofen 5 mg/400 mg, codeine/aspirin/butalbital/caffeine 50 mg/325 mg/40 mg/30 mg, and aspirin/caffeine/dihydrocodeine bitartrate 356.4 mg/30 mg/16 mg.

Tramadol hydrochloride was initially approved on March 3, 1995, under the brand name Ultram (NDA 20281). The mechanism of action of tramadol is not completely known, but the analgesic effect of tramadol is believed to be due to both binding to μ-opioid receptors and weak inhibition of re-uptake of norepinephrine and serotonin. Ultram is supplied as 50 mg strength scored tablets for oral use. Ultram is indicated in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The labeled dosage for Ultram is as below:

For patients not requiring rapid onset of analgesic effect, the tolerability of ULTRAM can be improved by initiating therapy with the following titration regimen: Start ULTRAM at 25 mg/day and titrated in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg four times a day). Thereafter the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg four times a day). After titration, ULTRAM 50 to 100 mg can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg/day.

For the subset of patients for whom rapid onset of analgesic effect is required and for whom the

benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, ULTRAM 50 mg to 100 mg can be administered as needed for pain relief every four to six hours, not to exceed 400 mg per day.

After the approval of Ultram, other products containing tramadol were approved, including a combination of tramadol and acetaminophen [Ultracet (tramadol hydrochloride 37.5 mg and acetaminophen 325 mg) tablets, NDA 21123, approved in 2000] and an extended release formulation [Ultram ER (tramadol hydrochloride extended-release 100 mg, 200 mg, and 300 mg) tablets, NDA 21692, approved in 2005].

On August 18, 2014, the United States Drug Enforcement Administration placed all tramadol-containing products (including its salts, isomers, and salts of isomers) into schedule IV of the Controlled Substances Act.

Pain: Current Treatment Landscape

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (IASP 2017). Pain is a multifactorial medical condition that can occur in a variety of clinical settings such as trauma, musculoskeletal injury, nerve injury, visceral distension or inflammation, and postsurgical procedures. Acute pain can be a serious medical condition that can significantly impact patients' function and quality of life (QOL). Acute pain is generally self-limiting and requires treatment for no more than a few weeks. Untreated or poorly treated acute pain can result in patient dissatisfaction, increased cost of treatment, prolonged hospital stays, and progression of acute pain to chronic pain.

The terms mild, moderate, or severe are often used by patients and heath care providers to describe pain severity. This description provides a subjective measure of pain level and generally correlates with pain scores within the clinical context under evaluation. However, severe pain following a dental extraction may not be qualitatively the same as severe pain following abdominal surgery, and each condition may need a different treatment approach.

Treatment of pain must be based on an individualized approach in each patient to achieve an optimal outcome. The goal of treatment is to control pain to improve physical function, ADLs, social and emotional wellbeing, and QOL. There are multiple therapeutic approaches for the treatment of pain, including prescription and nonprescription medications, invasive and non-invasive medical procedures such as nerve blocks, occupational and physical therapies, and complementary and alternative therapies such as acupuncture, herbal medicine, and biofeedback.

Pharmacologic treatment options for pain control include multiple classes of medications such as acetaminophen, NSAIDs, anesthetics (such as lidocaine), anticonvulsants, antidepressants, opioids (including tramadol and tapentadol), and combination products containing different medications. Pain medications can be administered through a variety of routes, such as oral, intramuscular injection, intravenous injection, and topical/transdermal systems.

The goal of treatment is to control pain with minimal side effects from pain medication. The

choice of medication for pain management should be based on the diagnosis, the mechanisms of pain, comorbidities, and a thorough benefit-risk assessment that demonstrates that the benefits of a medication outweigh the risks. Non-opioid treatment options must be considered as the first line therapy for pain management. Opioids or combination products that contain opioids may be necessary for treatment of moderate to severe pain for which alternative treatments are inadequate.

4 Benefit-Risk Integrated Assessment

The benefit-risk assessment of E-58425 incorporates the components described in the Agency's draft guidance *Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework*, guidance for industry (June 2019). These considerations are summarized here:

Benefits to the Patient Using the Drug as Labeled
1. The Applicant performed one Phase 3 factorial study (ESTEVE-SUSA-301) designed to fulfill the requirements for fixed-combination prescription drugs under 21 CFR 300.50 of the Federal Food, Drug and Cosmetic Act (FD&C Act). The study was designed to demonstrate that each component of E-58425 contributes to the efficacy of the product. This study provides evidence supporting a finding of analgesic efficacy for E-58425. 2. The Phase 3 study was performed in patients who had moderate to severe pain after bunionectomy. Postoperative acute pain is one of the pain models that is commonly used in clinical trials for analgesic drug development programs.
Risks to the Patient Using the Drug as Labeled
1. E-58425 contains celecoxib and tramadol as its active ingredients. Relative bioavailability studies of E-58425 demonstrated comparable or lower systemic exposure to celecoxib and tramadol compared to individual use of each drug within the labeled recommended dose range. The systemic safety of combination product E-5842 is expected to be comparable to the systemic safety of each individual component. Review of safety data from clinical studies of E-58425 did not reveal any novel risks. 2. E-58425 is not formulated with any excipients to deter abuse or resist manipulation. 3. There are no data to suggest that the drug characteristics of E-58425 increase or decrease the risk for respiratory depression, sedation, or development of opioid use disorder in patients relative to other tramadol products. Each E-58425 100-mg tablet contains 44 mg of tramadol. The proposed dosage of E-58425 is 200 mg every 12 hours, which contains tramadol 88 mg per dose with a total of 176 mg of tramadol per day. This is within the recommended maximum dose range for the reference product, Ultram, which is 200-400 mg per day. 4. In the clinical studies performed by the Applicant, the most common adverse events (AEs) reported with E-58425 were comparable to those reported with tramadol, including nausea, vomiting, and somnolence and dizziness. No unexpected safety issues were reported with the use of E-58425 in clinical studies performed by the Applicant.
Effectiveness and Safety of the New Drug Relative to Approved Analgesics

1. There are no adequate comparative efficacy data for E-58425 relative to other approved opioid or nonopioid analgesic drugs. The Phase 3 factorial study compared lower doses of the individual components of E-58425 than are optimal for treatment of acute pain and this study is not suitable for making comparative efficacy claims.
2. The clinical studies performed for this new drug application (NDA) were designed to evaluate the primary objectives of efficacy or bioavailability of E-58425. These studies were not designed to prospectively evaluate prespecified safety outcomes. Thus, no direct comparisons can be made regarding the comparative safety of E-58425 to other analgesics.
3. E-58425 is a fixed-dose combination product dosed every 12 hours, which provides less flexibility in making dose adjustments. This may be relevant in situations where patients do not tolerate the recommended initial dose of tramadol, which is on the upper end of the recommended dose range in the Ultram label.
4. There are no data to support that E-58425 has any advantage over other available approved analgesic drugs.
5. There was no evidence that AEs typically associated with opioid analgesic drugs occur at a higher rate or with greater severity with E-58425.

Broader Public Health Effects: Risks and Mitigation of Risks Related to Misuse, Abuse, Opioid Use Disorder, Accidental Exposures, and Overdose

1. The opioid epidemic, driven in part by increased prescribing, is a major public health issue. There has been concern that approval of new opioid analgesic drug products may lead to increased prescribing of opioid analgesics. However, in recent years the number of opioid analgesics dispensed has not trended in the same direction as numbers of opioid analgesic drug approvals. Examination of dispensed opioid prescriptions and opioid approvals showed a decrease in estimated annual numbers of opioid analgesics dispensed since 2010 and increasing numbers of opioid analgesic drug approvals per year since 2010 (Chai et al. 2018 [1]). While these data alone do not eliminate the overall concern, the observed trends do not support the hypothesis that new opioid analgesic approvals lead to increased prescribing of opioid analgesics.
2. As of August 18, 2014, the Drug Enforcement Administration (DEA) placed tramadol (including its salts, isomers, and salts of isomers) as Schedule IV under the Controlled Substances Act (CSA) (79 FR 37623), applicable to all tramadol-containing products. Schedule IV drugs are considered to have a lower potential for abuse relative to the drugs or substances in Schedule III of the CSA, have a currently accepted medical use in treatment in the U.S., and abuse of the drug may lead to limited physical dependence or psychological dependence relative to other drugs or substances in Schedule III [21 U.S.C. 812 (b) (4)]. [2]
3. Product-specific characteristics
   - E-58425 tablets are provided in oral tablet formulations. The method of delivery does not affect existing risk and does not introduce a novel risk.
   - There are no characteristics of E-58425 that would be expected to increase or decrease the risk of accidental exposure in children (e.g., tablet size, color, flavor,

[1] Chai, G, J Xu, J Osterhout, MA Liberatore, KL Miller, C Wolff, M Cruz, P Lurie, and G Dal Pan, 2018, New Opioid Analgesic Approvals and Outpatient Utilization of Opioid Analgesics in the United States, 1997 through 2015, Anesthesiology, 128(5):953-966.

[2] Re-evaluation of the scheduling status of tramadol substance was not considered as part of the review of this NDA.

packaging configuration, or appearance of tablets).
- There are no specific characteristics of E-58425 that would be expected to increase or decrease the risk of misuse, abuse, opioid use disorder, and related adverse outcomes such as overdose and infectious complications of injection compared to other opioids.

4. Summary of single-entity tramadol product postmarket data
    - The number of dispensed single-entity tramadol prescriptions gradually declined after the product was placed under Schedule IV in 2014. However, there was an increasing trend in tramadol as a percentage of the total opioid analgesic prescriptions in recent years.
    - 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.
5. Risks in special populations
    - The proposed patient population for E-58425 is adults. Per the agreed initial pediatric study plan, a clinical trial in adolescents (≥12 years and <17 years) would be initiated upon approval of E-58425. The planned nonclinical toxicological study will provide additional data for assessment of the benefit-risk of E-58425 in adolescents.
    - Currently, no data are available to inform a benefit-risk evaluation of E-58425 in the subpopulations of patients with mental health and/or substance use disorders.

Risk Management
• Tramadol is an opioid and a schedule IV controlled substance considered to have potential for abuse. E-58425 is subject to the Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of E-58425 outweigh potential risks in the outpatient setting.

5 Regulatory Background

On May 15, 2019, Esteve Pharmaceuticals, S.A. (Esteve, the Sponsor, or the Applicant) submitted NDA 213426 for E-58425, celecoxib and tramadol, tablet 100 mg, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, making reference to the FDA's previous findings on the safety and effectiveness of the two reference listed drugs (RLDs) (Celebrex and Ultram®) as well as original studies performed by the Applicant.

The development program for this product occurred under Investigational New Drug Application (IND) 128177. On February 25, 2016, a pre-IND meeting was held between the Division and the

Applicant. The following were discussed during the pre-IND meeting regarding the development program for E-58425:

1. If the Applicant intends to submit a 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for one or more listed drugs, they must establish that such reliance is scientifically appropriate, using the NDA product approved in the U.S.
2. Based on the Applicant's Phase 2 study conducted in Europe, the Division was concerned that twice-a-day (BID) dosing with E-58425 may not be appropriate as it was not supported by the time-to-rescue of 7 to 8 hours.
3. The Division recommended that the Applicant use SPID 48 as the primary endpoint to provide evidence of efficacy over the first 48 hours of treatment.
4. The requirements of the combination rule for E-58425 were discussed.
5. The Division advised that one adequate and well-controlled factorial study can support the NDA. The Division noted that the standard for comparative claims of superiority against another drug product is replicated evidence from clinical studies and thus two studies would be required to support a comparative claim.

The Food and Drug Administration Modernization Act (FDAMA) includes a provision that requires sponsors planning to submit an application for a drug subject to the Pediatric Research Equity Act (PREA) to submit an initial pediatric study plan (iPSP) early in the development process. The intent of the iPSP is to identify needed pediatric studies early in development and begin planning for these studies. The Division agreed to the submitted iPSP on August 28, 2017, which included a plan to request a partial waiver in pediatric age groups 0 - <12 years old and defer pediatric clinical studies in adolescents (≥12 years and <17 years) until after FDA approval of E-58425 in adults. The strength or strengths to be used in the pediatric clinical study will depend on the results of the toxicology studies and final agreement with the FDA on the clinical study protocol.

On May 17, 2018, a pre-NDA meeting was held between the Applicant and the Division. A summary of clinical issues discussed at that meeting is listed here:

1. Given that E-58425 is a combination of celecoxib and tramadol, an opioid analgesic, the Division anticipated that the application will be discussed at an Advisory Committee meeting to obtain input from outside experts and the public. The Applicant proposed to use "Co-crystal of Tramadol and Celecoxib" as the established name for the Co-crystal E-58425. The Division did not agree and recommended the established name of "(Celecoxib and tramadol) tablets."
2. The Division stated that the proposed product label should include safety information from the listed drugs and the completed clinical studies.
3. A risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse. Therefore, the Applicant will need to submit a proposed REMS with their application.
4. The Division agreed that no abuse potential studies need to be conducted at this time for E-58425. The Applicant should document AEs associated with potential abuse and overdose for all clinical studies, including cases of lack of compliance or patients who discontinue participation without returning the study medication.

5. Given that E-58425 is a fixed-dose combination product, it may be difficult to adjust the dose in several situations. The Applicant should clearly elaborate:
   - How E-58425 will be initiated, e.g., using the Ultram label as an example
   - Dosing recommendations regarding special populations, e.g., patients with hepatic or renal deficiencies and the elderly.
   - Dosing recommendations regarding drug-drug interactions, e.g., poor metabolizers of CYP2C9, inhibitors of CYP2D6 and 3A4, and inducers of CYP3A4.

6 Summary of Chemistry, Manufacturing and Controls Data

The proposed drug product from Esteve is formulated as an immediate release tablet containing co-crystal of celecoxib and tramadol hydrochloride. Co-crystals are crystalline materials composed of two or more different molecules in a defined stoichiometric ratio within the same crystal lattice that are associated by nonionic and noncovalent bonds. Per Regulatory Classification of Pharmaceutical Co-Crystals Guidance for Industry (Feb 2018), a co-crystal is not a new single active pharmaceutical ingredient (API) and treated as a fixed-dose combination. The submitted data indicate that the intrinsic dissolution rate of tramadol hydrochloride is slowed while that of celecoxib is slightly accelerated (only at high pH) due to the co-crystallization, when compared to the intrinsic dissolution rate of the respective single entity. The applicant believes that these characteristics will support dosing tramadol every 12 hours instead of every 6 hours, as recommended in the approved immediate-release tramadol-containing products. The excipients used in the proposed product are typically used in an immediate-release product. The Applicant has confirmed the presence of co-crystals by various analytical methods. The Applicant has conducted clinical studies using tablets with the same core formulation as the proposed to-be-marketed (TBM) product.

7 Summary of Clinical Pharmacology Data

The clinical pharmacology studies included a single-dose relative bioavailability (BA) study, a multiple-dose relative BA study, and a food effect pharmacokinetic (PK) study of E-58425 tablets. The purpose of these three studies was to evaluate single-dose and multiple-dose relative BA of E-58425 tablets compared to the reference drugs, and to evaluate food effect on E-58425 tablets:

We conclude from these studies that:

1. After single dose administration, for the tramadol component of E-58425 tablets (total dose 88 mg), the Cmax was 30% lower and the AUC (AUCt and AUCinf) was ~8% lower compared to Ultram tablets (total dose 100 mg). For the tramadol-M1 metabolite of E-58425 tablets, the Cmax was 30% lower and the AUC (AUCt and AUCinf) was ~12% lower compared to Ultram tablets. For the celecoxib component of E-58425 tablets (total dose 112 mg), the Cmax was 15% lower and the AUCt and AUCinf was ~18% lower when compared to Celebrex 100 mg capsules. This single dose relative BA study established the scientific bridge to the reference drugs Ultram and Celebrex for this 505(b)(2) application.

2. After multiple dose administration of E-58425 tablets, the accumulation ratio of tramadol Cmax and AUCτ values (15th dose/1st dose) were 2.20-fold and 2.37-fold, respectively. The accumulation ratio of celecoxib Cmax and AUCτ values (15th dose/1st dose) were 1.76-fold and 2.15-fold, respectively. After multiple dosing, the Cmax,ss and AUC,ss values of tramadol and celecoxib components of E-58425 tablets were lower than the reference drugs, Adolonta[3] and Celebrex. Based on pre-dose concentrations, the steady state appears to be achieved for all three analytes, tramadol, M1 metabolite, and celecoxib, of E-58425 tablets. There were no differences in the tramadol and celecoxib half-lives after multiple dosing between E-58425 tablets and reference drugs, Adolonta and Celebrex.
3. When E-58425 tablets was administered under fed conditions, the AUC, Cmax, and Tmax of the tramadol component were not significantly affected. For the celecoxib component, the Tmax was delayed by approximately 2.5 hours and resulted in an approximate 30% increase in Cmax and AUC, which was similar to the food effect described in the Celebrex label. It is reasonable to recommend that E-58425 tablets be taken without regard to food.

Refer to the Appendix for details about the Clinical Pharmacology program.

8 Overview of Clinical Studies

In this NDA submission, the Applicant included five Phase 1, one Phase 2, and one Phase 3 clinical studies. See supplemental table in appendix for additional study details.

Phase 1 studies in healthy volunteers included one comparative bioavailability study (single dose) using the U.S. references (ESTEVE-SUSA-101) and four studies using European references (ESTEVE-SACO4-102, ESTEVE-SACO4-103, ESTEVE-SACO4-104, and ESTEVE-SACO4-105). Study ESTEVE-SUSA-101 was used to provide bioavailability bridging data for reliance upon FDA's finding of safety and effectiveness of the RLDs, Celebrex and Ultram. The clinical pharmacology review findings are summarized above under Clinical Pharmacology.

ESTEVE-SACO4-201 was a Phase 2 dose finding study on postsurgical acute pain after oral surgical procedures involving extraction of two (ipsilateral) or more impacted third molars requiring bone removal. This study was a placebo-controlled, single dose study that provided the first set of efficacy data for use of E-58425 in acute pain, comparing different doses of the product with a formulation of tramadol marketed in Europe and placebo.

ESTEVE-SUSA-301 was a Phase 3 full factorial study comparing E-58425 to tramadol, celecoxib, and placebo in a postsurgical acute pain model (bunionectomy with osteotomy).

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[3] The Applicant has established the required scientific bridge for this 505(b)(2) application via single-dose relative BA between E-58425 tablets and US approved reference drugs Ultram (Tramadol 50 mg tablets) and Celebrex (100 mg capsule). Adolonta (Tramadol 50 mg capsule) is not a US-approved drug. The PK comparison between E-58425 tablets and Adolonta capsules after multiple doses was used as supportive information and is not required to establish the scientific bridge.

Additionally, Mundipharma Research Limited (MRL) performed one Phase 1 and two Phase 3 studies in Europe and Canada, using E-58425 under the name MR308. See supplemental table in Appendix for study details. The studies performed by MRL are not part of this NDA submission and are not included in the efficacy evaluation. Any SAEs that occurred in these studies are reported by the Applicant and are included in the safety review.

Consistent with FDA's recommendations, the Applicant submitted one Phase 3 factorial study, ESTEVE-SUSA-301.

The primary objective of this study was to establish the analgesic efficacy of E-58425 compared to tramadol and to celecoxib for the management of moderate to severe post-operative pain for 48 hours after bunionectomy by using assessments of pain intensity.

Study ESTEVE-SUSA-301 was a randomized, double-blind, active- (tramadol and celecoxib) and placebo-controlled, parallel group, Phase 3 study in patients with moderate to severe pain after bunionectomy. This study served as a full factorial study to fulfill the requirement of the combination rule for the study drug, celecoxib and tramadol tablet, or E-58425.

Table 1 and Table 2 show the study treatment arms and dosing scheme. Figure 1 shows the study design scheme.

Table 1: Treatment Arms for Study ESTEVE-SUSA-301

Treatment Arms		Posology	Total Daily Dose (mg) Tramadol	Total Daily Dose (mg) Celecoxib
ARM-1	Co-crystal E-58425	200 mg BID	176	224
ARM-2	Tramadol	50 mg QID	200	0
ARM-3	Celecoxib	100 mg BID	0	200
ARM-4	Placebo	0 mg QID	0	0

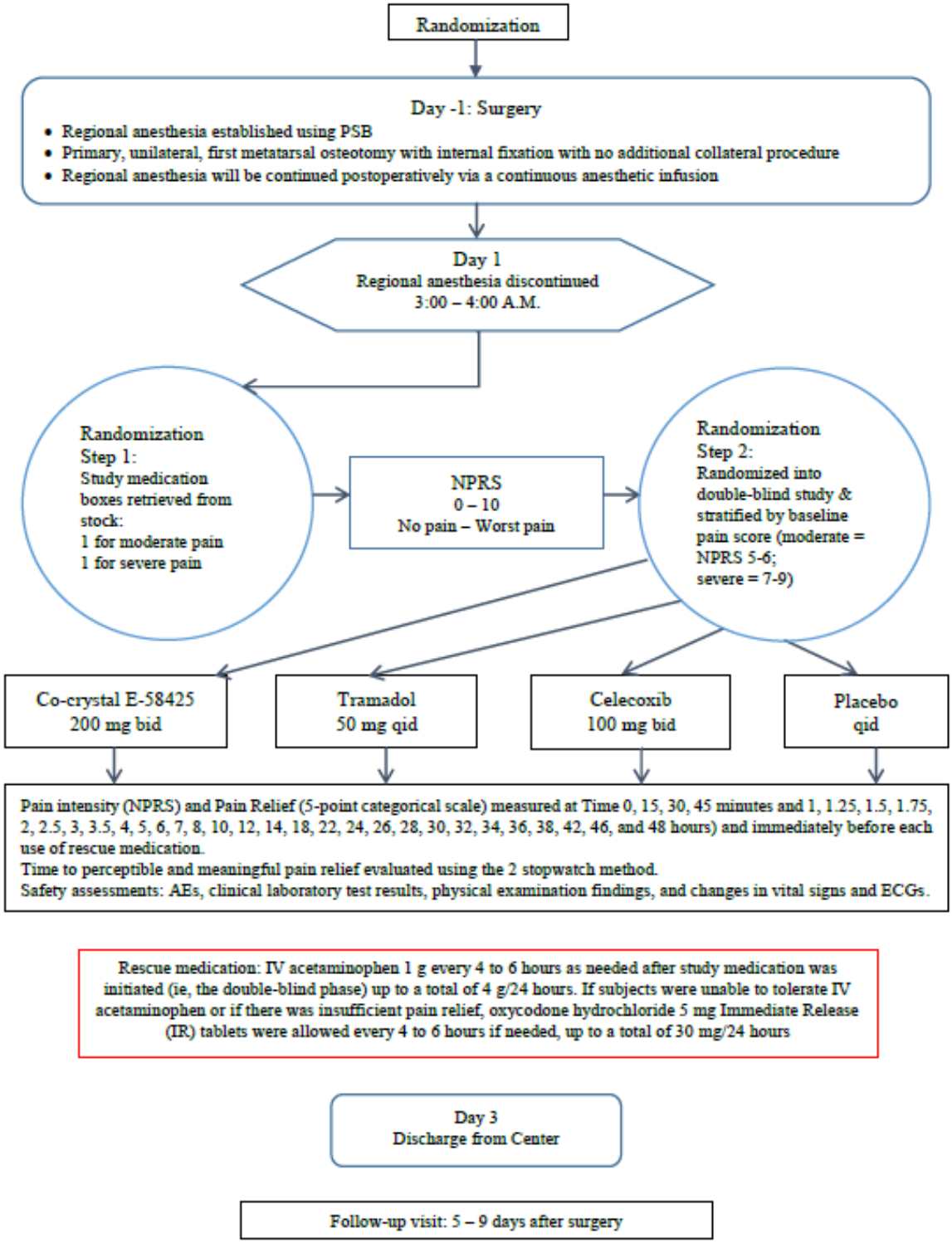
Abbreviations: BID – twice daily (every 12 hours); QID – 4 times daily (every 6 hours)
Source: Adapted from Applicant's submission, NDA 213426, 2.7.6. Synopses of Individual Studies

Table 2: Dosing Scheme for Study ESTEVE-SUSA-301

	Day 2[1]				Day 3[1]			
Treatment Group	**Dose 1 (0 h)**	**Dose 2 (6 h)**	**Dose 3 (12 h)**	**Dose 4 (18 h)**	**Dose 5 (24 h)**	**Dose 6 (30 h)**	**Dose 7 (36 h)**	**Dose 8 (42 h)**
Co-crystal E-58425	200	P	200	P	200	P	200	P
Tramadol	50	50	50	50	50	50	50	50
Celecoxib	100	P	100	P	100	P	100	P
Placebo	P	P	P	P	P	P	P	P

[1] Doses measured in mg
Abbreviations: h – hour; P – placebo
Source: Adapted from Applicant's submission, NDA 213426, 2.7.6. Synopses of Individual Studies

Figure 1: Study Design Scheme



Abbreviations: PSB – popliteal sciatic nerve block, NPRS – Numerical Pain Rating Scale, bid – twice daily, qid – four times daily, AE – adverse events, ECG – electrocardiogram, IR – immediate release
Source: Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SUSA-301

The study enrolled adults who were scheduled to undergo primary unilateral first metatarsal osteotomy with internal fixation with no additional collateral procedure. Subjects who had a pain

score of ≥5 and ≤9 on the 0-10 Numerical Pain Rating Scale (NPRS) at rest, after turning off the popliteal sciatic block, were eligible for randomization. Subjects who received any analgesic medication other than short-acting pre-operative or intra-operative anesthetic agents before the end of bunionectomy were excluded.

