# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 214044Orig1s000

# SUMMARY, CROSS DISCIPLINE TEAM LEADER AND CLINICAL REVIEW

# NDA Clinical/CDTL/Division Director Review

| | |
|---|---|
| Application Type | NDA |
| Application Number | 214044 |
| Priority or Standard | Standard |
| Submit Date | 11/01/2019 |
| Received Date | 11/01/2019 |
| PDUFA Goal Date | 09/01/2020 |
| Division/Office | DAAP/ON/OND |
| Reviewer Names | Izabella Khachikyan, MD<br>Naomi Lowy, MD, Acting Deputy Director |
| Review Completion Date | August 28, 2020 |
| Established/Proper Name | Tramadol HCl oral solution |
| Proposed Trade Name | QDOLO |
| Applicant | Athena Bioscience, LLC |
| Dosage Form | Oral solution |
| Applicant Proposed Dosing Regimen | Start at 25 mg/day and titrate 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, QDOLO 50 mg to 100 mg can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg/day. |
| Applicant Proposed Indication/Population | Management of pain severe enough to require an opioid analgesic for which alternative treatments are inadequate |
| Regulatory Action | Approval |

DAAP = Division of Anesthesiology, Addiction Medicine, and Pain Medicine
ON = Office of Neuroscience
OND = Office of New Drugs

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## Glossary

| | |
|---|---|
| AUC | area under the concentration-time curve |
| $AUC_{0-\infty}$ | area under the concentration-time curve from time zero to infinity (also $AUC_{0-inf}$) |
| $AUC_{0-t}$ | area under the concentration-time curve from time zero to time *t* |
| BMI | body mass index |
| $C_{max}$ | maximum concentration |
| CMC | chemistry, manufacturing, and controls |
| CSA | Controlled Substances Act |
| CSS | Controlled Substance Staff |
| CYP | cytochrome P450 |
| DEA | Drug Enforcement Administration |
| DEPI | Division of Epidemiology II |
| DMEPA | Division of Medication Error Prevention and Analysis |
| DPV | Division of Pharmacovigilance |
| ER | extended release |
| iPSP | initial pediatric study plan |
| IR | intermediate release |
| ISS | integrated summary of safety |
| N/A | not applicable |
| OTC | over the counter |
| PI | prescribing information |
| PK | pharmacokinetics |
| R | reference product |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| T | test product |

# 1. Executive Summary

## 1.1. Product Introduction

Tramadol is a μ-opioid agonist and a norepinephrine and serotonin re-uptake inhibitor. It has been marketed for more than 20 years with a relatively well-characterized safety profile. The Applicant has developed an oral solution of tramadol. This application is submitted as a 505(b)(2) New Drug Application (NDA) referencing Ultram (NDA 20281), rather than an Abbreviated New Drug Application (ANDA) to an approved tramadol product because the dosage form, an oral solution, is novel compared to Ultram tablets.

This drug is an oral solution of tramadol for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The Applicant is seeking the same indication and the same dosing as Ultram and is relying on previous findings on its safety and effectiveness.

Dosing recommendations emphasize the need to individual therapy and to use the lowest effective dose for the shortest duration needed. Specific instructions are: Start at 25 mg/day and titrate 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, QDOLO 50 mg to