To fulfill the requirement of a full factorial study, Study ESTEVE-SUSA-301 included the following arms: active control tramadol arm, active control celecoxib arm, E-58425 arm, and placebo arm. After the surgery, eligible subjects were stratified by baseline pain score (moderate pain: NPRS 5-6; severe pain: NPRS 7-9) and were randomized to a study treatment arm in a 2:2:2:1 ratio.

- The subjects in the E-58425 arm took two tablets of E-58425 every 12 hours, i.e., celecoxib 112 mg and tramadol 88 mg, twice per day. The Applicant's rationale for dose selection of E-58425 was based on Study ESTEVE-SACO4-201.
- The subjects in the celecoxib arm took Celebrex 100 mg every 12 hours, which is lower than recommended dose of Celebrex for acute pain per its label. The recommended dosage of Celebrex for acute pain per its label is:

  > For management of acute pain and treatment of primary dysmenorrhea, the dosage is 400 mg initially, followed by an additional 200 mg dose if needed on the first day. On subsequent days, the recommended dose is 200 mg twice daily as needed.

- The subjects in the tramadol arm took Ultram 50 mg every 6 hours, which is an acceptable regimen for use of tramadol in the clinical context of acute pain. The label for Ultram states the following:

  > For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, ULTRAM 50 mg to 100 mg can be administered as needed for pain relief every four to six hours, not to exceed 400 mg per day.

Allowed rescue medications were acetaminophen 1 g intravenous every 4 to 6 hours, up to 4 g/24 hours, or oxycodone hydrochloride 5 mg IR tablet every 4 to 6 hours if needed, up to a total of 30 mg/24 hours.

The primary efficacy endpoint was the time-weighted SPID from 0 to 48 hours ($SPID_{48}$). This was an appropriate primary efficacy endpoint that the Applicant used per the Division recommendation to provide evidence of efficacy over the first 48 hours of treatment.

Pain intensity (PI) was measured by the NPRS with 0 indicating "No Pain" and 10 indicating "Worst Possible Pain." In the study, each subject assessed his or her pain intensity at multiple time points (see figure 1 for time points), and immediately before each use of rescue analgesia. Pain assessment was performed during the night only if the subject was awake. The protocol specified that pain measurements were excluded from the analysis if they differed from the nominal time as follows:

- by >3 minutes in the first 2 hours,
- by >6 minutes after 2 hours and up to 4 hours,

- by >10 minutes after 4 hours and up to 8 hours, and
- by >15 minutes after 8 hours.

In acute pain studies with subjects in hospital settings, there is usually a small percentage of subjects with missing pain scores. In the reviewed study, a pain assessment was not performed if the subject was sleeping during the night and pain measurements out of the assessment windows were excluded from the analysis, which resulted in a larger proportion of missing pain measurements than is typical for a study of this type.

There were multiple secondary efficacy endpoints including:

- Time to onset of analgesia, time to perceptible pain relief, and time to meaningful pain relief
- Rescue medication use
  - Proportion of subjects who took at least 1 dose of rescue medication up to 4, up to 6, up to 12, up to 24, and up to 48 hours after first dose of study medication; number of doses of rescue medication for the same time intervals
  - Time to first use of rescue medication

See section 12.2 in the Appendix for the summaries of the Statistical Analysis Plan (SAP).

9 Efficacy Results: Clinical and Statistical Summary

Patient Disposition

Figure 2 shows disposition of study subjects in Study ESTEVE-SUSA-301. An overview of the number of subjects who discontinued study medication or withdrew from the study is given in Table 3.

Figure 2: Disposition of Subjects for Study ESTEVE-SUSA-301

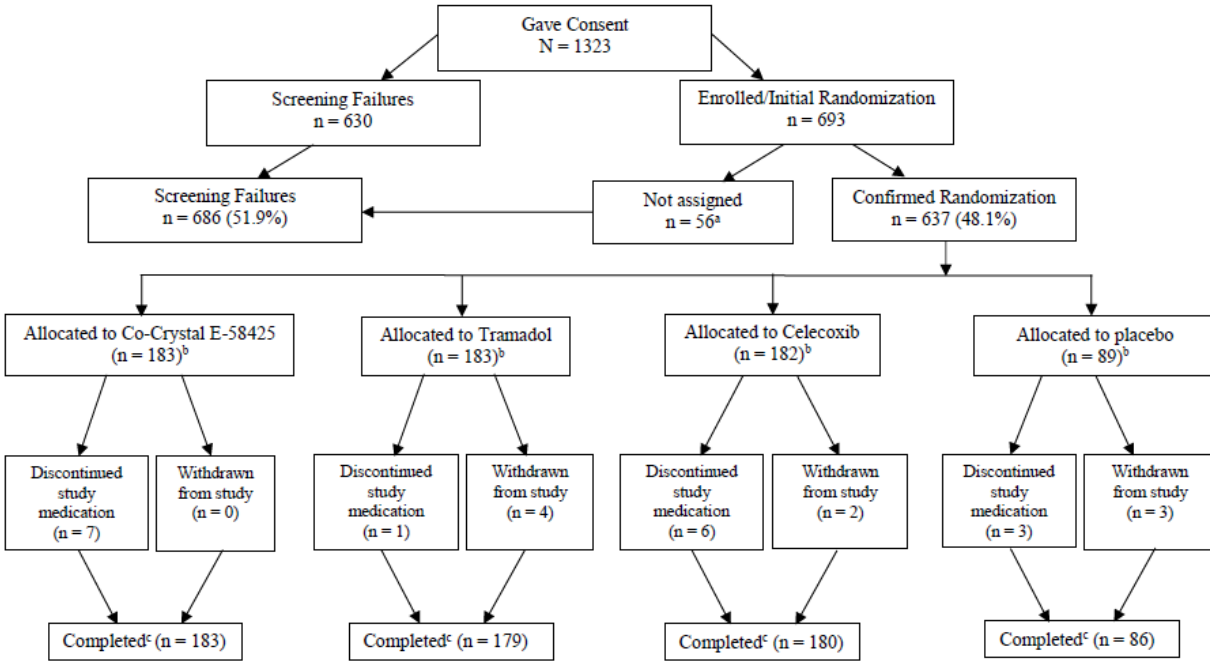


Figure 10-1: Disposition of Subjects (All Subjects)

Source: Section 14.1, Table 14.1.3, Table 14.1.5; Table 14.1.7; Appendix 16.2, Listing 16.2.1.2; Listing 16.2.1.3

a Not assigned to a unique treatment arm/strata primarily due to not meeting required pain scores (<5 or >9 on a 0-10 NPRS) per Inclusion Criterion #6/Exclusion Criterion #1.

b Safety Analysis Set, based on the treatment received. Three subjects were misrandomized; they are evaluated in the FAS based on the treatment to which they were assigned: 184 subjects in co-crystal E-58425, 183 subjects in tramadol, 181 subjects in celecoxib, and 89 subjects in the placebo group.

c Per Table 14.1.3

Source: Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SUSA-301

Table 3: Summary of Reasons for Discontinuation of Study Medications or Withdrawal from Study

Study Medication Discontinuations or Withdrawals from the Study	E-58425 (N=183) n (%)	Tramadol (N=183) n (%)	Celecoxib (N=182) n (%)	Placebo (N=89) n (%)	Total (N=637) n (%)
Discontinuation of study medication[a]	7 (3.8)	1 (0.5)	6 (3.3)	3 (3.4)	17 (2.7)
Reason:					
Withdrawal by subject	2 (1.1)[b]	1 (0.5)[c]	2 (1.1)	0	5 (0.8)
Adverse event	1 (0.5)[d]	0	0	0	1 (0.2)
Unspecified reasons	4 (2.2)[e]	0	4 (2.2)	3 (3.4)	11 (1.7)

Study Medication Discontinuations or Withdrawals from the Study	E-58425 (N=183) n (%)	Tramadol (N=183) n (%)	Celecoxib (N=182) n (%)	Placebo (N=89) n (%)	Total (N=637) n (%)
Withdrawals from study	0	4 (2.2)	2 (1.1)	3 (3.4)	9 (1.4)
Reason:					
Adverse event	0	1 (0.5)[f]	0	0	1 (0.2)
Lack of efficacy	0	0	0	1 (1.1)	1 (0.2)
Lost to follow-up[g]	0	1 (0.5)	2 (1.1)	0	3 (0.5)
Protocol deviation	0	1 (0.5)	0	0	1 (0.2)
Withdrawal by subject	0	1 (0.5)[h]	0	2 (2.2)	3 (0.5)
Total	**7 (3.8)**	**5 (2.7)**	**8 (4.4)**	**6 (6.7)**	**26 (4.1)**

[a] Reasons for discontinuation of study medication were entered by the investigator as free text, and were grouped for this table.
[b] Subject (b) (6) had an AE that led to discontinuation of study medication.
[c] Subject (b) (6) had an AE that led to discontinuation of study medication.
[d] Subject (b) (6) had an AE that led to discontinuation of study medication.
[e] Subject (b) (6) had an AE that led to discontinuation of study medication.
[f] Subject (b) (6) had an AE that led to discontinuation of study medication.
[g] Received all 8 doses of study medication and included in PPAS.
[h] Subject (b) (6) had an AE that led to discontinuation of study medication.
Abbreviations: n – number of observations; N – number of subjects; PPAS – per-protocol analysis set
Source: Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SUSA-301. Table 10-1.

Demographic and Baseline Characteristics

Overall, the mean age was approximately 46 years. The majority of subjects in the study were female (85.9%), white (73.8%), and not Hispanic or Latino (76.3%). Given the bunionectomy procedure as the pain model, the higher ratio of female subjects in this study is not unexpected. The four treatment groups were similar in the distribution of demographic characteristics.

Only a small number of subjects (58 subjects, 9%) were over 65 years of age in this study and only 6% of subjects in the E-58425 group were over 65 years of age.

The baseline pain scores are displayed in Table 4 for all four treatment groups. There was no imbalance in the baseline pain scores across treatment groups.

Table 4: Baseline Pain Group (Full Analysis Set)

Baseline Pain Score	Co-crystal E-58425 (N=183) n (%)	Tramadol (N=183) n (%)	Celecoxib (N=182) n (%)	Placebo (N=89) n (%)	Total (N=637) n (%)
Moderate (NPRS 5-6)	89 (48.4)	90 (49.2)	86 (47.5)	42 (47.2)	307 (48.2)
Severe (NPRS 7-9)	95 (51.6)	93 (50.8)	95 (52.5)	47 (52.8)	330 (51.8)

Source: Adapted from Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SUSA-301. Table 10-6.

Efficacy Results: Primary Endpoint

There were 184 subjects from the E-58425 treatment group, 183 subjects from the tramadol group, 181 subjects from the celecoxib group, and 89 subjects from the placebo group included in the full analysis set. The mean observed PI scores over the 48-hour post-operative period for each treatment group are displayed in Figure 3. At all timepoints through 48 hours, the means of observed Pain Intensity (PI) scores were lower in the E-58425 group compared with all other treatment groups. Figure 4 shows the mean of PI scores for each treatment group where the PI scores observed within 4 hours after the use of rescue medications were imputed by the PI scores recorded immediately prior to rescue use. In Figure 4, the means of PI scores were still lower in

the E-58425 group compared with all other three treatment groups.

Figure 3: Mean Pain Intensity Scores Over Time (Using Observed PI Scores)

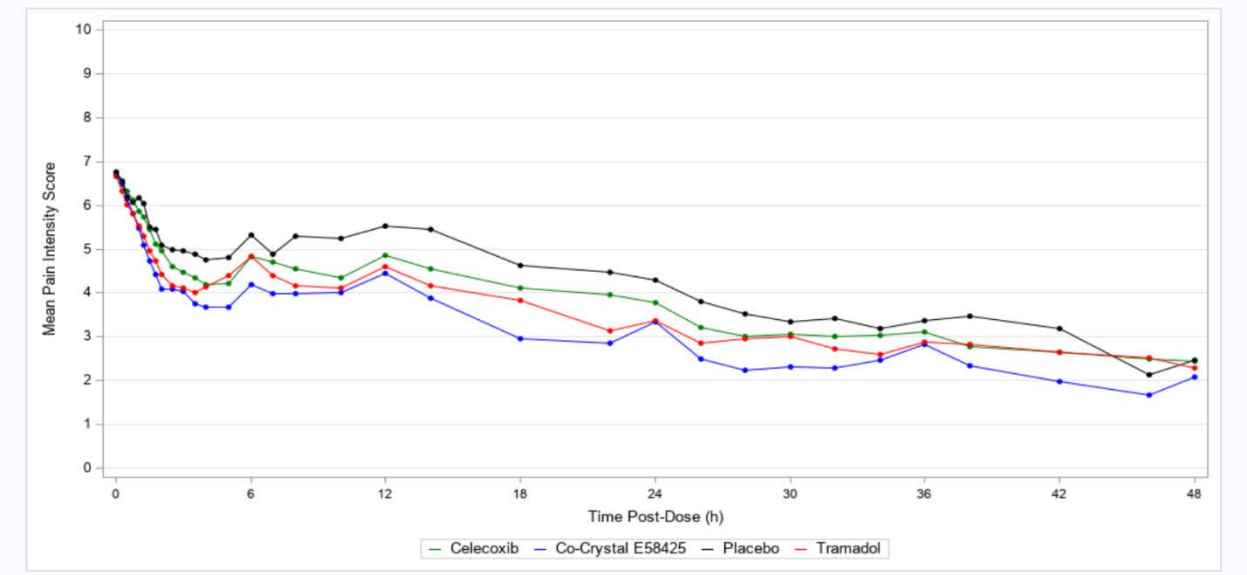
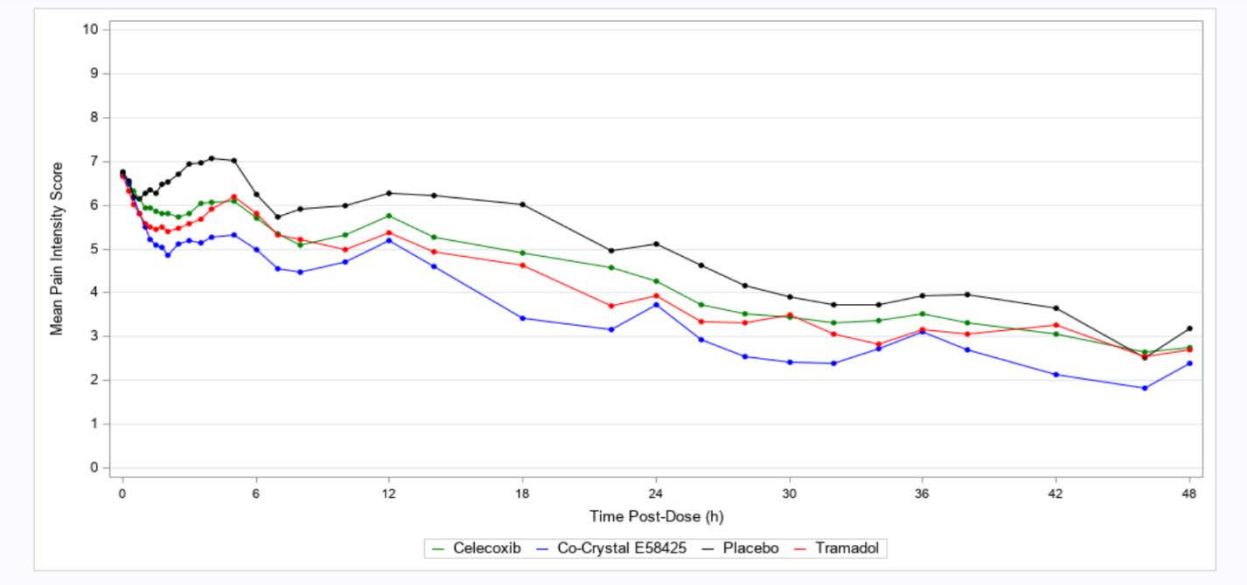


Figure 4: Mean PI Scores Over Time (Pre-Rescue PI Score Was Imputed up to 4 Hours After Rescue Use)



Source: Reviewer's analysis results.

The reviewer was able to reproduce the Applicant's analyses of the primary efficacy endpoint where missing PI scores were imputed by the BOCF method and the PI scores observed within 4 hours after the use of rescue medications were imputed by the PI scores recorded immediately prior to rescue use. Results from the ANCOVA model are shown in Table 5. The E-58425 group

had statistically significantly better mean $SPID_{48}$ scores than any of the other groups after bunionectomy.

Table 5: $SPID_{48}$: Primary Analysis Results (BOCF Method)

Treatment	LS Mean	95% CI of LS mean	Comparison	P-Value	Estimate of Difference in LS Means	95% CI for Difference in LS Means
E-58425	-139.12	(-151.75, -126.49)				
Tramadol	-109.08	(-121.74, -96.42)	E-58425 minus tramadol	0.0008	-30.04	(-47.47, -12.61)
Celecoxib	-103.69	(-116.39, -90.99)	E-58425 minus celecoxib	<0.0001	-35.45	(-52.90, -17.95)
Placebo	-74.55	(-92.48, -56.61)	E-58425 minus placebo	<0.0001	-64.57	(-86.12, -43.02)

Abbreviations: BOCF – baseline observation carried forward CI – confidence interval; LS – least square
Source: Reviewer's analysis results.

As was noted in the previous section discussing the primary endpoint, there were a lot of missing data in the study because pain measurements out of the assessment windows were excluded from the analysis and subjects were not woken during the night to collect pain assessments. For example, there were approximately 47% of subjects with the Hour 22 assessment missing and approximately 46% of subjects with the Hour 46 assessment missing. Given such a large proportion of missing data, the single imputation BOCF method in the primary analysis underestimated the variability of imputation. The MI method described in the summaries of the SAP (Appendix, section 12.2) accounted for the imputation variability. Moreover, it may assign bad outcomes to the subjects discontinued due to AEs. The reviewer's results from the MI method are shown in Table 6. These are slightly different from those of the Applicant, as the Applicant did not set the range (between 0 and 10) for the imputed PI scores. Furthermore, the Applicant only did linear interpolation for missing PI scores at Hour 22 and 46, while the reviewer did linear interpolation for missing PI scores at all time points. Nevertheless, the E-58425 group had statistically significantly better mean SPID48 scores than any of the other groups after bunionectomy.

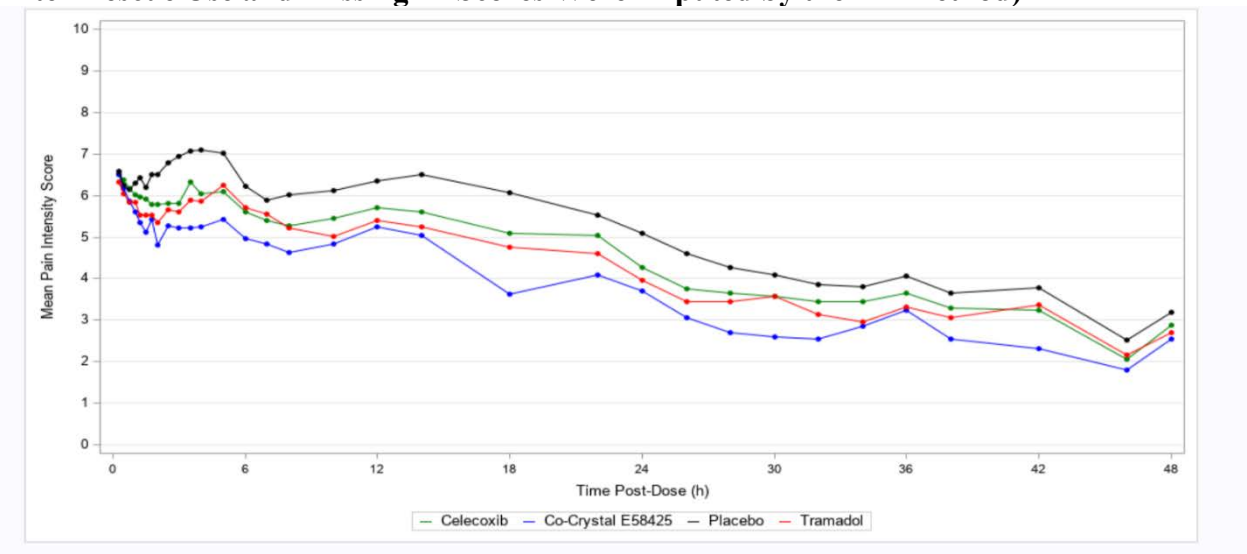
Figure 5 shows the mean of PI scores for each treatment group where the PI scores observed within 4 hours after the use of rescue medications were imputed by the PI scores recorded immediately prior to rescue use and missing PI scores were imputed by the MI method. In Figure 5, the means of PI scores were still lower in the E-58425 group compared with the other three treatment groups.

Table 6: $SPID_{48}$: Analysis Results from the MI Method

Treatment	LS Mean	95% CI of LS Mean	Comparison	P-Value	Estimate of Difference in LS Means	95% CI for Difference in LS Means
E-58425	-130.63	(-142.16, -119.11)				
Tramadol	-105.53	(-117.10, -93.96)	E-58425 minus Tramadol	0.0015	-25.10	(-40.59, -9.61)
Celecoxib	-97.42	(-109.14, -85.71)	E-58425 minus Celecoxib	<0.0001	-33.20	(-48.78, -17.64)
Placebo	-66.98	(-84.14, -49.82)	E-58425 minus placebo	<0.0001	-63.65	(-83.44, -43.86)

Abbreviations: CI – confidence interval; LS – least square
Source: Reviewer's analysis results.

Figure 5: Mean PI Scores Over Time (Pre-Rescue PI Score Was Imputed up to 4 Hours After Rescue Use and Missing PI Scores Were Imputed by the MI Method)



Source: Reviewer's analysis results.

Secondary and other relevant endpoints

The reviewer analyzed three secondary efficacy endpoints: rescue medication use, time to the first rescue use, and time to meaningful pain relief.

Rescue Medication Use

As displayed in Table 7, a total of 83.5% of subjects used rescue medication at some point during the study. The majority of subjects used acetaminophen as rescue medication (82.7%), and approximately half the subjects used oxycodone HCl (55.9%). When compared across treatment groups, the E-58425 group had the smallest proportion of subjects using rescue medications at any time point.

Table 7: Rescue Medication Use (Full Analysis Set)

Time/ Type of Rescue Medication	E-58425 (N=184) n (%)	Tramadol (N=183) n (%)	Celecoxib (N=181) n (%)	Placebo (N=89) n (%)	Total (N=637) n (%)
Any Rescue medication at any time	140 (76.1)	153 (83.6)	160 (88.4)	79 (88.8)	532 (83.5)
Acetaminophen	138 (75.0)	151 (82.5)	159 (87.8)	79 (88.8)	527 (82.7)
Oxycodone HCl	77 (41.8)	100 (54.6)	117 (64.6)	62 (69.7)	356 (55.9)
Other	1 (0.5)	0	0	0	1 (0.2)
Within first 4 hours after dosing	91 (49.5)	113 (61.7)	118 (65.2)	67 (75.3)	389 (61.1)
Acetaminophen	91 (49.5)	113 (61.7)	117 (64.6)	67 (75.3)	388 (60.9)
Oxycodone HCl	27 (14.7)	49 (26.8)	61 (33.7)	31 (34.8)	168 (26.4)
Within first 6 hours after dosing	102 (55.4)	131(71.6)	126 (69.6)	71 (79.8)	430 (67.5)
Acetaminophen	101 (54.9)	131 (71.6)	125 (69.1)	71 (79.8)	428 (67.2)
Oxycodone HCl	37 (20.1)	58 (31.7)	67 (37.0)	38 (42.7)	200 (31.4)
Other	1 (0.5)	0	0	0	1 (0.2)
Within first 12 hours after dosing	132 (71.7)	148 (80.9)	152 (84.0)	76 (85.4)	508 (79.7)
Acetaminophen	130 (70.7)	147 (80.3)	152 (84.0)	76 (85.4)	505 (79.3)
Oxycodone HCl	55 (29.9)	71 (38.8)	90 (49.7)	50 (56.2)	266 (41.8)
Other	1 (0.5)	0	0	0	1 (0.2)
Within first 24 hours after dosing	139 (75.5)	152 (83.1)	158 (87.3)	79 (88.8)	528 (82.9)
Acetaminophen	138 (75.0)	151 (82.5)	157 (86.7)	79 (88.8)	525 (82.4)
Oxycodone HCl	69 (37.5)	91 (49.7)	112 (61.9)	60 (67.4)	332 (52.1)
Other	1 (0.5)	0	0	0	1 (0.2)
Within first 48 hours after dosing	140 (76.1	153 (83.6)	160 (88.4)	79 (88.8)	532 (83.5)
Acetaminophen	138 (75.0)	151 (82.5)	159 (87.8)	79 (88.8)	527 (82.7)
Oxycodone HCl	77 (41.8)	100 (54.6)	117 (64.6)	62 (69.7)	356 (55.9)
Other	1 (0.5)	0	0	0	1 (0.2)

Abbreviation: HCl –hydrochloride
Source: Adapted from Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SUSA-301. Table 11-14.

Time to First Rescue Use

Time to first rescue use is displayed in Table 8. The estimated median time to first rescue use in the E-58425 group was 4.16 hours which was later than the estimated median time in the other three treatment groups. The Cox regression analysis results displayed in Table 9 also indicated that there was a statistically significantly longer time to use of rescue medication in the E-58425 group compared to other groups.

Table 8: Time (hours) to First Use of Rescue Medication: Quartiles of Distribution (Full Analysis Set)

Treatment Group	Percentile of Survival Distribution	Point Estimate	95% CI
E-58425	25	1.39	[1.30 to 1.75]
	50	4.16	[2.95 to 7.22]
	75	19.23	[10.28 to .]
Tramadol	25	1.27	[1.17 to 1.40]
	50	2.15	[1.73 to 3.20]
	75	7.78	[5.15 to 12.58]
Celecoxib	25	1.23	[1.17 to 1.32]
	50	2.14	[1.65 to 3.08]
	75	8.19	[5.05 to 9.68]
Placebo	25	1.17	[1.07 to 1.18]
	50	1.58	[1.23 to 2.20]
	75	3.93	[3.02 to 8.23]

Abbreviations: CI – confidence interval
Source: Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SUSA-301. Table 11-16.

Table 9: Time to First Use of Rescue Medication: Cox Regression Analysis (Full Analysis Set)

Variable	Comparison	P-Value	Hazard Ratios[a,b]	95% CI
Time to first use of rescue medication (h)	E-58425 vs Tramadol	0.0042	0.714	[0.567 to 0.899]
	E-58425 vs Celecoxib	0.0003	0.657	[0.523 to 0.826]
	E-58425 vs Placebo	<0.0001	0.536	[0.406 to 0.709]

Abbreviations: CI – confidence interval
[a] A hazard ratio of > 1 means that subjects in the E-58425 group had a shorter time than subjects in the reference group.
[b] Cox proportional hazards regression adjusted for center and Baseline pain.
Source: Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SUSA-301. Table 11-17.

Time to Meaningful Pain Relief

As shown in Table 10, the estimated median time to meaningful pain relief was 1.87 hours for the E-58425 group, compared with 2.75 hours for the tramadol group and 2.51 hours for the celecoxib group. The median time was not reached for the placebo group. The E-58425 group had shorter times to achieve each percentile than each of the other groups.

Table 10: Time to Meaningful Pain Relief (Full Analysis Set)

Variable	Treatment Group	Percentile of Survival Distribution	Point Estimate	95% CI
Time to meaningful pain relief (h)	E-58425	25	1.03	[0.94 to 1.17]
		50	1.87	[1.56 to 2.53]
		75	5.78	[3.15 to .]
	Tramadol	25	1.12	[0.99 to 1.26]
		50	2.75	[1.96 to 3.42]
		75	6.66	[4.00 to .]
	Celecoxib	25	1.28	[1.15 to 1.51]
		50	2.51	[1.96 to 6.50]
		75	8.00	[6.50 to .]
	Placebo	25	1.34	[0.94 to 3.01]
		50	.	[2.53 to .]
		75	.	[. to .]

Abbreviations: CI – confidence interval
Source: Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SUSA-301. Table 14.2.15.1.

Dose/Dose Response
In the single dose study, ESTEVE-SACO4-201, the higher doses of E-58425 (100, 150, and 200 mg) had a greater effect on SPID and TOTPAR compared to 100 mg tramadol and placebo. The subjects who received the highest doses of E-58425 (150 mg and 200 mg) required lower amount of rescue medication and showed longer mean times to intake of rescue medication compared to the tramadol 100 mg and placebo groups. For details of ESTEVE-SACO4-201, see the Appendix.

10 Safety: Overview and Findings

The two active ingredients in the proposed product have been widely used in the U.S. since their approvals (1998 and 1995, respectively). The Applicant submitted a 505(b)(2) application that relies in part on FDA's finding of safety for Celebrex (celecoxib) and Ultram (tramadol hydrochloride or tramadol) as individual components. The Applicant did not perform specific safety studies, but they collected safety data in their clinical studies. The safety review includes data from all seven clinical studies. Given the differences in study designs, objectives, populations (healthy volunteers versus patients), and drug dosing regimens, the data from clinical studies are analyzed in different groups:

- Phase 1 studies in healthy volunteers (four single dose studies and one multiple dose study)
- Phase 2 single dose, dose-finding study in patients with moderate to severe pain
- Phase 3 multiple dose, factorial study in patients with moderate to severe pain

The SAEs that occurred during MRL studies are included in the safety review.

The safety database was adequate for the target population of acute pain patients. The data were collected in patients that are generalizable to the U.S. target population. A total of 550 subjects received at least one dose of E-58425, including 145 healthy volunteers in Phase 1 studies (E-58425 200 mg), 222 subjects in the Phase 2 dose finding study, and 183 subjects in the Phase 3 factorial study. A total of 183 patients received the proposed dose of E-58425 200 mg every 12 hours for 48 hours in the Phase 3 factorial study for pain after bunionectomy. A total of 57 patients received the E-58425 200 mg as a single dose treatment in the Phase 2 dose finding study for pain after dental surgery. The longest duration of exposure to E-58425 at proposed dose of 200 mg twice per day was 7.5 days in the Phase 1 multiple dose study in healthy volunteers (32 healthy volunteers were included in the cross-over study and 29 of them received E-58425 200 mg). Of the 550 subjects who were exposed to E-58425, 385 subjects received E-58425 200 mg, which is the dose proposed for marketing, and 165 received lower doses. See Appendix for table of cumulative subject exposure for the safety population.

There were no significant differences between treatment groups in demographic or baseline characteristics in controlled studies.

The methodology and frequency of routine clinical testing were adequate for clinical studies under this NDA.

Similarly, the methodology and frequency of routine clinical testing were adequate for Study ESTEVE-SACO4-201 after dental surgery and for Phase 1 studies in healthy volunteers.

There were no deaths in any of the clinical studies during the development program for E-58425.

A total of 21 SAEs were reported in 17 subjects from a pool of more than 2,000 subjects who received E-58425, including studies that were performed by MRL outside the U.S. There were no SAEs reported in subjects in the placebo groups, including 143 subjects in studies performed be the Applicant and more than 200 subjects in studies performed by MRL. Review of SAEs does not raise any new safety concerns that are not included in the labeling for Celebrex and Ultram.

Review of discontinued cases due to adverse events did not raise any new safety concerns with the proposed product.

In general, the safety analysis of AEs for E-58425 was comparable to that for tramadol. There were no AEs that represented any new significant safety concern with E-58425. Adverse events were analyzed with a focus on common AE preferred terms (PTs) associated with opioid-related safety and compilation of abuse-related AE terms as recommended in the Agency's guidance, Assessment of Abuse Potential of Drugs (January 2017). Abuse-related AEs such as euphoria occurred at low rates (0-3%) in Phase 1-3 studies conducted by the Sponsor. In studies in which tramadol alone was used as a comparator, the rates of euphoria were similar in the E-58425 and tramadol treated subjects. Of note, in Study ESTEVE-SUSA-301 somnolence was reported with a slightly higher incidence in the E-58425 group (8.2%) compared to the tramadol group (5.5%). Because somnolence, sedation, and fatigue are all related to central nervous system (CNS) depression, they are presented together as shown in Table 11 to examine the overall effect by

treatment group in Study ESTEVE-SUSA-301. This analysis showed more AEs related to CNS depression in the E-58425 group (8.7%) compared to the tramadol group (6%). Additionally, the PT asthenia (reported as weakness or decreased energy) had an incidence of 0.5% in the E-58425 group and 2.2% in the tramadol group. Taking into consideration that the terms fatigue, weakness, and decreased energy may be used in similar contexts by patients in the clinical setting, the small difference in the incidence of PTs related to CNS depression does not appear to be clinically meaningful.

Table 11: TEAEs in Study ESTEVE-SUSA-301 by Preferred Terms Related to CNS Depression

Preferred Term (PT)	E-58425 (N=183) n (%)	Tramadol (N=183) n (%)	Celecoxib (N=182) n (%)	Placebo (N=89) n (%)
PTs related to CNS depression	16 (8.7%)	11 (6.0%)	6 (3.3%)	3 (3.4%)
Somnolence	15 (8.2)	10 (5.5)	4 (2.2)	3 (3.4)
Sedation	0	1 (0.5)	0	0
Fatigue	1 (0.5)	0	2 (1.1)	0
Other				
Asthenia	1 (0.5)	4 (2.2)	0	0

Abbreviations: TEAE – Treatment-Emergent Adverse Event, PT – preferred term, CNS - central nervous system
Source: Reviewer-generated, based on reported AEs of Study ESTEVE-SUSA-301

In general, review of TEAEs did not raise any new safety concerns with the proposed product. The most frequent TEAEs reported in the E-58425 group were nausea, vomiting, constipation, dizziness, headache, and somnolence. All had a higher incidence in the E-58425 group than placebo with the exception of constipation.

Most AEs occurred with a similar incidence in the E-58425 group and the tramadol group except somnolence, which occurred in 8% of subjects in the E-58425 group and 6% of subjects in the tramadol group as discussed above in the section for adverse events of interest. Reported AEs are listed in the labels for Ultram and Celebrex. Refer to the Appendix for summary tables.

There was the highest incidence of severe TEAEs in the tramadol group (2.2% of subjects in the tramadol group experiencing 5 severe TEAEs of nausea, vomiting, dizziness, headache, and supraventricular tachycardia), followed by the placebo group (2.2% of subjects in the placebo group experiencing 3 severe TEAEs of pain in extremity, arthralgia, and tendon pain), the E-58425 group (1.1% of subjects in the E-58425 group experiencing 4 severe TEAEs of nausea x2, dizziness, and hot flush), and the celecoxib group (1.1% of subjects in the celecoxib group experiencing 2 severe TEAEs (headache and pruritus).). Nausea was the most common TEAE and had the highest proportion of severe TEAEs with severe nausea occurring in two subjects (1.1%) in the E-58425 group and in one subject (0.5%) in the tramadol group. Severe vomiting was reported in one subject (0.5%) in the tramadol group versus none in the E-58425 group.

Antiemetics and antinauseants were used more in the E-58425 and tramadol groups (21% and 22%, respectively) than in the celecoxib and the placebo groups (7% and 6%, respectively).

Review of laboratory findings including hematology tests, serum chemistry tests, and urinalysis (dipstick) did not show any significant findings of laboratory-related AEs for the analyzed parameters.

Review of vital signs did not reveal any specific trend that would suggest a new safety concern in any of the treatment groups.

No clinically relevant trend in the measured ECG parameters was observed for any study.

QT changes observed in the E-58425 program do not raise new concerns beyond what is currently described in the reference product labels. QT prolongation is linked to C_{max} value and the labeled doses for the reference products include starting doses for which the C_{max} value of tramadol and celecoxib components exceed the C_{max} values of tramadol and celecoxib observed after E-58425 administration in the relative bioavailability studies. Thus, the systemic safety, including QT prolongation, for E-58425 is expected to be comparable to Ultram and Celebrex.

Safety Analyses by Demographic Subgroups

Each individual component of E-58425, celecoxib and tramadol, has a relatively well-known safety profile. The relative bioavailability studies performed by the Applicant showed that the C_{max} value of each component, tramadol and celecoxib, was lower than the respective listed drugs Ultram (or Adolonta) and Celebrex. Safety analysis of E-58425 for demographic subgroups is expected to be comparable to the safety profile of Ultram and Celebrex for demographic subgroups. Thus, the label for E-58425 will include information from the labels for Ultram and Celebrex. The safety findings for demographic subgroups from the clinical studies in this NDA are summarized in this section. In general, review of available data did not raise new safety concerns regarding safety analysis of E-58425 in demographic subgroups.

The safety and effectiveness of E-58425 in pediatric patients have not been established. If approved, the Applicant will be required to perform pediatric studies of their product after approval. Refer to Regulatory Background for details of required pediatric studies. Ultram (tramadol) is contraindicated in children younger than 12 years of age, children younger than 18 years of age following tonsillectomy and/or adenoidectomy, and adolescents 12 to 18 years of

age who have other risk factors that may increase their sensitivity to respiratory depression. Given that E-58425 contains tramadol, the same contraindications as for Ultram are proposed for inclusion in E-58425's label.

Data for elderly subjects with TEAEs were analyzed in a pool of patients from Study ESTEVE-SACO4-201 (single dose) and Study ESTEVE-SUSA-301 (multiple dose). The Phase 3 study ESTEVE-SUSA-301 included 58 (9.1%) subjects over 65 years of age. There were no subjects older than 65 years of age in Study ESTEVE-SACO4-201, which is likely related to the study population of patients with pain after molar extraction (the oldest subject in this study was 48 years old). In general, patients over 65 years of age had slightly higher incidence of at least one TEAE compared to younger patients, and a similar trend was noted for the tramadol group and placebo group. There were no notable trends in the available data for SAEs or discontinuation due to AEs in older subjects that would raise new safety concerns.

No significant difference in safety was noted in subgroups by race or sex.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
E-58425 contains tramadol. All tramadol-containing products are currently Schedule IV controlled substances under the Controlled Substances Act.

Schedule IV drugs are considered to have a lower potential for abuse relative to the drugs or substances in Schedule III of the CSA, have a currently accepted medical use in treatment in the U.S., and abuse of the drug may lead to limited physical dependence or psychological dependence relative to other drugs or substances in Schedule III [21 U.S.C. 812 (b) (4)].

11 Safety in the Postmarket Setting

E-58425 has not been marketed anywhere in the world. Celecoxib and tramadol have been widely marketed worldwide for more than 20 years and have well-known safety profiles. The safety of celecoxib and tramadol have been under regular review through pharmacovigilance.

Recent pharmacovigilance, epidemiology, and drug utilization reviews have been completed to examine recent data for marketed tramadol-containing products.

<u>Pharmacovigilance</u>
The Division of Pharmacovigilance II (DPV II) recently completed a pharmacovigilance review to assess for new safety concerns relating to tramadol. The review included an aggregate analysis of adverse events reported to the FDA Adverse Event Reporting System (FAERS) for tramadol, tramadol-specific adverse events reported in the published literature (PubMed), and analysis of FAERS data in Empirica Signal, one of FDA's primary data mining tools. This analysis resulted in the identification of four potential signals that we determined to be of significant clinical importance. These events are hypoglycemia, hyponatremia, hallucinations, and mania. DPV II is currently completing comprehensive, individual reviews for each of these potential signals with a possible outcome of updating the prescribing information, if needed.

Epidemiology and Drug Utilization

The following is excerpted from the Executive Summary of the attached Integrated Review of Epidemiology and Drug Utilization. Refer to the attached review for additional detail.

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.

Risk Management

If approved, celecoxib and tramadol oral tablets (NDA 213426), will be required to become a member of the Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits of the drug outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. The Opioid Analgesic REMS is a shared system REMS that was initially approved as the Extended-Release (ER) and Long-Acting (LA) (ER/LA) REMS in July 2012 and was expanded in September 2018 to include all application holders of immediate-release (IR) opioid analgesics that are expected to be used in the outpatient setting and that are not already covered by another REMS program. Refer to the Division of Risk Management summary for further details.

12 Appendices

12.1 Clinical Pharmacology Supplementary Information

Single dose relative BA of E-58425 tablets to reference drugs

Relative BA of E-58425 tablets to reference drugs, Ultram tablets (tramadol) and Celebrex

capsule (celecoxib) after single dose was assessed in study ESTEVE-SUSA-101 or ETV-P5-669.

Treatments administered:

Treatment 1	200 mg dose (Test; 2 x E-58425 100 mg tablets; 88 mg tramadol HCl and 112 mg celecoxib), administered alone
Treatment 2	100 mg dose (Reference-1; 2 x Ultram 50 mg tablets, 100 mg tramadol HCl), administered alone
Treatment 3	100 mg dose (Reference-2; 1 x Celebrex 100 mg capsule), administered alone
Treatment 4	100 mg dose (Reference-1; 2 x Ultram 50 mg tablets, 100 mg tramadol HCl) co-administered with 100 mg dose (Reference-2; 1 x Celebrex 100 mg capsule)

The mean PK parameters of tramadol, its metabolite M1 (hereafter called as M1 in the text) and celecoxib of E-58425 tablets (test drug) versus Ultram tablets or Celebrex capsule (reference drugs) are shown in Table 12. The relative BA assessment is shown in Table 13.

Table 12: The mean PK parameters of tramadol, M1 and celecoxib parameters of E-58425 tablets (test drug) and Ultram tablets or Celebrex capsule (reference drugs).

Analyte	***Parameter Athematic Mean (% CV)***	***Trt 1:*** *Test 2 x E-58425 100mg (88 mg tramadol + 112 mg celecoxib)*	***Trt 2:*** *Reference-1 2 x Ultram 50 mg (100 mg tramadol)*	***Trt 3:*** *Reference-2 1x Celebrex 100 mg*	***Trt 4:*** *Reference-1 2x Ultram 50 mg (100 mg tramadol) + Reference-2 1x Celebrex 100 mg*
		n=33	*n=32*	*n=33*	*n=32*
Tramadol	Cmax (ng/mL)	214 (29)	305 (23)	-	312 (22)
	Tmax (h) $	3.0 (1.25, 8.0)	2.0 (0.75, 3.0)	-	1.88 (1.0, 6.0)
	AUCt (ng·h/mL)	2507 (36)	2709 (35)	-	2888 (34)
	AUC∞ (ng·h/mL)	2590 (35) [a]	2802(32) [b]	-	2990 (32) [b]
	T½ (h)	6.5 (15)	6.1 (17)	-	6.2 (16)
M1	Cmax (ng/mL)	55 (29)	79 (29)	-	78 (29)
	Tmax (h) $	4.0 (2.5, 8.0)	2.5 (1.25, 6.0)	-	2.5 (1.25, 8.0)
	AUCt (ng·h/mL)	846 (27)	965 (25)	-	1010 (25)
	AUC∞ (ng·h/mL)	879 (24) [a]	1002 (21) [b]	-	1049 (21) [b]
	T½ (h)	7.2 (14)	6.7 (14)	-	7.0 (15)
Celecoxib	Cmax (ng/mL)	260 (34)	-	317 (47)	165 (46)
	Tmax (h) $	1.5 (0.75, 6.0)	-	3.0 (1.25, 8.0)	2.5 (1.0, 12.0)
	AUCt (ng·h/mL)	1930 (41)	-	2348 (40)	1929 (38)
	AUC∞ (ng·h/mL)	2128 (42) [c]	-	2553 (43) [d]	2224 (39) [e]
	T½ (h)	13 (27)	-	11 (46)	14 (29)

$ Median (minimum, maximum); [a] n=32, [b] n=31, [c] n=28, [d] n=27, [e] n=21

Table 13: Relative BA assessment of tramadol and celecoxib of E-58425 tablets versus Ultram tablets (tramadol) or Celebrex capsule (Celecoxib).

Tramadol PK parameter	Geometric LS means			Comparison	Ratio	90% Confidence limits (%)
	Trt 1: (N=33)	*Trt 2: (N=32)*	*Trt 4: (N=32)*			
Cmax (ng/mL)	205.10	296.00	304.15	Trt-1 *vs* Trt-2 Trt-1 *vs* Trt-4	69.29 67.43	66.24, 72.48 64.47, 70.53
AUCt (ng·h/mL)	2334.71	2528.69	2698.05	Trt-1 *vs* Trt-2 Trt-1 *vs* Trt-4	92.33 86.53	88.09, 96.77 82.56, 90.69
AUC∞ (ng·h/mL)	2424.32 [a]	2641.29 [b]	2816.85 [b]	Trt-1 *vs* Trt-2 Trt-1 *vs* Trt-4	91.79 86.06	87.64, 96.12 82.19, 90.13

Celecoxib PK parameter	Geometric LS means			Comparison	Ratio	90% Confidence limits (%)
	Trt 1: (N=33)	*Trt 3: (N=33)*	*Trt 4: (N=32)*			
Cmax (ng/mL)	244.29	286.92	153.44	Trt-1 *vs* Trt-3 Trt-1 *vs* Trt-4	85.14 159.21	74.83, 96.88 139.74, 181.38
AUCt (ng·h/mL)	1807.84	2208.09	1823.37	Trt-1 *vs* Trt-3 Trt-1 *vs* Trt-4	81.87 99.15	77.27, 86.75 93.51, 105.12
AUC∞ (ng·h/mL)	1988.53 [c]	2396.44 [d]	2107.10 [e]	Trt-1 *vs* Trt-3 Trt-1 *vs* Trt-4	82.98 94.37	78.89, 87.28 89.21, 99.83

[a] n=32, [b] n=31, [c] n=28, [d] n=27, [e] n=21

For the tramadol component of E-58425 tablets (total dose 88 mg, treatment 1), the Cmax was 30% lower and the AUC (AUCt and AUCinf) was ~8% lower compared to Ultram tablets (total dose 100 mg, treatment 2). The median Tmax of tramadol of E-58425 tablets (3 h) was delayed by 1 h compared to Ultram tablets (2 h) (Table 12).

For M1 of E-58425 tablets (treatment 1), the Cmax was 30% lower and the AUC (AUCt and AUCinf) was ~12% lower, and median Tmax was 1.5 h delayed compared to M1 of Ultram tablets (treatment 2) (Table 12).

For the celecoxib component of E-58425 tablets (total dose 112 mg, treatment 1), the Cmax was 15% lower and the AUCt and AUCinf was ~18% lower when compared to Celebrex 100 mg capsule (treatment 3). The median Tmax of celecoxib of E-58425 (1.5 h) was 1.5 h earlier compared to Celebrex capsule (3 h) (Table 12).

The concomitant administration of tramadol and celecoxib results in no change in tramadol Cmax and 6% increase in tramadol AUC compared to when tramadol was administered alone. The concomitant administration of tramadol and celecoxib results in 48% lower celecoxib Cmax and 13% lower celecoxib AUC compared to when celecoxib was administered alone.

Multiple dose relative BA of E-58425 tablets to reference drugs
The multiple-dose PK of E-58425 tablets was evaluated in study ESTEVE-SUSA-105.

Treatments administered:

Treatment 1:	2 x Test (E-58425 100 mg tablets, total dose: 88 mg tramadol HCl; 112 mg celecoxib), administered BID, 12 hours apart, for a total of 15 consecutive doses
Treatment 2:	2 x Reference-1 (Adolonta 50 mg capsules, total dose: 100 mg tramadol HCl), administered BID, 12 hours apart, for a total of 15 consecutive doses

Treatment 3:	1 x Reference-2 (Celebrex 100 mg capsule), administered twice daily, 12 hours apart, for a total of 15 consecutive doses
Treatment 4:	2 x Reference-1 (Adolonta 50 mg capsules, total dose: 100 mg tramadol HCl) plus 1 x Reference-2 (Celebrex 100 mg capsule), administered twice daily, 12 hours apart, for a total of 15 consecutive doses

Note: Adolonta 50 mg capsule is not an US-approved drug.

The mean PK parameters of tramadol, M1 and celecoxib are shown in Table 14.

Table 14: Mean PK parameters of tramadol, M1 and celecoxib of E-58425 tablets (test drug) and Adolonta or Celebrex (reference drugs) administered BID, 12 hours apart, for 15 consecutive doses.

	PK Parameter Athematic Mean (% CV)	***Treatment 1: Test (2 x E-58425 100mg tablets) (88 mg tramadol + 112 mg celecoxib) (N= 29)***			**Treatment-2** ***Reference-1 2x Adolonta 50 mg (100 mg Tramadol) (N=28)***		***Treatment 3: Reference-2 1x Celebrex 100 mg (N= 28)***
		Tramadol	***M1***	***Celecoxib***	***Tramadol***	***M1***	***Celecoxib***
Single dose	Cmax	220 (25)	41 (45)	276 (39)	330 (16)	56 (48)	358 (37)
	Tmax (h) [$]	3.5 (1.0, 6.0)	4.0 (2.0, 12.0)	2.0 (0.5, 6.0)	1.75 (1.0, 4.0)	2.0 (1.0, 8.0)	3.0 (1.5, 8.0)
	AUCτ (ng·h/mL)	1770 (27)	353 (42)	1442 (33)	2220 (25)	440 (40)	1929 (35)
Multiple dose	Cmax,ss (ng/mL) [a]	485 (22)	66 (37)	498 (27)	632 (24)	87 (34)	536 (33)
	Tmax,ss (hours)	3.0 (1.0, 6.0)	3.0 (1.5, 8.0)	2.0 (0.5, 4.0)	2.0 (1.0, 4.0)	2.0 (1.0, 6.0)	2.0 (1.5, 4.0)
	AUCτ,ss (ng•h/mL) [b]	4201 (32)	637 (36)	3139 (28)	4990 (30)	791 (35)	3366 (27)
	Cavg (ng/mL) [c]	351 (32)	53 (36)	261 (28)	416 (30)	66 (36)	281 (27)
	T½ (hours)	9 (25)	10 (20)	13 (31)	9 (22)	10 (24)	10 (30)
	AUC∞ (ng·h/mL)	7749 (50)	1247 (35)	5810 (32)	8749 (48)	1468 (37)	5343 (34)
	RA(Cmax) [d]	2.20	1.63	1.80	1.91	1.55	1.50
	RA(AUC) [e]	2.37	1.82	2.17	2.25	1.80	1.74

[$] Median (minimum, maximum) [$]
[a] Cmax,ss: Cmax after last multiple dose
[b] AUCτ,ss AUC over the dosing interval at steady state
[c] Cavg: average concentration over the doing interval, AUCτ,ss /12 h
[d] RA(Cmax): Accumulation ratio, Cmax,ss at steady state /Cmax after single dose.
[e] RA(AUC): Accumulation ratio, AUCτ,ss at steady state /AUCτ after single dose.

The mean pre-dose concentrations prior to the 13th, 14th and 15th doses of E-58425 tablets were 227, 229, and 239 ng/mL, respectively for tramadol; 42, 41, and 42 ng/mL, respectively for M1; and 173, 140, and 181 ng/mL, respectively for celecoxib. Based on pre-dose concentrations, the

steady state appears to be achieved for all three analytes, tramadol, M1 and celecoxib of E-58425 tablets.

After multiple dosing of E-58425 tablets, the accumulation ratio of tramadol Cmax and AUCτ values (15th dose/ 1st dose) were 2.20-fold and 2.37-fold, respectively. The accumulation ratio of Celecoxib Cmax and AUCτ values (15th dose/ 1st dose) were 1.76-fold and 2.15-fold, respectively.
After multiple dosing of E-58425 tablets, the tramadol Cmax,ss and AUC,ss values are 24% and 16% lower, respectively, compared to the Adolonta (tramadol) tablets. After multiple dosing of E-58425 tablets, the celecoxib Cmax,ss and AUC,ss values are 10% and 7% lower, respectively compared to the Celebrex (celecoxib). There were no differences in the tramadol and celecoxib half-lives after multiple dosing between E-58425 tablets and reference drugs, Adolonta or Celebrex (Table 14).

Food effect on E-58425 tablets
The Sponsor assessed the food effect on E-58425 tablets (E-58425 fed versus E-58425 fasting) in Study ESTEVE-SACO4-104.

The mean PK parameters of tramadol, M1 and celecoxib of E-58425 tablets administered under fed versus fasting conditions are shown in Table 15. The relative bioavailability assessment is shown in Table 16.

Table 15: The mean PK parameters of tramadol, M1 and celecoxib parameters of E-58425 tablets under fed versus fasting conditions.

	Athematic Mean (% CV)					
Parameter	***Tramadol***		***M1***		***Celecoxib***	
	Fed (n=33)	**Fasting (n=33)**	**Fed (n=33)**	**Fasting (n=33)**	**Fed (n=33)**	**Fasting (n=33)**
Cmax (ng/mL)	267 (21)	244 (23)	56 (31)	53 (36)	526 (35)	410 (42)
Tmax (hours) $	3.7 (1.75, 5.5)	2.7 (1.5, 6.0)	4.5 (2.3, 6.0)	4.0 (2.3, 8.0)	3.7 (1.0, 6.0)	1.25 (0.75, 6.0)
AUCt (ng·h/mL)	2720 (34)	2773 (34)	764 (28)	803 (29)	4411 (58)	3450 (73)
AUC∞ (ng·h/mL)	2802 (32)	2857 (32)	782 (27)	825 (28)	4514 (67)	3615 (81) *
T½ (hours)	6.1 (25)	6.6 (24)	6.7 (22)	7.4 (20)	8.2 (37)	11.3 (39) *

$ Median (minimum, maximum)
* n=30, terminal phase of celecoxib could not be adequately estimated in 3 subjects out of 33 subjects

Table 16: Food-effect relative bioavailability assessment of E-58425 tablets (fed versus fasting conditions).

Analyte PK parameter	**Geometric LS means**		**Ratio**	**90% Confidence limits (%)**
Tramadol	**Fed state**	**Fasting state**		
Cmax (ng/mL)	261.05	236.40	110.43	105.34, 115.76
AUCt (ng·h/mL)	2570.81	2616.33	98.26	94.48, 102.20
AUC∞ (ng·h/mL)	2660.36	2704.35	98.37	94.85, 102.02
M1				

Cmax (ng/mL)	53.27	49.66	107.29	101.60, 113.30
AUCt (ng·h/mL)	733.18	768.41	95.41	92.40, 98.53
AUC∞ (ng·h/mL)	752.37	791.27	95.08	92.08, 98.19
Celecoxib				
Cmax (ng/mL)	499.47	381.54	**130.91**	116.98, **146.49**
AUCt (ng·h/mL)	4037.17	3065.13	**131.71**	124.54, **139.30**
AUC∞ (ng·h/mL)	4087.73	3160.35	**129.34**	121.78, **137.38**

For tramadol and M1, the food does not affect either Cmax or AUC. The point estimate of geometric mean ratios (fed/fasting) and corresponding 90% CIs for Cmax, AUCt and AUCinf of tramadol and M1 were within the 80-125% BE limits. Under fed conditions, the median Tmax of tramadol and M1 are delayed for 1-h and 0.5-h conditions, respectively compared to fasting conditions. Although median Tmax of Tramadol under fed conditions was slightly delayed compared to the fasting conditions, the range of individual Tmax (min, max) is comparable between fed (1.75 h, 5.5 h) and fasting conditions (1.5 h, 6.0 h) (Table 15)

For the celecoxib component of E-58425 tablets, food increases Cmax and AUC approximately by 30% compared to the fasting conditions. Under fed conditions the median Tmax of celecoxib is delayed for ~2.5-h compared to fasting conditions.

Comments on food effect
When E-58425 tablets were administered under fed conditions, the AUC, Cmax and Tmax of tramadol component were not significantly affected. However, for the celecoxib component, the Tmax was delayed approximately by ~2.5-h and Cmax and AUC resulted in around 30% increase for both parameters. The Celebrex label also reports that, under fed conditions the celecoxib Tmax was delayed 1 to 2 hours with 10 to 20% increase in AUC. The Celebrex label states that "Celebrex, at doses up to 200 mg twice daily, can be administered without regard to timing of meals."

For E-58425 tablets, since there was no significant food-effect on the tramadol component and the food-effect on celecoxib component is approximately similar to Celebrex's food effect, it is reasonable to recommend E-58425 tablets to be labeled to taken without regard to food.

12.2 Clinical Supplementary Information

Table 17: Listing of Clinical Trials Conducted by the Applicant Relevant to This NDA

Trial Identity/ Report Date	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						

Trial Identity/ Report Date	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
ESTEVE-SUSA-301 (83245) / 2018	NCT03108482	Randomized, Double-blind, Active- and Placebo-controlled, Parallel Groups, Phase 3 study	• E-58425 200 mg every 12h • Tramadol 50 mg every 6h • Celecoxib 100 mg every 12h • Placebo every 6h Multiple dose / oral	Sum of Pain Intensity Differences (SPID) from 0-48 hours	A maximum of 2 days / The last follow-up visit was done 5-9 days after surgery.	637 (90 male, 547 female)	Patients with moderate to severe post-operative pain after bunion-ectomy	Six centers in the United States
ESTEVE-SACO4-201 (82100) / 2013	N/A (the study was conducted in Spain)	Randomized, Double-blind, Controlled with Active Treatment (Tramadol 100 mg) and Placebo, Parallel Groups, Phase 2 study	• E-58425 50 mg • E-58425 100 mg • E-58425 150 mg • E-58425 200 mg • Adolonta (Tramadol HCl) 100-mg dose (2 x 50 mg oral capsule) • 2 tablets of placebo Single dose / Oral	Sum of Pain Intensity Difference (SPID) from 0-8 hours	Single dose / The last follow-up visit was done 7 days after the procedure.	334 (142 male, 192 female)	Patients with moderate to severe dental pain after extraction of two or more impacted third molars requiring bone removal	Nine centers in Spain
		Studies to Support Safety						
-								
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
ESTEVE-SUSA-101 (ETV-P5-669) / 2017	N/A	Phase 1, single oral dose, bioavailability, fasting, cross-over study	• E-58425 200 mg (2 x 100-mg tablets) Single dose / Oral	N/A	Single dose / 48-hour follow up	36	Healthy males and females (18-55 years)	One center in the United States

Trial Identity/ Report Date	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
ESTEVE-SACO4-103 (80845 or TAI-P0-692) / 2011	N/A	Phase 1, single oral dose, bioavailability, fasting, cross-over study	• E-58425 200 mg (2 x 100-mg tablets); Formulation 1 and 2 Single dose / Oral	N/A	Single dose / 48-hour follow up	12	Healthy males and females (18-55 years)	One center in Canada
ESTEVE-SACO4-102 (80841 or TAI-P0-584) / 2011	N/A	Phase 1, single oral dose, bioavailability, fasting, cross-over study	• E-58425 200 mg (2 x 100-mg tablets) Single dose / Oral	N/A	Single dose / 48-hour follow up	36	Healthy males and females (18-55 years)	One center in Canada
ESTEVE-SACO4-104 (80877 or TAI-P1-585) / 2012	N/A	Phase 1, bioavailability fed/fasting, cross-over study	• E-58425 200 mg (2 x 100-mg tablets) after fasting and fed condition Single dose / Oral	N/A	Single dose / 48-hour follow up (blood sampling)	36	Healthy males and females (18-55 years)	One center in Canada
ESTEVE-SACO4-105 (82608 or TAI-P3-526) / 2014	N/A	Phase 1, single and multiple oral dose, bioavailability, cross-over study	E-58425 200 mg (2 x 100 mg tablets) every 12 h Multiple dose / Oral	N/A	Multiple dose (15 doses) / 7.5 days	32	Healthy males and females (18-50 years)	One center in Canada

Abbreviations: SPID – Sum of Pain Intensity Difference, NCT – National Clinical Trial
Source: reviewer-generated based on the Applicant's submission, 5.2. Tabular Listing of all Clinical Studies

Table 18: Listing of Clinical Trials Performed by Mundipharma Research Ltd*

Trial Identity	Title and Short Description	Country
MR308-1501	A Phase 1, open-label, three-period, randomized, crossover study to assess the pharmacokinetics and dose proportionality of single doses of Co-crystal E-58425 at 100 mg, 150 mg and 200 mg in Japanese and Caucasian healthy subjects (N=60)	United Kingdom
MR308-3501	A Phase 3, randomized, double-blind, multicenter, placebo- and active comparator-controlled study to evaluate efficacy and safety of MR308 in the treatment of acute pain after third molar tooth extraction (STARDOM1) A total of 726 patients were randomized into five treatment groups of CTC 100 mg bid, CTC 150 mg bid, CTC 200 mg bid, tramadol 100 mg bid, or placebo, according to a 2:2:2:2:1 randomization ratio. Primary efficacy endpoint was SPID 0-4 hours. Duration of double-blind treatment was 3 days.	Europe and Canada
MR308-3502	A Phase 3, randomized, double-blind, multicenter, placebo- and active comparator-controlled study to evaluate efficacy and safety of MR308 in the treatment of acute pain after abdominal hysterectomy surgery under general anesthesia (STARDOM2) A total of 1138 patients were randomized into six treatment groups of CTC 100 mg bid, CTC 150 mg bid, CTC 200 mg bid, tramadol 100 mg qid, celecoxib 100 mg bid, or placebo.	Europe and Canada

* Mundipharma Research Ltd (MRL) is an independent third-party company that conducted one Phase 1 study and two Phase 3 studies outside the U.S. with celecoxib and tramadol, tablets, under the code name MR308 or CTC. The ISE and ISS do not include data from these studies. Any SAEs from these studies are included in the safety review.
Abbreviations: bid – twice daily, qid – four times daily, CTC – co-crystal tramadol celecoxib, SPID – Sum of Pain Intensity Difference
Source: reviewer-generated based on the Applicant's submission, 5.2. Tabular Listing of all Clinical Studies

ESTEVE-SUSA-301 Summary of Statistical Analysis Plan

The full analysis set included all subjects who underwent the complete randomization process and were assigned to a specific randomization stratum and to a unique treatment arm, irrespective of whether they actually received any dose of study medication. In the primary efficacy analysis, $SPID_{48}$ was compared between the treatment groups. Three separate null hypotheses were tested:

- The mean $SPID_{48}$ in the E-58425 group was equal to the mean $SPID_{48}$ in the tramadol group;
- The mean $SPID_{48}$ in the E-58425 group was equal to the mean $SPID_{48}$ in the celecoxib group;
- The mean $SPID_{48}$ in the E-58425 group was equal to the mean $SPID_{48}$ in the placebo group.

For a full factorial study to be declared successful, all three of those null hypotheses must have been rejected. Therefore, adjustment for multiple comparisons was not necessary. The hypotheses were tested in an analysis of covariance (ANCOVA) model including terms for treatment, center, and baseline pain (as a continuous variable). Estimates of least square (LS) means of the $SPID_{48}$ for each treatment group and estimates of the difference in LS means between the E-58425 group and each of the three control groups were calculated from the ANCOVA model, along with 95% confidence intervals and p-values associated with those differences.

The intermittent missing PI scores were imputed by a linear interpolation method. For subjects

who discontinued the study before 48 hours, the baseline observation carried forward (BOCF) method was used to impute missing PI scores after their withdrawal. The Applicant also conducted the following sensitivity analyses to impute missing PI scores in the study: the worst observation carried forward (WOCF) method for all dropouts; the WOCF method for dropouts due to related AEs or lack of efficacy, and the last observation carried forward (LOCF) method for dropouts due to all other reasons; and a multiple imputation (MI) method. The Applicant called their MI method as a jump to control MI analysis method, which is described as follows:

- For subjects in the placebo group, missing PI scores were imputed using the observed PI scores from placebo subjects at the same sites with similar baseline and post-baseline pain scores. The variables included in the imputation model were sex, center, baseline pain, and post-baseline pain. A minimum of 1,000 imputations were conducted.
- For subjects in each active treatment group, the intermittent missing PI scores were firstly imputed assuming the intermittent missing values were missing at random. Then, the monotone post-withdrawal missing PI scores were imputed using a method proposed by O'Kelly (Ratitich and O'Kelly 2011). Missing PI scores at each timepoint were imputed using available PI scores for treated subjects and complete data for all placebo subjects (observed and imputed in step *i*) at that timepoint. A minimum of 1,000 imputations were conducted.
- For each dataset containing imputed PI scores from step *i* and *ii*, E-58425 was compared with other treatment groups by an ANCOVA model using the terms treatment, center, and baseline pain. The ANCOVA results from the multiple imputed datasets were then combined using the Rubin's rule (Little and Rubin 1987). A significance test of the treatment difference was performed at the two-sided 0.05 level and corresponding 95% confidence intervals were calculated.

To account for the use of rescue medications, PI scores assessed immediately prior to rescue use were utilized to impute all scores observed in the 4 hours after the use of rescue medications. If subjects took analgesic medications during the study other than allowed rescue medications, all subsequent pain assessment were treated as missing. A sensitivity analysis was also conducted in which all observed PI scores after the rescue use were analyzed as recorded.

As recommended in ICH E9 (R1) addendum, a primary estimand of interest should be prespecified for a clinical trial. The applicant did not prespecify the estimand of interest. However, they stated in their MI method, "The causal estimand will be estimated using the difference in the least squares means between the co-crystal E-58425 group and the other treatment groups."

The applicant used single imputation methods to impute missing PI scores in the study: the BOCF method in the primary efficacy analysis and the WOCF or LOCF method in the sensitivity analyses. However, as these methods are based on questionable assumptions and as single imputation methods underestimate variability of imputations, they are not recommended by the National Academy of Science (NAS) report on missing data. The MI method considered in the sensitivity analyses accounted for the variability of imputations. Moreover, it assigned bad outcomes to subjects discontinued the study due to AEs.

ESTEVE-SACO4-201
In addition to the Phase 3 study ESTEVE-SUSA-301 submitted to support of an efficacy finding for E-58425, the Applicant submitted the results of ESTEVE-SACO4-201, a Phase 2 dose-finding study, as supportive information.

Overview and Objective
The primary objective of this study was to establish the effective dose between four strengths of E-58425 for moderate to severe pain based on PI, TOTPAR, use of supplementary analgesic medication, time of onset of pain relief (PAR), and overall assessment.

The Applicant included the Phase 2 Study ESTEVE-SACO4-201 in their efficacy assessment. However, we note the following limitations in the design of this study that made it inadequate to be considered for evaluation of efficacy of E-58425:

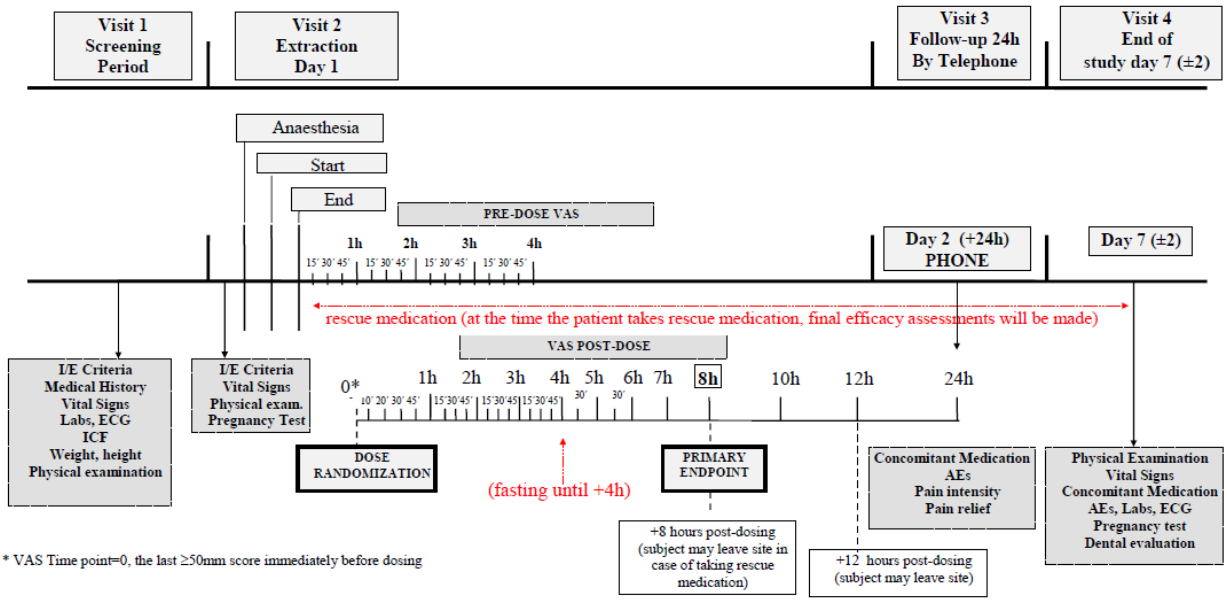
- The primary endpoint, SPID 0-8, is not an appropriate endpoint to support the proposed indication of acute pain.
- Study ESTEVE-SACO4-201 was a single dose study.

Thus, limited conclusions could be drawn from Study ESTEVE-SACO4-201 regarding the efficacy of E-58425 for acute pain, and this study was not reviewed in detail for assessment of efficacy. In general, the results of this study did not raise any concern against the efficacy findings for Study ESTEVE-SUSA-301.

Trial Design

Basic Study Design
Study ESTEVE-SACO4-201 was a randomized, double-blind, active- (tramadol) and placebo-controlled, parallel group, single dose, Phase 2, dose finding study in patients with moderate to severe pain dental pain after extraction of two or more impacted third molars requiring bone removal. This study was conducted using a standard design in accordance with the European Medicines Agency note for guidance on clinical investigation of medicinal products for treatment of nociceptive pain (May 2003) (The European Agency for the Evaluation of Medicinal Products May 2003). Figure 6 shows an overview of Study ESTEVE-SACO4-201.

Figure 6: Overview of Study ESTEVE-SACO4-201



Abbreviations: VAS – visual analog scale, ECG – electrocardiogram, ICF – information consent form, AE – adverse event
Source: Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SACO4-201

The study consisted of three visits at the site and one telephone interview (a total of four visits): screening (Visit 1), dental extraction (Day 1, Visit 2), telephone interview (24-hour post-surgery follow-up, Visit 3), and final examination (Day 7, Visit 4).

After the dental extraction, the pain intensity of the subject was assessed on a VAS at 15-minute intervals until a pain intensity of 50 mm VAS was reached. If a subject did not reach the required pain intensity within 4 hours after the dental procedure, he/she was excluded from the study.

Study treatment was administered as a single dose administration. After administration of the study medication, pain intensity and pain relief were assessed at several time points. The time to perceptible and meaningful pain relief was assessed by stopwatch. Patients were required to remain at the study site for 12 hours after the randomization (i.e., for a maximum of 16 hours after dental extraction).

At any time during the 12-hour observation period, the subject could choose to receive rescue medication. Current pain and pain relief were assessed prior to the intake of rescue medication and stopped thereafter. Subjects taking rescue medication were asked to remain at the study site for 8 hours after randomization. The subject was to make an overall assessment of the study medication at the end of the 12-hour observation period or, if the subject withdrew prior to completing the observation period, at the time of withdrawal, or at the time of taking rescue medication, whichever occurred first.

In a subgroup of subjects from two centers, a total of three blood samples (0, 2, and 6 hours postdosing or at the time of withdrawal) were collected to determine the plasma concentrations of E-58425.

Dose Selection, Study Arms, and Randomization
Subjects who were eligible were randomly assigned to one of the following six treatment groups:

- Treatment 1: 1 tablet of E-58425 50 mg +1 tablet of placebo
- Treatment 2: 1 tablet of E-58425 100 mg +1 tablet of placebo
- Treatment 3: 1 tablet of E-58425 50 mg +1 tablet of E-58425 100 mg
- Treatment 4: 1 tablet of E-58425 100 mg +1 tablet of E-58425 100 mg
- Treatment 5: 2 capsules of tramadol 50 mg (Adolonta®)
- Treatment 6: 2 tablets of placebo

Study Endpoints
The primary efficacy endpoint was the SPID from 0-8 hours. The pain intensity difference (PID) was defined as below.

- $PIDt = PI_t - PI_0$, where PI_0 is the pain intensity at t =0 hours and PI_t is the pain intensity at specific time points. Positive values therefore correspond to an increase in pain, while negative values correspond to a decrease in pain.
- The SPID was defined as the sum of that pain intensity difference (PID) between time 0 and time t weighted with the time between two consecutive values, i.e., each PID_t value was multiplied with the time interval since the previous evaluation and summated.

Summary of Statistical Analysis Plan
The primary analysis endpoint was analyzed using an analysis of variance (ANOVA) model which included treatment and center effects and was to be performed to detect any global treatment or center effect. For the secondary efficacy endpoints SPID from 0-12 hours, pain intensity difference (PID) at each time point, PAR at each time point, TOTPAR from 0-8 hours, and TOTPAR from 0-12 hours, the same ANOVA was applied as for the primary efficacy endpoint.

For subjects discontinued from the study, missing PI scores were imputed using the LOCF method. For subjects used rescue medication in the study, PI scores were only collected until rescue medication was taken and missing PI scores after rescue use were imputed using the LOCF method.

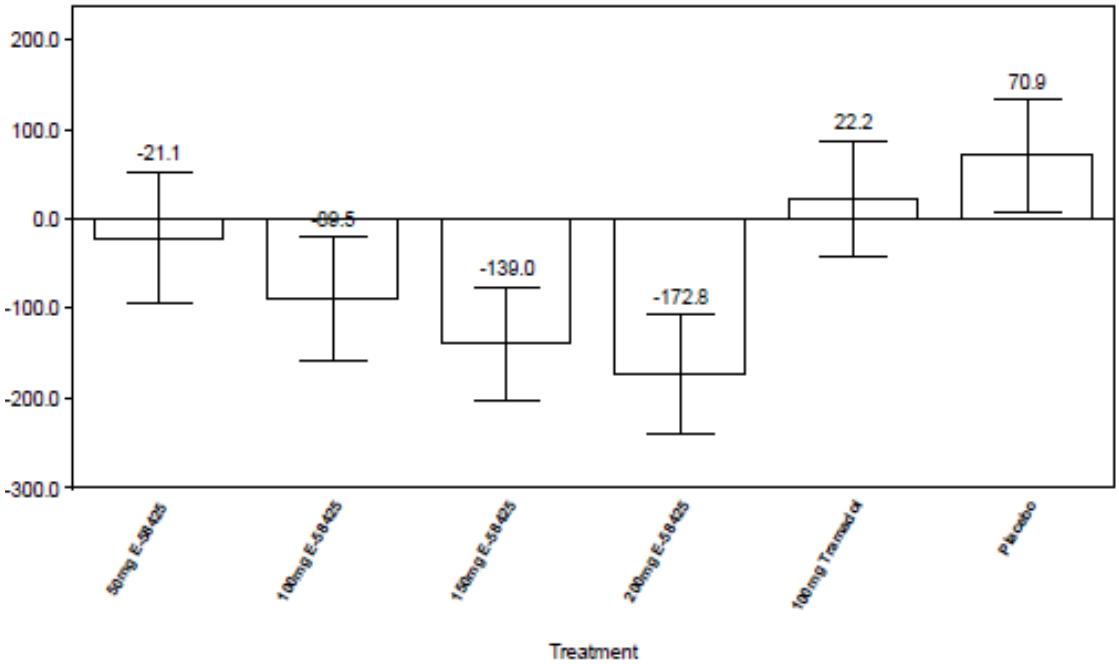
The overall assessment of the study medication was analyzed using the Cochran-Mantel-Haenszel test stratified by center to detect any treatment differences.

Patient Disposition
The study was planned to include 360 subjects, 60 subjects per treatment group. A total of 334 subjects were randomized with the following number of subjects per treatment group: 55 in E-58425 50 mg, 53 in E-58425 100 mg, 57 in E-58425 150 mg, 57 in E-58425 200 mg, 58 in tramadol 100 mg, and 54 in the placebo group.

Efficacy Results – Primary Endpoint
Study subjects in E-58425 groups experienced decrease in pain that was dose dependent. E-58425 50, 100, 150, and 200 mg led to a mean SPID 8 of -21.05, -89.53, -139.04, and -172.82

h*mm, respectively, with negative values indicating a decrease in pain. Tramadol 100 mg and placebo led to an increase in pain (SPID: 22.16 and 70.91 h*mm, respectively). See Figure 7 for a graphic presentation and Table 19 for descriptive statistics of the primary endpoint (SPID 8).

Figure 7: Mean SPID (0-8 hours) With 95% CI, Last-Observation-Carried-Forward (LOCF), PP Set[a]



[a] Graph of means by treatment (mean ±95% CI) PARAM = SPID (0-8h) [h*mm]
Abbreviations: SPID – Sum of Pain Intensity Difference, LOCF – last-observed-carried-forward, CI – confidence interval
Source: Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SACO4-201

Table 19: SPID (0-8 hours), Last-Observation-Carried-Forward (LOCF), PP Set

[h*mm]	50mg E-58425 (N=45)	100mg E-58425 (N=47)	150mg E-58425 (N=54)	200mg E-58425 (N=46)	100mg Tramadol (N=49)	Placebo (N=47)	p-value
Mean	-21.05	-89.53	-139.04	-172.82	22.16	70.91	<0.001[1]
Median	22.30	-50.92	-187.54	-219.54	73.33	99.58	0.4712[2]
SD	242.985	233.626	226.775	224.241	228.242	212.612	
Min	-760.5	-516.3	-662.8	-486.2	-506.9	-396.4	
Max	356.0	329.2	318.3	320.7	366.4	359.7	
n	45	47	54	46	49	47	

[1] p-value for treatment from ANOVA with factors treatment and center without interaction
[2] p-value for center
Abbreviations: SPID – Sum of Pain Intensity Difference; LOCF – last-observed-carried-forward; CI – confidence interval; SD – standard deviation
Source: Applicant's submission, NDA 213426, 5.3.5.1. Clinical Study Report ESTEVE-SACO4-201 ("Section 14.3.1.2.2")

The Applicant used the LOCF method to impute PI scores after rescue use. For any subject using rescue medications, the PI score collected prior to the rescue use was carried forward until Hour 8. The PI prior to the rescue use may be larger than the PI at baseline and there was a high percentage of subjects using rescue medications in the tramadol 100 mg (74%) and placebo group (81%), which may account for the positive SPID8 in these two groups.

The study provides some support for a dose-response relationship for E-58425 and does not contradict the findings in Study ESTEVE-SUSA-301.

12.3 Supplementary Tables Relevant to Clinical Safety Evaluation

Table 20: Cumulative Subject Exposure for Safety Population

Safety Database for the E-58425 Individuals Exposed to any Treatment in This NDA (N[1]=1123)								
Clinical Trial Groups	**E-58425 50 mg (n=55)**	**E-58425 100 mg (n=53)**	**Co-crystal 150 mg (n=57)**	**E-58425 200 mg (n=385)**	**Tramadol 100 mg (n=338)**	**Celecoxib 100 mg (n=279)**	**Tramadol 100 mg + Celecoxib 100 mg (n=106)**	**Placebo (n=143)**
Healthy volunteers: Five Phase 1 studies (N=152)	0	0	0	145	97	97	106	0
Dose finding study: ESTEVE-SACO4-201 (N=334)	55	53	57	57	58	0	0	54
Controlled trials: ESTEVE-SUSA-301 (N=637)	0	0	0	183	183	182	0	89

N[1] = Total number of subjects who were included in the clinical studies under NDA 213426. Note that all Phase 1 studies were cross-over design and subjects received more than one treatment.
Source: Reviewer-generated based on the Applicant's submission, Table 2.7.4-3

Table 21: Most Frequently Reported TEAEs in >5% of Subjects in Any Treatment Group by System Organ Class and Preferred Term in Study ESTEVE-SUSA-301

System Organ Class Preferred Term	E-58425 (N=183) n (%)	Tramadol (N=183) n (%)	Celecoxib (N=182) n (%)	Placebo (N=89) n (%)	Total (N=637) n (%)
Any adverse event	116 (63.4)	116 (63.4)	95 (52.2)	51 (57.3)	378 (59.3)
Gastrointestinal disorders	63 (34.4)	87 (47.5)	46 (25.3)	22 (24.7)	218 (34.2)
Nausea	55 (30.1)	69 (37.7)	30 (16.5)	17 (19.1)	171 (26.8)
Vomiting	29 (15.8)	30 (16.4)	4 (2.2)	2 (2.2)	65 (10.2)
Constipation	4 (2.2)	13 (7.1)	9 (4.9)	3 (3.4)	29 (4.6)
Nervous system disorders	58 (31.7)	64 (35.0)	40 (22.0)	22 (24.7)	184 (28.9)
Dizziness	31 (16.9)	34 (18.6)	9 (4.9)	13 (14.6)	87 (13.7)
Headache	21 (11.5)	33 (18.0)	20 (11.0)	6 (6.7)	80 (12.6)
Somnolence	15 (8.2)	10 (5.5)	4 (2.2)	3 (3.4)	32 (5.0)
Metabolism and nutrition disorders	7 (3.8)	11 (6.0)	1 (0.5)	0	19 (3.0)
Decreased appetite	6 (3.3)	11 (6.0)	1 (0.5)	0	18 (2.8)

Abbreviations: N – number of subjects; n – number of observations; TEAE – treatment-emergent adverse event
Source: Adapted from Applicant's submission; CSR ESTEVE-SUSA-301; Table 12-2 ("Section 14.3, Table 14.3.1.2")

Table 22: Common TEAEs (>5% of Subjects) in Any Group by Severity, System Organ Class, and Preferred Term in Study ESTEVE-SUSA-301

System Organ Class Preferred Term	Severity	E-58425 (N=183) n (%)	Tramadol (N=183) n (%)	Celecoxib (N=182) n (%)	Placebo (N=89) n (%)	Total (N=637) n (%)
Any TEAE		116 (63.4)	116 (63.4)	95 (52.2)	51 (57.3)	378 (59.3)
	Mild	73 (39.9)	64 (35.0)	70 (38.5)	34 (38.2)	241 (37.8)
	Moderate	41 (22.4)	48 (26.2)	23 (12.6)	15 (16.9)	127 (19.9)
	Severe	2 (1.1)	4 (2.2)	2 (1.1)	2 (2.2)	10 (1.6)
Gastrointestinal disorders	Mild	39 (21.3)	49 (26.8)	33 (18.1)	14 (15.7)	135 (21.2)
	Moderate	22 (12.0)	36 (19.7)	13 (7.1)	8 (9.0)	79 (12.4)
	Severe	2 (1.1)	2 (1.1)	0	0	4 (0.6)
Nausea	Mild	39 (21.3)	48 (26.2)	20 (11.0)	9 (10.1)	116 (18.2)
	Moderate	14 (7.7)	20 (10.9)	10 (5.5)	8 (9.0)	52 (8.2)
	Severe	2 (1.1)	1 (0.5)	0	0	3 (0.5)
Vomiting	Mild	15 (8.2)	13 (7.1)	2 (1.1)	2 (2.2)	32 (5.0)
	Moderate	14 (7.7)	16 (8.7)	2 (1.1)	0	32 (5.0)
	Severe	0	1 (0.5)	0	0	1 (0.2)
Constipation	Mild	4 (2.2)	10 (5.5)	6 (3.3)	3 (3.4)	23 (3.6)
	Moderate	0	3 (1.6)	3 (1.6)	0	6 (0.9)
Nervous system disorders	Mild	40 (21.9)	50 (27.3)	34 (18.7)	16 (18.0)	140 (22.0)
	Moderate	17 (9.3)	12 (6.6)	5 (2.7)	6 (6.7)	40 (6.3)
	Severe	1 (0.5)	2 (1.1)	1 (0.5)	0	4 (0.6)
Dizziness	Mild	20 (10.9)	29 (15.8)	7 (3.8)	9 (10.1)	65 (10.2)
	Moderate	10 (5.5)	4 (2.2)	2 (1.1)	4 (4.5)	20 (3.1)
	Severe	1 (0.5)	1 (0.5)	0	0	2 (0.3)
Headache	Mild	16 (8.7)	25 (13.7)	17 (9.3)	4 (4.5)	62 (9.7)
	Moderate	5 (2.7)	7 (3.8)	2 (1.1)	2 (2.2)	16 (2.5)
	Severe	0	1 (0.5)	1 (0.5)	0	2 (0.3)
Somnolence	Mild	12 (6.6)	9 (4.9)	4 (2.2)	3 (3.4)	28 (4.4)
	Moderate	3 (1.6)	1 (0.5)	0	0	4 (0.6)
General disorders and administration site conditions	Mild	17 (9.3)	12 (6.6)	15 (8.2)	7 (7.9)	51 (8.0)
	Moderate	1 (0.5)	5 (2.7)	1 (0.5)	0	7 (1.1)
Musculoskeletal and connective tissue disorders	Mild	9 (4.9)	9 (4.9)	15 (8.2)	8 (9.0)	41 (6.4)
	Moderate	4 (2.2)	3 (1.6)	2 (1.1)	1 (1.1)	10 (1.6)
	Severe	0	0	0	2 (2.2)	2 (0.3)
Skin and subcutaneous tissue disorders	Mild	14 (7.7)	12 (6.6)	7 (3.8)	3 (3.4)	36 (5.7)
	Moderate	3 (1.6)	4 (2.2)	1 (0.5)	1 (1.1)	9 (1.4)
	Severe	0	0	1 (0.5)	0	1 (0.2)
Investigations	Mild	8 (4.4)	10 (5.5)	10 (5.5)	6 (6.7)	34 (5.3)
	Moderate	0	2 (1.1)	3 (1.6)	2 (2.2)	7 (1.1)
Metabolism and nutrition disorders	Mild	4 (2.2)	11 (6.0)	1 (0.5)	0	16 (2.5)
	Moderate	3 (1.6)	0	0	0	3 (0.5)
Decreased appetite	Mild	4 (2.2)	11 (6.0)	1 (0.5)	0	16 (2.5)
	Moderate	2 (1.1)	0	0	0	2 (0.3)

Abbreviations: N – number of subjects; n – number of observations; TEAE – treatment-emergent adverse event
Each subject will be counted only once within each preferred term. If a subject experiences more than 1 TEAE within a preferred term, only the TEAE with the strongest relationship, as appropriate, was included in the summaries of relationship.
Source: Adapted from Applicant's submission; CSR ESTEVE-SUSA-301; Table 12-3 ("Section 14.3, Table 14.3.1.3"

13 Attachments

Integrated Review of Epidemiology and Drug Utilization

Risk Management Summary

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:	December 17, 2019
Reviewers:	Saranrat Wittayanukorn, PhD *Drug Abuse Team* 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.
**

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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.

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 2018[4], representing an increase from 5,344 in 2015[5] 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	Sales distribution data IQVIA National Sales Perspectives (NSP), 2018	Determine the primary setting of care for utilization of tramadol-containing products
	Prescription data 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
	Diagnosis data 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	General population 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)
	People seeking treatment for adverse effects of non-medical use 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	General population NSDUH, 2015-2018 Monitoring the Future (MTF), 2009-2018	Prevalence of misuse/abuse for tramadol and comparator drugs in general population
	Calls for advice after non-medical use 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
	People entering or being assessed for treatment for opioid or substance use disorders (OUD/SUD) 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	Calls for advice after non-medical use NPDS exposure calls to PCC, 2009-2018	Routes of abuse for single-substance exposure calls
	People entering or being assessed for treatment for OUD/SUD RADARS TCP, 2017-2018 Inflexxion NAVIPPRO™ ASI-MV®, 2017-2018	Product-specific routes of abuse among people entering or being assessed for SUD treatment RADARS TCP and NAVIPPRO™
Morbidity and mortality involving tramadol and comparator opioid analgesics	People seeking treatment for adverse effects of non-medical use NEISS-CADES, 2016-2017	Assess outcomes such as need for healthcare intervention associated with specific opioids
	Calls for advice after non-medical use 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
	General population 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 website[9] 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.

<u>Inclusion criteria:</u>

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 results[20] 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.

3. RESULTS

3.1 DRUG UTILIZATION

3.1.1 SETTINGS OF CARE

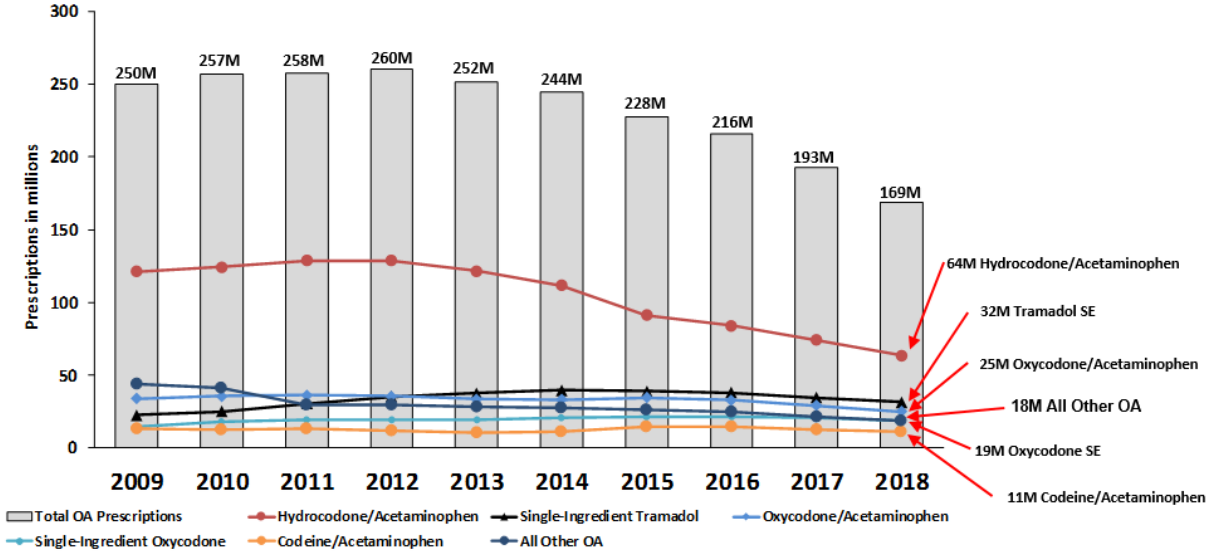
Based on manufacturer sales distribution data in 2018, approximately 58% of all bottles or packages of tramadol-containing products were sold from manufacturers and wholesalers to retail pharmacies, followed by 37% to non-retail pharmacies, and 5% to mail-order/specialty pharmacies.[1] As a result of 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



In 2018, tramadol-containing prescriptions accounted for an estimated 19% of the total opioid analgesic prescriptions
*SE- Single ingredient

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

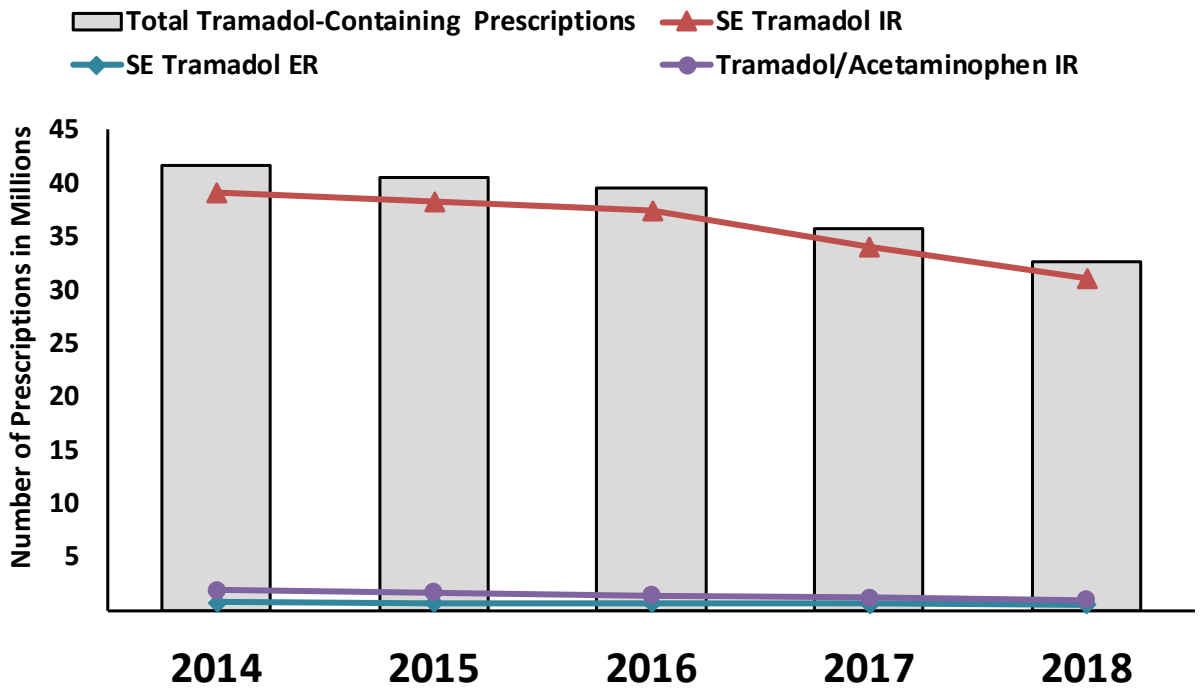
Approximately 11 billion units (tablets, capsules, etc.) of OA were dispensed from U.S. retail pharmacy settings in 2018. **Table 2** in **Appendix A** provides the total OA units dispensed from U.S. retail pharmacy settings from 2009 through 2018. Similar to dispensed prescription data, the top five 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 12 million 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).

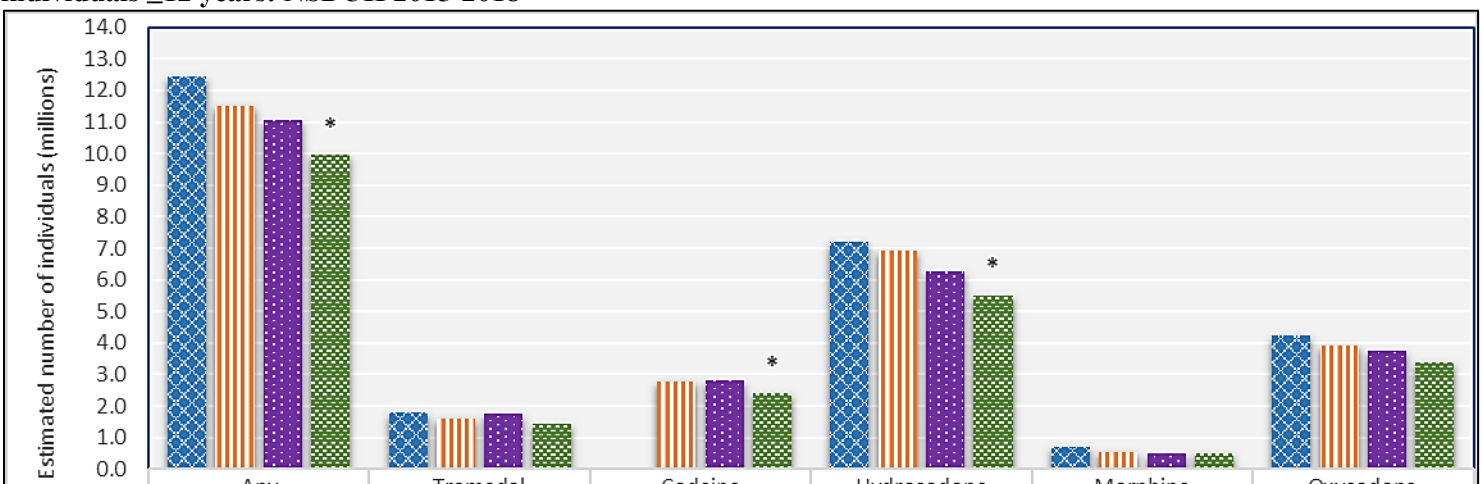
3.2 NSDUH

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

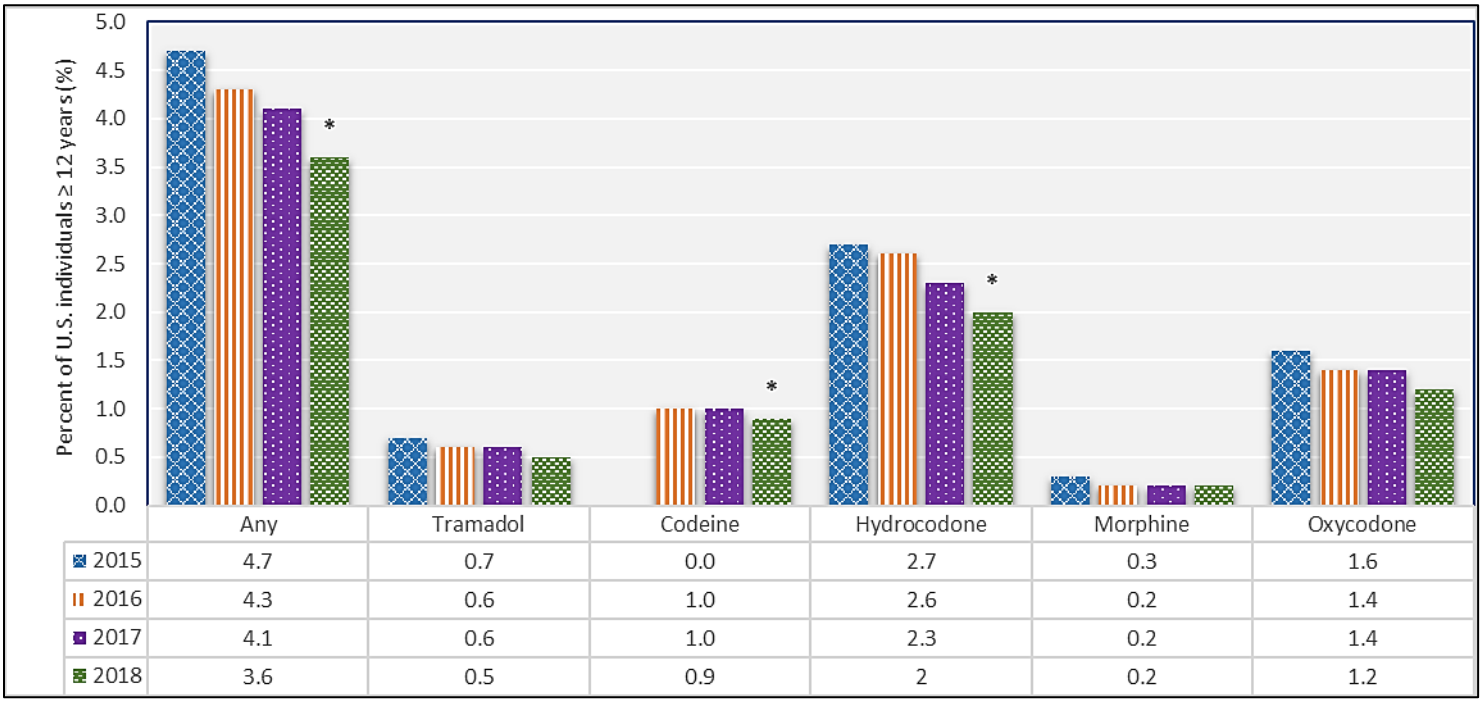


	Any	Tramadol	Codeine	Hydrocodone	Morphine	Oxycodone
2015	12.46	1.79	0.00	7.19	0.70	4.26
2016	11.52	1.59	2.77	6.92	0.54	3.91
2017	11.08	1.75	2.83	6.26	0.50	3.74
2018	9.95	1.46	2.39	5.50	0.49	3.37

* 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

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



	Any	Tramadol	Codeine	Hydrocodone	Morphine	Oxycodone
2015	4.7	0.7	0.0	2.7	0.3	1.6
2016	4.3	0.6	1.0	2.6	0.2	1.4
2017	4.1	0.6	1.0	2.3	0.2	1.4
2018	3.6	0.5	0.9	2	0.2	1.2

* 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

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**.

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
Intentional Abuse	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)
Intentional Misuse	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)
Suspected Suicide	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)
*Intentional Unknown**	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
Withdrawal, single-substance	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
Intentional Abuse	8 (4.7)	969 (14.5)	1823 (12.7)	1949 (9.6)	1483 (6.3)	122 (4.3)	297 (12.0)
Intentional Misuse	67 (39.7)	554 (8.3)	2200 (15.4)	2945 (14.5)	2627 (11.1)	584 (20.4)	563 (22.7)
Suspected Suicide	57 (33.7)	4812 (72.1)	9596 (67.0)	14369 (70.6)	18244 (77.0)	1932 (67.6)	1251 (50.5)
Intentional Unknown	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
Withdrawal, single-substance	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

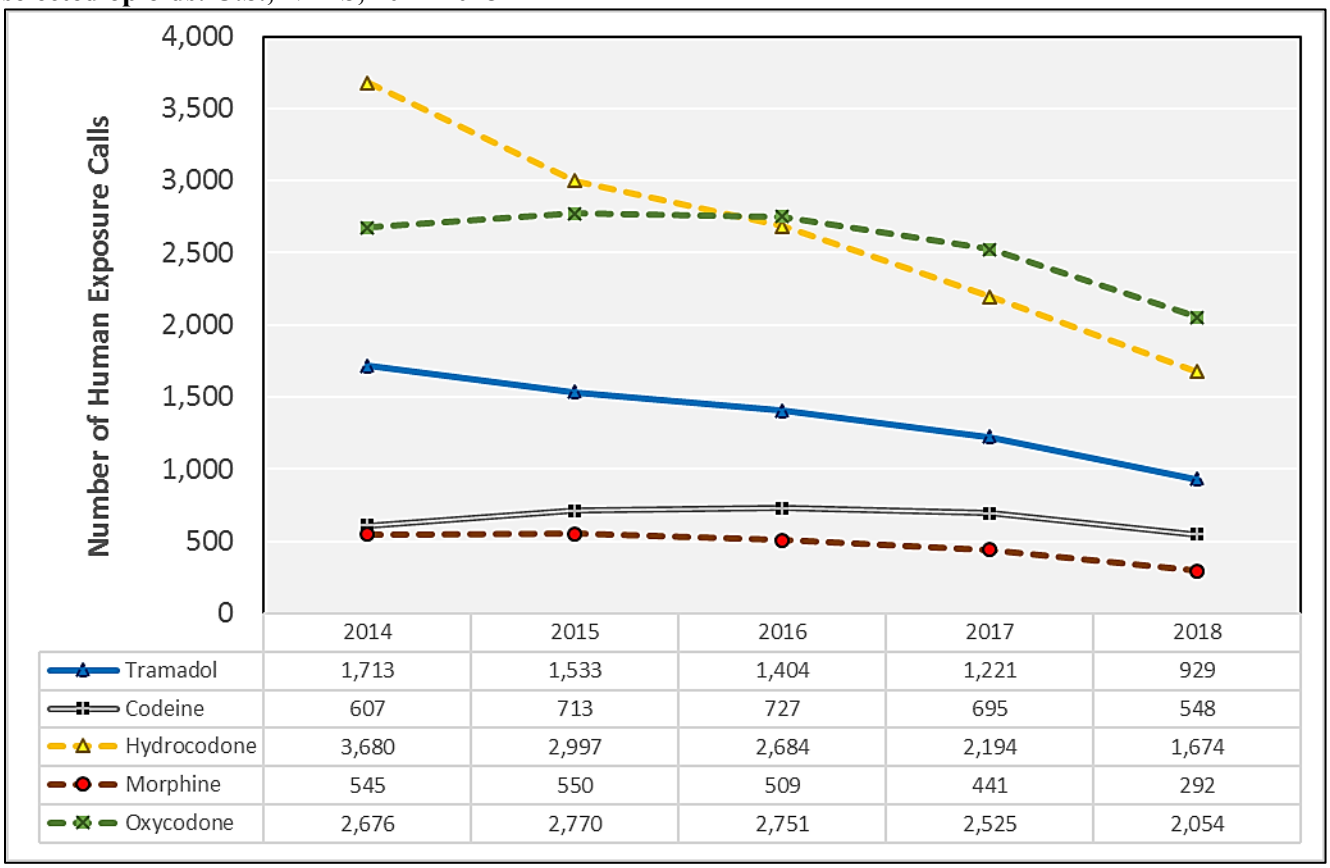
Medical Outcomes	Single substance exposures	Multiple-substance exposures
Total, n	2,138	1,845
Minor effect, n (%)	903 (42.2)	787 (42.7)
Moderate effect	1,045 (48.9)	896 (48.6)
Major Effect	187 (8.8)	131 (7.1)
Death	3 (0.1)	31 (1.7)

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.

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



	2014	2015	2016	2017	2018
Tramadol	1,713	1,533	1,404	1,221	929
Codeine	607	713	727	695	548
Hydrocodone	3,680	2,997	2,684	2,194	1,674
Morphine	545	550	509	441	292
Oxycodone	2,676	2,770	2,751	2,525	2,054

NPDS: National Poison Data System

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%.

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 Intentional*	33,857	12,571	60,799	7,502	42,543
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).**

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

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

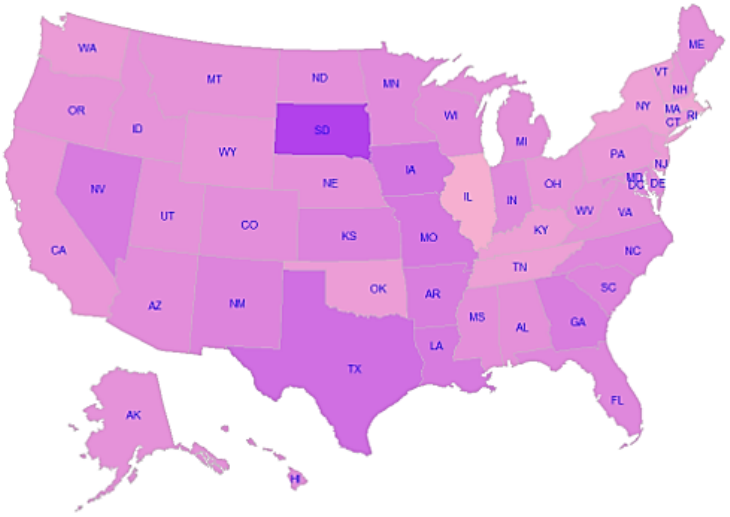
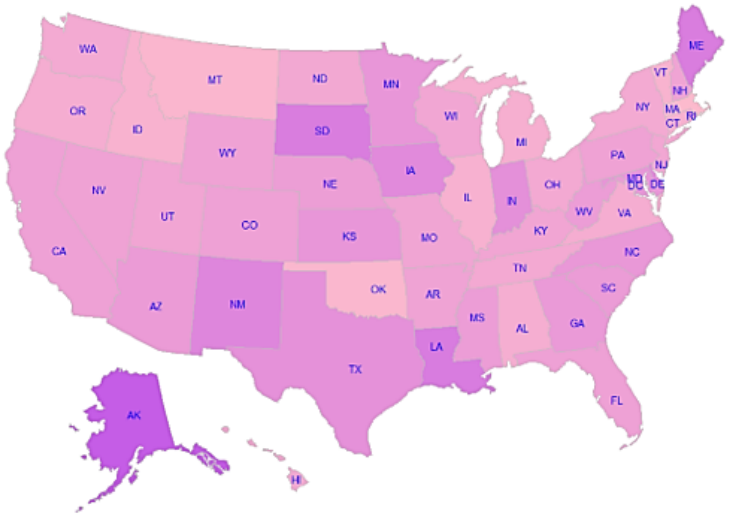


Figure 5B. % Tramadol misuse/abuse exposure calls among total human exposure calls: U.S. NPDS, 2018



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

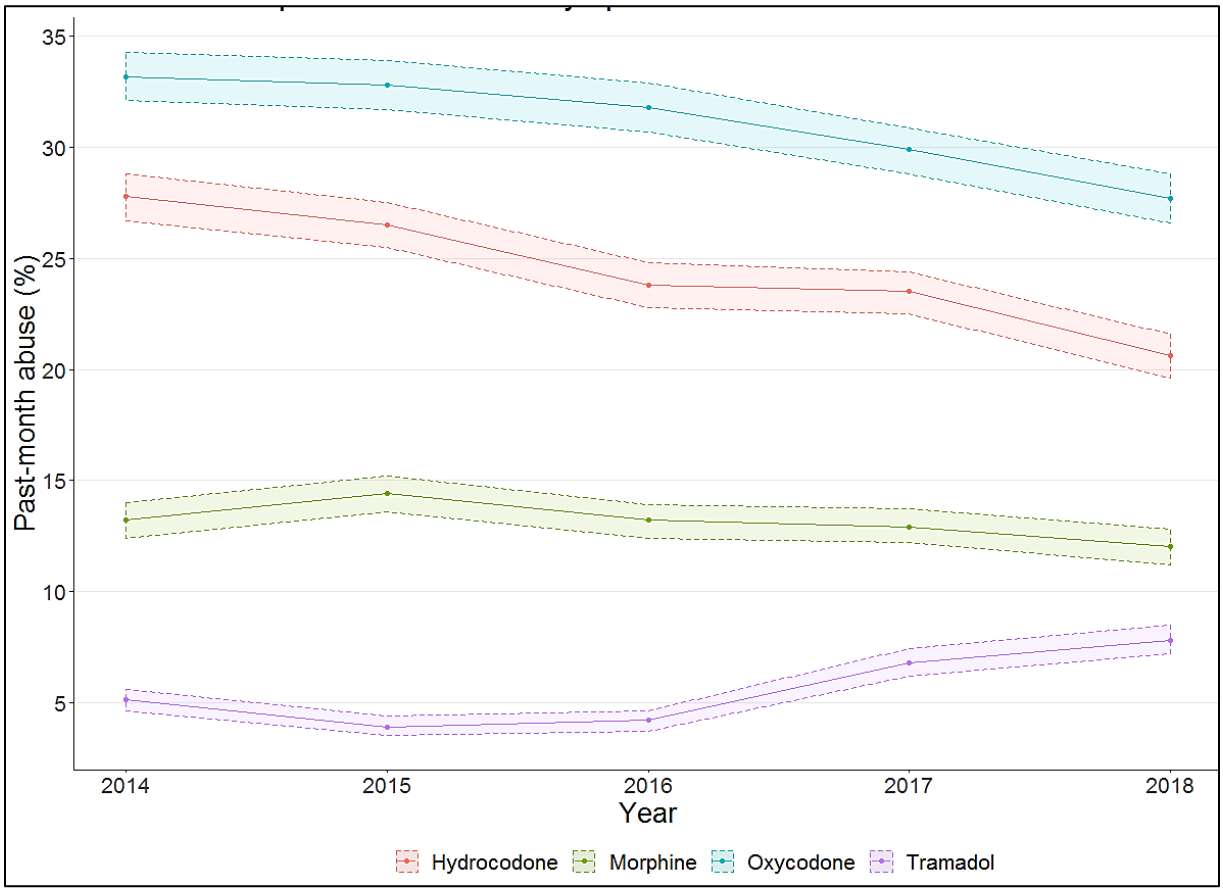
RADARS®: Researched Abuse, Diversion, and Addiction-Related Surveillance; TCP: Treatment Center Program; CI: confidence interval

*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 *careless response.*

**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 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

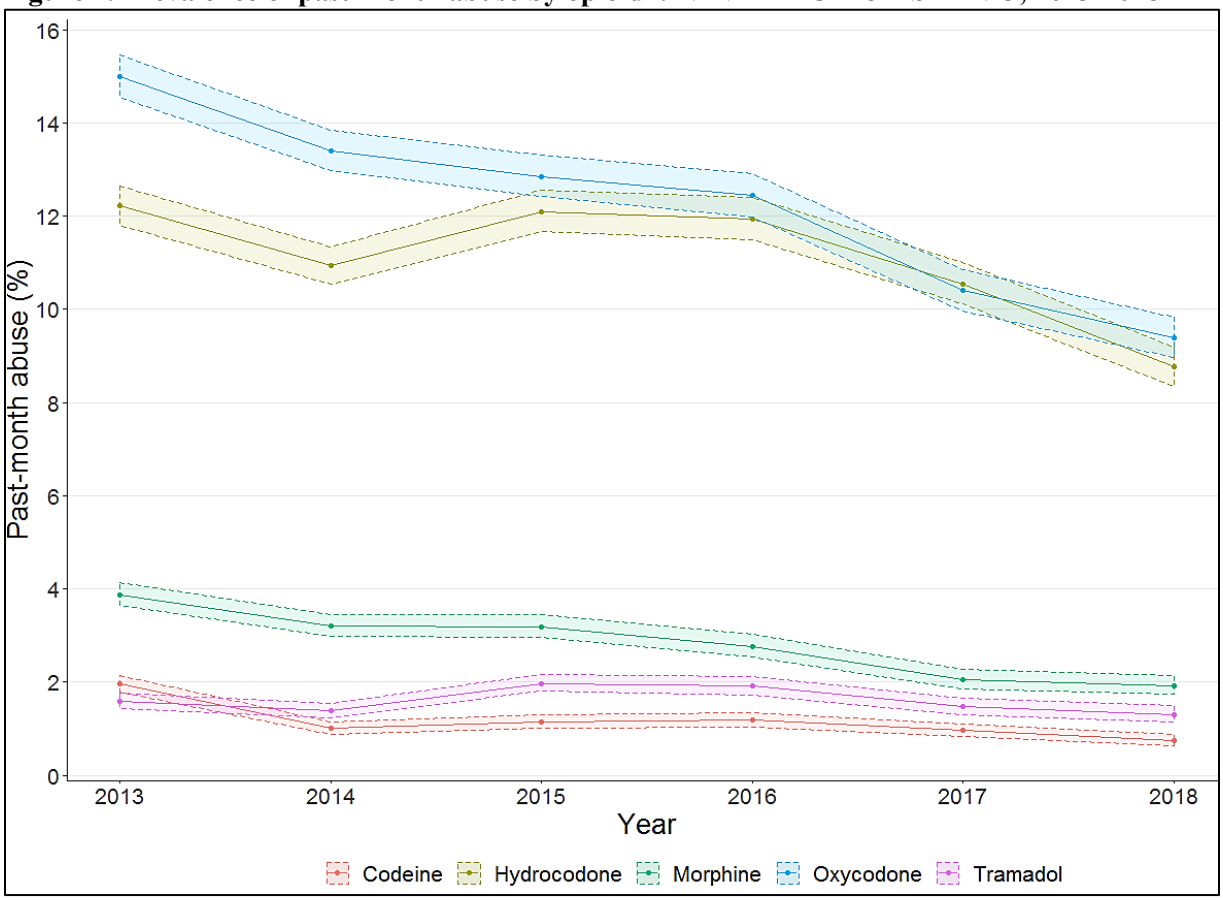
Opioid Molecule	Past-Month Abuse, Unadjusted		Swallowed Whole		Chewed		Snorted		Injected	
	N	% Respondents (95% CI)	N	%	N	%	N	%	N	%
Tramadol	1,553	1.5 (1.4-1.6)	1,300	83.7	136	8.8	128	8.2	22	1.4
Codeine	993	0.9 (0.9-1.0)	—	—	—	—	—	—	—	—
Hydrocodone	8,719	8.3 (8.1-8.5)	7,028	80.6	1,796	20.6	2,393	27.5	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

[a]Cases 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.

[b]Excludes opioid-containing cough and cold products.

[c]Includes opioid-containing cough and cold products.

[d]Includes pharmaceutical abuse, therapeutic misuse (use other than as directed by a clinician), and opioid overdoses without indication of intent.

[e]Includes 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.
[b]Excludes opioid-containing cough and cold products.
[c]Includes opioid-containing cough and cold products.
[d]For 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).
[e]For 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).
[f]Includes pharmaceutical abuse, therapeutic misuse (use other than as directed by a clinician), and opioid overdoses without indication of intent.
[g]Includes 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.

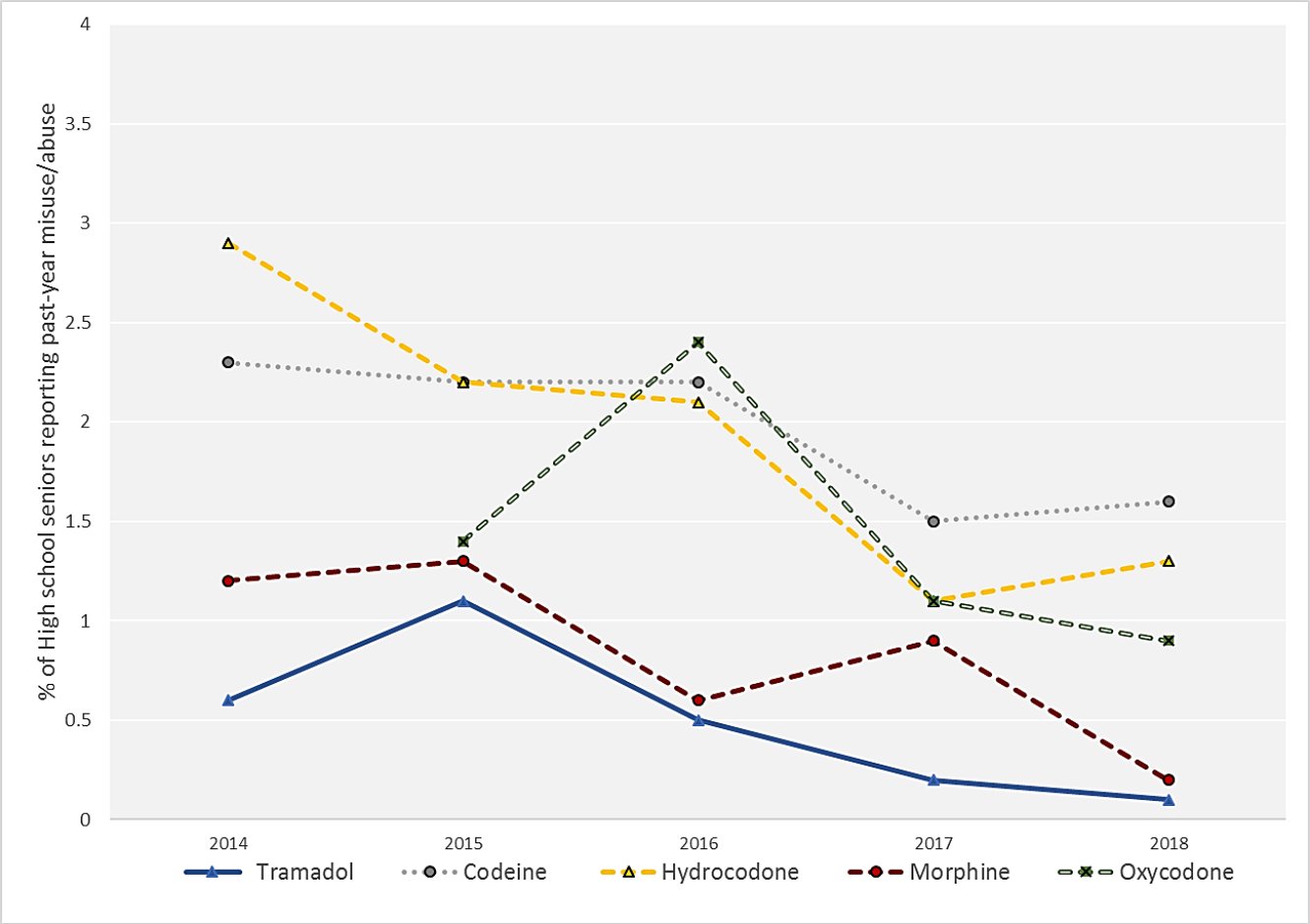
Among surveillance cases of ED visits involving non-medical use of tramadol (n=138), the most common adverse event manifestation was altered mental status (n=58). Of these, 10 cases specifically documented convulsions. In many cases of altered mental status after non-medical use of tramadol, the patient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

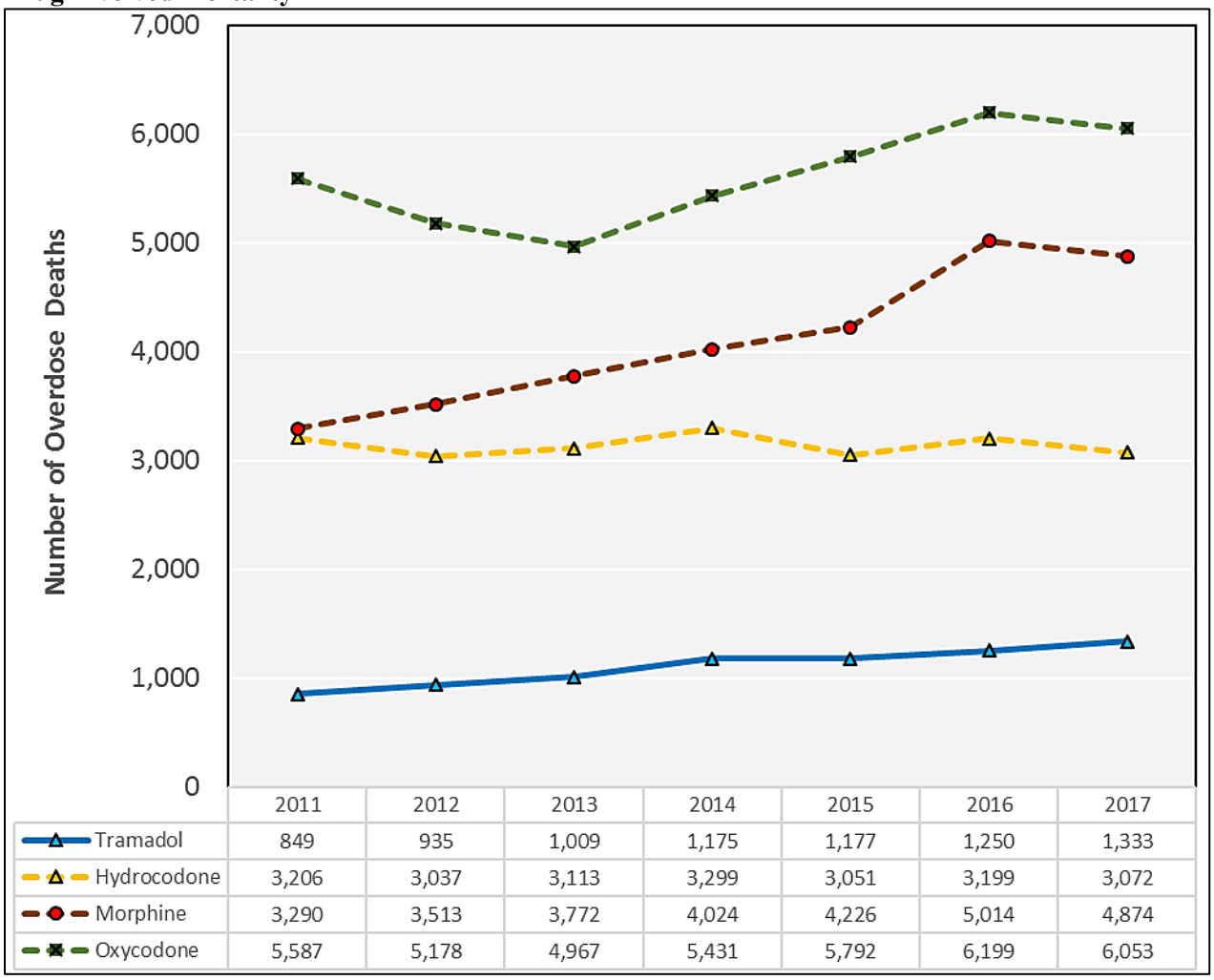


Source: The Monitoring the Future (MTF) study, the University of Michigan. Table C-4 Specific Narcotics Other than Heroin: Trends in Annual Prevalence of Use for All Seniors. http://www.monitoringthefuture.org//pubs/monographs/mtf-vol1_2018.pdf.

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



	2011	2012	2013	2014	2015	2016	2017
Tramadol	849	935	1,009	1,175	1,177	1,250	1,333
Hydrocodone	3,206	3,037	3,113	3,299	3,051	3,199	3,072
Morphine	3,290	3,513	3,772	4,024	4,226	5,014	4,874
Oxycodone	5,587	5,178	4,967	5,431	5,792	6,199	6,053

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

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[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.

6. REFERENCES

1. Centers for Disease Control and Prevention. Drug Overdose Deaths. 2018. https://www.cdc.gov/drugoverdose/data/statedeaths.html. Accessed 10/23/2019.
2. Centers for Disease Control and Prevention. Overdose Death Maps. Overdose Deaths Involving Prescription Opioids. 2018. https://www.cdc.gov/drugoverdose/data/prescribing/overdose-death-maps.html. Accessed 10/23/2019.
3. Hedegaard H, Bastian BA, Trinidad JP, Spencer M, Warner M. Regional Differences in the Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2017. *Natl Vital Stat Rep.* 2019;68(12):1-15.
4. U.S. Drug Enforcement Administration DCD. National Forensic Laboratory Information System: NFLIS-Drug 2018 Annual Report. 2019. https://www.nflis.deadiversion.usdoj.gov/DesktopModules/ReportDownloads/Reports/NFLIS-Drug-AR2018.pdf. Accessed 10/23/2019.
5. U.S. Drug Enforcement Administration DCD. National Forensic Laboratory Information System: Year 2015 Annual Report. 2016. https://www.nflis.deadiversion.usdoj.gov/DesktopModules/ReportDownloads/Reports/NFLIS2015AR.pdf. Accessed 10/23/2019.
6. World Health Organization. Critical Review Report: Tramadol 2018. https://www.who.int/medicines/access/controlled-substances/Tramadol.pdf?ua=1. Accessed 10/23/2019.
7. Food and Drug Administration. Draft Guidance for Industry: Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products 2019. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-abuse-and-dependence-section-labeling-human-prescription-drug-and-biological-products-content. Accessed 11/13/2019.
8. Substance Abuse and Mental Health Services Administration. 2018 National Survey on Drug Use and Health. Methodological Summary and Definitions. 2019. https://www.samhsa.gov/data/report/2018-methodological-summary-and-definitions. Accessed 10/7/2019.
9. Reports and Detailed Tables From the National Survey on Drug Use and Health (NSDUH). https://www.samhsa.gov/data/nsduh/reports-detailed-tables-2018-NSDUH. Published 2018. Accessed 10/9/2019.
10. Substance Abuse and Mental Health Services Administration. 2018 National Survey on Drug Use and Health: Methodological summary and definitions. Center for Behavioral Health Statistics and Quality. 2019. https://www.samhsa.gov/data/. Accessed 10/6/2019.
11. Gummin DD, Mowry JB, Spyker DA, Brooks DE, Osterthaler KM, Banner W. 2017 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 35th Annual Report. *Clin Toxicol (Phila).* 2018;56(12):1213-1415.
12. Butler SF, Budman SH, Licari A, et al. National addictions vigilance intervention and prevention program (NAVIPPRO): a real-time, product-specific, public health

surveillance system for monitoring prescription drug abuse. *Pharmacoepidemiol Drug Saf.* 2008;17(12):1142-1154.
13. Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. *JAMA.* 2006;296(15):1858-1866.
14. Jhung MA, Budnitz DS, Mendelsohn AB, Weidenbach KN, Nelson TD, Pollock DA. Evaluation and overview of the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance Project (NEISS-CADES). *Med Care.* 2007;45(10 Supl 2):S96-102.
15. Schroeder TJ, Ault K. National Electronic Injury Surveillance System (NEISS) sample design and implementation from 1997 to present. . 2001. https://www.cpsc.gov/s3fs-public/pdfs/blk_media_2001d011-6b6.pdf. Accessed 10/5/2019.
16. Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS. US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014. *JAMA.* 2016;316(20):2115-2125.
17. Geller AI, Dowell D, Lovegrove MC, et al. U.S. Emergency Department Visits Resulting From Nonmedical Use of Pharmaceuticals, 2016. *Am J Prev Med.* 2019;56(5):639-647.
18. Lovegrove MC, Dowell D, Geller AI, et al. US Emergency Department Visits for Acute Harms From Prescription Opioid Use, 2016-2017. *Am J Public Health.* 2019;109(5):784-791.
19. Johnston LD, Miech RA, O'Malley PM, Bachman JG, Schulenberg JE, Patrick ME. Monitoring the Future national survey results on drug use 1975-2018: Overview, key findings on adolescent drug use 2019. http://www.monitoringthefuture.org//pubs/monographs/mtf-overview2018.pdf. Accessed 10/27/2019.
20. Miech RA, Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE, Patrick ME. Monitoring the Future national survey results on drug use, 1975–2018: Volume I, Secondary school students. . 2019. http://www.monitoringthefuture.org/pubs/monographs/mtf-vol1_2018.pdf. Accessed 10/27/2019.
21. Centers of Disease Control and Prevention. National Center for Health Statistics. About the National Vital Statistics System. 2016. https://www.cdc.gov/nchs/nvss/about_nvss.htm. Accessed 10/23/2019.
22. Trinidad JP, Warner M, Bastian BA, Minino AM, Hedegaard H. Using Literal Text From the Death Certificate to Enhance Mortality Statistics: Characterizing Drug Involvement in Deaths. *Natl Vital Stat Rep.* 2016;65(9):1-15.
23. Hedegaard H, Bastian BA, Trinidad JP, Spencer M, Warner M. Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2011-2016. *Natl Vital Stat Rep.* 2018;67(9):1-14.
24. Hoppe-Roberts JM, Lloyd LM, Chyka PA. Poisoning mortality in the United States: comparison of national mortality statistics and poison control center reports. *Ann Emerg Med.* 2000;35(5):440-448.
25. Mallama CA, Trinidad JP, Swain RS, Zhao Y, Woods C, McAninch JK. A comparison of opioid-involved fatalities captured in the National Poison Data System to data

derived from US death certificate literal text. *Pharmacoepidemiol Drug Saf.* 2019;28(10):1377-1385.

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 neoplm	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

Appendix C1. AAPCC NPDS list of product codes

Note: These product codes must be redacted for public release

(b) (4)

Appendix C1. AAPCC NPDS list of product codes

Note: These product codes must be redacted for public release

(b) (4)

Appendix C1. AAPCC NPDS list of product codes

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(b) (4)

Appendix C1. AAPCC NPDS list of product codes

Note: These product codes must be redacted for public release

(b) (4)

Appendix C1. AAPCC NPDS list of product codes

Note: These product codes must be redacted for public release

(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 Percent Estimate (%), 95% CI	2015 Percent Estimate (%), 95% CI	2016 Percent Estimate (%), 95% CI	2017 Percent Estimate (%), 95% CI	2018 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 Percent Estimate (%), 95% CI	2014 Percent Estimate (%), 95% CI	2015 Percent Estimate (%), 95% CI	2016 Percent Estimate (%), 95% CI	2017 Percent Estimate (%), 95% CI	2018 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

[a]Cases 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.

[b]Includes pharmaceutical abuse, therapeutic misuse (use other than as directed by a clinician), and opioid overdoses without indication of intent.

[c]Estimates based on <20 cases or total estimates <1,200 are considered statistically unstable and are not shown (--).

[d]Adverse 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).

[e]Average annual estimates were based on total non-medical use visits attributed to tramadol-containing products, from 2016 through 2017.

[f]1 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											
Tramadol	—	—	—	—	0.8	0.6	1.1	0.5	0.2	0.1	0.0
Ultram	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
Vicodin	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

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

Date:	**January 15, 2020**
To:	**Members of the Joint Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management (DSaRM) Advisory Committee**
From:	**Division of Risk Management (DRISK)** **Office of Medication Error Prevention and Risk Management (OMEPRM)** **Office of Surveillance and Epidemiology (OSE)**
Drug Name:	**Celecoxib and Tramadol Tablets**
Application Number:	**NDA 213426**
Subject:	**Risk Evaluation and Mitigation Strategy (REMS)**

If approved, celecoxib and tramadol oral tablets (NDA 213426), will be required to become a member of the Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits of the drug outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. The Opioid Analgesic REMS is a shared system REMS that was initially approved as the Extended-Release (ER) and Long-Acting (LA) (ER/LA) REMS in July 2012 and was expanded in September 2018 to include all application holders of immediate-release (IR) opioid analgesics that are expected to be used in the outpatient setting and that are not already covered by another REMS program.

The Opioid Analgesic REMS is intended to reduce risks and improve safe use of opioid analgesics while continuing to provide access to these medications for patients in pain. The central component of the Opioid Analgesics REMS is an education program for healthcare providers , including prescribers, nurses, and pharmacists, involved in the treatment and monitoring of patients with pain. Under the Opioid Analgesic REMS, application holders[1] are required to make education programs available to healthcare providers. The application holders

1 Application holders refers to all the manufacturers of the new drug applications (NDAs) and abbreviated new drug applications (ANDAs) for opioid analgesics that are subject to the REMS requirements. ANDAs refer to generic drugs. The applicant holders have come together as a consortium and formed the REMS Program Companies (RPC). Throughout this background document, the manufacturers may be referred to as application holders or RPC.

are meeting this requirement by providing educational grants to accredited continuing education (CE) providers who offer training to healthcare providers at no or nominal cost. The training must include successful completion of a knowledge assessment and proof of successful program completion.

To be considered compliant with the Opioid Analgesic REMS, the CE courses are required to include the content and messages of a "blueprint" developed by FDA for this purpose. The currently approved FDA Blueprint, *FDA's Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain,* focuses on the fundamentals of acute and chronic pain management and provides a contextual framework for the safe prescribing of opioid analgesics. This includes principles related to the acute and chronic pain management; non-pharmacologic treatments for pain; and pharmacologic treatments for pain (both non-opioid analgesic and opioid analgesic). The FDA Blueprint covers basic information about addiction medicine and opioid use disorder. The core messages are directed to prescribers, pharmacists, and nurses, but are also relevant for other healthcare providers who participate in the management of pain.[2]

The Opioid Analgesics REMS also includes a patient counseling guide for healthcare providers to assist in properly counseling patients on their responsibilities for using these medicines safely and to provide patients with additional written instructions as needed. The approved labeling for opioid analgesics includes a product-specific one-page Medication Guide to be given to patients each time they receive a prescription of their opioid analgesic medicine. The Medication Guide contains consumer-friendly information on the safe use and disposal of opioid analgesics and instructions for patients to consult their healthcare providers before changing doses, signs of potential overdose and emergency contact instructions, and advice on safe storage to prevent accidental exposure to family members.

Attachments: Opioid Analgesic REMS Blueprint

2 Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain. The FDA Blueprint contains core messages intended for use by CE providers to develop educational materials to train HCPs under the REMS.

Introduction
FDA's Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain

Background

In July 2012, FDA approved the Extended-Release and Long-Acting (ER/LA) Opioid Analgesic Risk Evaluation and Mitigation Strategy (ER/LA REMS) to ensure that the benefits of ER and LA opioid analgesics used in the outpatient setting outweigh the risks. That REMS was modified and the new *Opioid Analgesic REMS* includes, in addition to ER/LA opioid analgesics, all immediate-release (IR) opioids used in the outpatient setting that are not already covered by another REMS program. The *Opioid Analgesic REMS* is intended to support other national efforts underway to address the misuse and abuse of prescription opioid analgesics.

As part of the Opioid Analgesic REMS, all opioid analgesic companies must provide the following:

- Education for health care providers (HCPs) who participate in the treatment and monitoring of pain. For the purpose of the Opioid Analgesic REMS, HCPs will include not only prescribers, but also HCPs who participate in the treatment and monitoring of patients who receive opioid analgesics, including pharmacists and nurses.
    - Education will be offered through accredited continuing education (CE) activities. These activities will be supported by unrestricted educational grants from opioid analgesic companies.
- Information for HCPs to use when counseling patients about the risks of ER, LA, and IR opioid analgesic use.

To facilitate the development of CE educational materials and activities as part of the Opioid Analgesic REMS, FDA has also revised the education blueprint — originally designed to facilitate development of CE educational materials under the ER/LA REMS. FDA has completed the revisions to the *FDA Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain* (FDA Blueprint), following publication of a draft version and consideration of received public comments.

The FDA Blueprint contains a high-level outline of the core educational messages that will be included in the educational programs developed under the Opioid Analgesic REMS. The FDA Blueprint focuses on the fundamentals of acute and chronic pain management and provides a contextual framework for the safe prescribing of opioid analgesics. The core messages are directed to prescribers, pharmacists, and nurses, but are also relevant for other HCPs who participate in the management of pain. The course work is not intended to be exhaustive nor a substitute for a more comprehensive pain management course.

Accrediting bodies and CE providers will ensure that the CE activities developed comply with the standards for CE of the Accreditation Council for Continuing Medical Education, [1,2] or another CE accrediting body, depending on the target audience's medical specialty or health care profession.

FDA is making the FDA Blueprint, approved as part of the Opioid Analgesic REMS, available on the REMS@FDA Website (www.fda.gov/REMS), where it will remain posted for use by CE providers as they develop the CE materials and activities. A list of the REMS-compliant CE activities supported by unrestricted educational grants from the opioid analgesic companies to accredited CE providers will be posted at www.opioidanalgesicREMS.com as that information becomes available.

Reasons Why HCP Education Is So Important

Adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse of opioids have emerged as major public health problems. It is critical that HCPs are knowledgeable about the risks associated with opioid analgesics as they pertain to their patients as well as from a public health perspective. The data continue to show problems associated with prescription opioid analgesics.

- In 2015, over 52,404 Americans died from drug poisonings, and of these, 24% or approximately 12,570 deaths involved opioid analgesics.[3]

- Based on the 2016 National Survey on Drug Use and Health (NSDUH), an estimated 11.5 million Americans aged 12 or older misused a prescription pain reliever in the past year — with hydrocodone, oxycodone, and codeine products being the most commonly reported.[4]

- The most common source of pain relievers in the 2016 NSDUH was "a friend or relative" (53%). "A physician's prescription" was the second most common source, reported by approximately 35% of respondents.[5]

The nation is facing competing public health problems: the need to adequately treat a large number of Americans with acute and chronic pain and an epidemic of prescription opioid abuse.

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[1] Accreditation Council for Continuing Medical Education. 2016. Accreditation Requirements. Criteria for CME Providers-Accreditation Criteria. Accessed July 2018.

[2] Accreditation Council for Continuing Medical Education. 2016. Accreditation Requirements. Criteria for CME Providers-Standards for Commercial Support. Accessed July 2018.

[3] See https://www.cdc.gov/nchs/data/factsheets/factsheet_drug_poisoning.pdf. Accessed July 2018.

[4] Substance Abuse and Mental Health Services Administration. (2017). *Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health* (HHS Publication No. SMA 17-5044, NSDUH Series H-52). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration.

[5] Ibid.

Described in the 2011 report by the National Academies of Science, Engineering, and Medicine (NASEM), *Relieving PAIN in America, A Blueprint for Transforming Prevention, Care, Education, and Research*,[6] 100 million Americans suffer from common chronic pain conditions; fewer than half of Americans undergoing surgery report adequate pain relief; and 60% of Americans visiting the emergency department with acute painful conditions receive analgesics.

The increasing availability of prescription opioids since the 1990's has been accompanied by an epidemic of opioid addiction. The Substance Abuse and Mental Health Services Administration's *National Survey of Drug Use and Health* has shown that most people who use prescription analgesics "nonmedically" obtain them from friends or family, who it is believed obtained the drugs from a doctor's prescription.[7]

Some of the immediate consequences of untreated or undertreated pain include reduced quality of life, impaired physical function, and high economic costs. Chronic pain is associated with physical disability, fear, anger, depression, anxiety, and reduced ability to carry out the roles of family member, friend, and employee. It is critically important that HCPs have all the information they need to properly treat their patients and safely manage their pain. It is also critical for HCPs to understand when opioid analgesics are the appropriate treatment and how to implement best practices to ensure their patients' safety. A 2017 report by NASEM, *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use,* describes the challenges of providing adequate pain management and calls for the establishment of "comprehensive pain education materials and curricula" for HCPs.[8]

Having broad knowledge about how to manage patients with pain can create the opportunity for HCPs to consider ***all*** options for pain management, including nonpharmacologic and non-opioid pharmacologic options, and to reserve opioids for when non-opioid options are inadequate and when the benefits of the opioids are expected to outweigh the risks. This information can also aid HCPs in identifying and intervening when encountering obstacles that may reduce access to nonpharmacological and non-opioid medication options. Fully informed HCPs can help contribute to national efforts to address opioid addiction and reduce opioid misuse and abuse.

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[6] http://www.nationalacademies.org/hmd/Reports/2011/Relieving-Pain-in-America-A-Blueprint-for-Transforming-Prevention-Care-Education-Research.aspx. Accessed July 2018.

[7] https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2016/NSDUH-DetTabs-2016.pdf, Table 6.53A. Accessed July 2018.

[8] http://nationalacademies.org/hmd/Reports/2017/pain-management-and-the-opioid-epidemic.aspx. Accessed July 2018.

FDA Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain

Purpose of the Opioid Analgesic REMS HCP Educational Effort

Following completion of educational activities under the Opioid Analgesic REMS, HCPs should be knowledgeable about the following.

- The fundamental concepts of pain management, including definitions and mechanisms of pain
- How to assess patients in pain, identifying risk factors for abuse and addiction
- The range of therapeutic options for managing pain, including nonpharmacologic approaches and pharmacologic (non-opioid and opioid analgesics) therapies
- How to integrate opioid analgesics into a pain treatment plan individualized to the needs of the patient
- How to safely and effectively manage patients on opioid analgesics in the acute and chronic pain settings, including initiating therapy, titrating, and discontinuing use of opioid analgesics
- How to counsel patients and caregivers about the safe use of opioid analgesics, including proper storage and disposal
- How to counsel patients and caregivers about the use of naloxone for opioid overdose
- When referral to a pain specialist is appropriate
- The fundamental elements of addiction medicine
- How to identify and manage patients with opioid use disorder

In addition, HCPs will gain an understanding of current information about safe opioid practices and about current Federal[9] and State regulations, national guidelines,[10] and professional organization[11] and medical specialty guidelines on treating pain and prescribing opioids. HCPs will also become familiar with the use of naloxone and with the importance of its availability for use by patients and caregivers both in the community and in the home.

[9] For example, see https://www.deadiversion.usdoj.gov/21cfr/cfr/2106cfrt.htm and https://www.deadiversion.usdoj.gov/21cfr/21usc/829 htm. Accessed July 2018.

[10] For example, see Dowell D, Haegerich TM, Chou R. 2016. CDC Guideline for Prescribing Opioids for Chronic Pain –United States, 2016. MMWR Recomm Rep 2016; 65 (No.RR-1): 1-49. Accessed July 2018.

[11] For example, see Federation of State Medical Boards' Guidelines for the Chronic Use of Opioid Analgesics. Accessed July 2018.

Section 1: The Basics of Pain Management

I. THE NEED FOR COMPREHENSIVE PAIN EDUCATION

The FDA Blueprint was developed with two, competing, U.S. public health concerns in mind, (1) the large number of Americans with acute and chronic pain and (2) the epidemic of prescription opioid abuse.

1. Providing health care providers (HCPs) with a thorough understanding of the risks associated with opioids can give HCPs the opportunity to consider all pain management options, including nonpharmacologic and pharmacologic options, prescribing opioids only when non-opioid options are inadequate and when the benefits of using an opioid are expected to outweigh the risks.

2. When HCPs have information about the risks of opioid misuse and abuse, they will be better able to create opportunities for patient counseling and other strategies to reduce these risks.

II. DEFINITIONS AND MECHANISMS OF PAIN

Pain can be categorized according to its duration, underlying pathophysiology of the original insult, and whether a central sensitization component has developed. An understanding of these different categorizations can help direct therapeutic decisions.

When defining, and classifying pain, the following should be taken into consideration:

1. Biological significance of pain (survival value)
2. Relationship between acute and chronic pain
3. Distinction between nociceptive and neuropathic pain

III. ASSESSING PATIENTS IN PAIN

HCPs should be knowledgeable about how to assess each patient when initiating a pain management program. When appropriate, evidence-based, standardized scales and tools can be used to document pain characteristics and guide management decisions throughout treatment, noting the strengths and weaknesses regarding specificity and sensitivity of these scales.

Important elements of an initial assessment should include the following:

1. Patient history

2. Screening tools to evaluate the known risk factors for development of chronic pain after an acute injury or disease

3. Screening tools to evaluate the known risk factors for opioid use disorder (OUD) or abuse

4. Queries of state prescription drug monitoring programs (PDMPs)

5. Pain assessment scales/tools

6. Functional assessment scales

7. Physical examination

8. Family planning, including information about use of contraceptives, pregnancy intent/status and plans to breastfeed

9. Psychological and social evaluation

10. Diagnostic studies when indicated

Section 2: Creating the Pain Treatment Plan

A comprehensive pain treatment plan should be developed and customized to the needs of the individual patient. The treatment plan should include the types of therapies planned, the goals of treatment, and an explanation of the patient and prescriber roles and responsibilities. The goals of treatment should be based on (1) expected outcomes of pain reduction; (2) improvement in functional outcomes impaired by pain (e.g., activities of daily living); and (3) quality of life.

If HCPs encounter potential barriers to managing patients with pharmacologic and/or nonpharmacologic treatment options, such as lack of insurance coverage or inadequate availability of certain HCPs who treat patients with pain, attempts should be made to address these barriers. The overall treatment approach and plan should be well documented in the patient record, including written agreements and informed consent/patient provider agreements (PPAs) that reinforce patient-provider responsibilities and avoid punitive tones.

I. COMPONENTS OF AN EFFECTIVE TREATMENT PLAN

1. The goals of treatment, including the degree of improvement in pain and function when function has been impaired by pain

2. Possible constituents of the treatment plan, including nonpharmacologic approaches and pharmacologic therapies

3. Patient/prescriber/health care team interactions, including

- Patient responsibilities/compliance with the plan
- Responsibilities of the prescriber and health care team, including patient monitoring
- Plans for reviewing functional goals
- Use of supplemental medication for intermittent increases in pain
- Use of PPAs

II. GENERAL PRINCIPLES OF NONPHARMACOLOGIC APPROACHES

Pain can arise from a wide variety of causes. There are a number of nonpharmacologic and self-management treatment options that have been found to be effective alone or as part of a comprehensive pain management plan, particularly for musculoskeletal pain and chronic pain. Examples include, but are not limited to, psychological, physical rehabilitative, and surgical approaches, complementary therapies,[12] and use of approved/cleared medical devices for pain management. HCPs should be knowledgeable about the range of treatment options available, the types of pain that may be responsive to those options, and when they should be used as part of a multidisciplinary approach to pain management. HCPs should also be aware that not all nonpharmacologic options have the same strength of evidence to support their utility in the management of pain, and some may be more applicable for some conditions than others.

III. GENERAL PRINCIPLES OF PHARMACOLOGIC ANALGESIC THERAPY

A variety of analgesics, including non-opioid and opioid medications, are available for use to manage pain symptoms. HCPs should be well informed about the range of analgesics available and the types of pain that may be responsive to those analgesics.

A. Non-opioid medications

When using non-opioid medications in pain management, HCPs should be knowledgeable about the following:

1. Mechanism of action of analgesic effect
2. Indications and uses for pain management
3. Routes of administration and formulations used in pain management
4. Initial dosing, dose titration, dose tapering (when appropriate) for analgesia
5. Contraindications
6. Adverse events, with emphasis on labeled warnings
7. Drug interactions — both pharmacodynamic and pharmacokinetic

B. Opioid analgesic medications

Opioid analgesic medications can be used successfully as a component of pain management. However, opioids carry risks not present with most non-opioid analgesics, specifically the risks

[12] For example, see https://nccih.nih.gov. Accessed July 2018.

of addiction, abuse and misuse, which can lead to respiratory depression, overdose and death. Therefore, it is the responsibility of HCPs to be knowledgeable, not just about the presence of such risks, but about how to weigh these risks before prescribing an opioid and about how to properly manage patients who are prescribed opioids, both for short-term and long-term use. When using opioid analgesics as part of pain management, HCPs should be knowledgeable about the following:

1. General precautions
   a. Even at prescribed doses, opioid analgesics carry the risk of misuse, abuse, opioid use disorder, overdose, and death
   b. Importance of the appropriate use of PDMPs[13] and their use as a clinical decision support tool
   c. DSM-5 (R) criteria (or the most recent version) for OUD and the concepts of abuse (taking an opioid to get high) vs. misuse (taking more than prescribed for pain or giving to someone else in pain)[14]
   d. The concepts of tolerance and physiological dependence and how they differ from OUD (addiction)
   e. Recognition that some opioid analgesics (e.g., Transmucosal Immediate Release Fentanyl products, some ER/LA products) are safe only for opioid-tolerant patients

2. Mechanism of action and analgesic effect

3. Types of opioids (full agonists, partial agonists)

4. Indications and uses for pain management

5. Range of opioid analgesic products available for pain management and their related safety concerns
   a. Routes of administration including oral, transmucosal, transdermal
   b. Release characteristics of immediate release (IR), extended-release (ER), long-acting (LA)
   c. Abuse-deterrent formulations (ADFs)
      - Definition of ADF based on the FDA guidance for industry, *Abuse-Deterrent Opioids – Evaluation and Labeling*[15]
      - Recognition that all ADFs have the same potential for addiction and overdose death as non-abuse-deterrent opioids
      - How to understand FDA-approved ADF product labeling

6. Initial dosing, dose titration, dose tapering (when appropriate) for analgesia
   a. Concepts and limitations of the conversion charts in labeling and the limitations of relative potency or equianalgesic dosing tables in literature

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[13] SAMHSA Prescription Drug Monitoring Programs: A Guide for Healthcare Providers. Accessed July 2018.

[14] American Psychiatric Association DSM-5-Opioid Use Disorder Diagnostic Criteria. Accessed July 2018.

[15] See FDA guidance for industry *Abuse-Deterrent Opioids —Evaluation and Labeling*. Accessed July 2018.

   b. Interindividual variability of response
   c. Special populations
      - Pregnant, postpartum, breastfeeding, and neonatal opioid withdrawal syndrome
      - Renal and hepatic impairment
      - Children and adolescents
      - Genetic and phenotypic variations
      - Older adults
      - Sleep disorders
      - Common and uncommon psychiatric disorders

7. Contraindications

8. Adverse Events
   a. Medication errors
   b. Periods of greater risk for significant respiratory depression, including at treatment initiation and with dose increases
   c. Serious adverse drug reactions (including overdose and death)
   d. Labeled warnings
   e. Common adverse drug reactions

9. Drug interactions
   a. Pharmacokinetic interactions based on metabolic pathway
   b. Pharmacokinetic and pharmacodynamic interactions with alcohol
   c. Concerns with particular drug–drug interactions, including, but not limited to:
      - Benzodiazepines and other central nervous system depressants, including alcohol
      - Monoamine oxidase inhibitors
      - Antidiuretic hormone drugs

10. Key safety strategies for use with opioid medications
    a. Dosing instructions including daily maximum
    b. Safe storage to reduce risk of accidental exposure/ingestion by household contacts, especially children/teens and to reduce risk of theft
    c. Naloxone products for use in the home to reduce risk of overdose deaths in patients and household contacts
    d. Proper disposal of used (e.g., transdermal systems) and unused opioids
    e. Pain management after an opioid overdose
    f. Driving and work safety

IV. MANAGING PATIENTS ON OPIOID ANALGESICS

HCPs should be knowledgeable about the appropriate use of opioids in patients with acute and chronic pain, including the importance of balancing potential benefits with the risks of serious adverse outcomes such as overdose and death.

A. Initiating treatment with opioids — acute pain

1. Patient selection — consider when an opioid is an appropriate option and consult the PDMP

2. Dosing — as needed vs. around-the clock dosing, prescribing an appropriate quantity based on the expected duration of pain, i.e., the least amount of medication necessary to treat pain and for the shortest amount of time

3. Naloxone for home use — prescribe and discuss the use of naloxone products and the various means of administration

4. Screening tools for risk of abuse

B. Initiating treatment with opioids — chronic pain

1. Patient selection
   a. Differences in benefit and risk and expected outcomes for patients with chronic pain, palliative care, or end-of-life care
   b. Differences in initiating treatment in opioid nontolerant vs. opioid-tolerant patients

2. Dosing
   a. As needed vs. around-the-clock
   b. How to determine a safe initial dose
   c. Safe conversion from other opioids

3. Considerations in opioid selection
   a. IR or ER/LA
   b. Special precautions with methadone
   c. Products restricted to opioid-tolerant patients

4. When and how to use an opioid or non-opioid analgesic to supplement pain management

C. Ongoing management of patients on opioid analgesics

1. Periodic review of pain and functional goals

2. Review adverse events at each visit
   - Eliciting signs or symptoms of opioid abuse
   - Screening for endocrine function may be recommended

- Importance of adverse event reporting and mechanisms to report

3. Review refill history/review PDMP

4. How to determine when an opioid analgesic is no longer necessary/beneficial

D. Long-term management

1. Evaluation of the patient with worsening pain for changes in underlying condition and for signs of OUD before increasing opioid dosage

2. Changing opioid medications
   - Concept of incomplete cross-tolerance when converting patients from one opioid to another
   - Concepts and limitations of the conversion charts in labeling and the limitations of relative potency or equianalgesic dosing tables in literature

3. Monitoring of patient adherence to the treatment plan, especially regarding misuse and abuse:
   - Perform medication reconciliation — recognize, document, and address aberrant drug-related behavior
   - Determine if nonadherence is due to inadequate pain management
   - Understand the utility and interpretation of urine drug testing (e.g., screening and confirmatory tests) and use as indicated
   - Screen and refer for substance use disorder treatment when concerns arise

E. How to recognize and intervene upon suspicion or identification of an OUD

HCPs should understand how to monitor patients taking opioid analgesics and identify the signs and symptoms of opioid misuse, abuse, and OUD and be knowledgeable about how to begin the process of intervention upon suspicion of an OUD.

F. When to consult with a pain specialist

HCPs should be knowledgeable about when referral to a pain management specialist is indicated, including identifying patients at high risk for OUD and patients unable to achieve adequate pain management.

G. Medically directed opioid tapering

HCPs should be knowledgeable about how to safely taper opioid analgesics, including how to recognize and manage signs and symptoms of opioid withdrawal. HCPs should be knowledgeable about the particular risks associated with tapering during pregnancy.

H. Importance of patient education

HCPs should recognize their role in reducing the risks associated with opioid analgesics through patient education at initiation of an opioid and throughout long-term management.

1. Inform patients about pain management expectations and managing pain through different pharmacologic and nonpharmacologic modalities.

2. Use the *Patient Counseling Guide: What You Need to Know About Opioid Pain Medicines* as part of discussion with patients and caregivers when prescribing opioid analgesics.

3. Counsel the patient about the following:
   a. Importance of adherence to prescribed dosing regimen
   b. Patients should use the least amount of medication necessary to treat pain and for the shortest amount of time
   c. The risk of serious adverse events that can lead to death
   d. The risk of addiction that can occur even when product is used as recommended
   e. Known risk factors for serious adverse events, including signs and symptoms of overdose and opioid-induced respiratory depression, GI obstruction, and allergic reactions, among others
   f. The most common side effects, along with the risk of falls, working with heavy machinery, and driving
   g. When to call the prescriber (e.g., managing adverse events, ongoing pain)
   h. How to handle missed doses
   i. The importance of full disclosure of all medications and supplements to all HCPs and the risks associated with the use of alcohol and other opioids/benzodiazepines
   j. Product-specific concerns, such as not to crush or chew ER products; transdermal systems and buccal films should not be cut, torn, or damaged before use, etc.
   k. How to safely taper dose to avoid withdrawal symptoms
   l. Safe storage and disposal, risks of theft by family members and household visitors
   m. Never share any opioid analgesic with another person
   n. How and when to use naloxone products and their various means of administration
   o. Seeking emergency medical treatment if an opioid overdose occurs
   p. How to report adverse events and medication errors to FDA (1-800-fda-1088 or via http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf)

V. ADDICTION MEDICINE PRIMER

HCPs should be knowledgeable about the basic elements of addiction medicine and be familiar with the definition, neurobiology, and pharmacotherapy of OUDs. In particular, stigmatizing or blaming language should be replaced with language that acknowledges that addiction,

reclassified as *substance use disorder*[16] in the revised Diagnostic Statistical Manual–V, is a disease. The term *opioid use disorder* [17] should be used when referring to the use of opioids, rather than other substances.

It should also be noted that there may be a different approach with a patient who misuses an opioid analgesic by taking the product differently than prescribed for the purpose of managing pain, in contrast to the patient who abuses an opioid analgesic with the intent of getting high. HCPs should be familiar with the following:

1. The neurobiology of OUD (addictive cycle)

2. Use of screening tools to identify patients at risk, based on known risk factors, and to identify patients developing signs of opioid dependence or addiction as early as possible.

3. Management of OUD, including the types of pharmacologic and nonpharmacologic treatments available and when to refer to an addiction medicine specialist.

[16] Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association.

[17] Id.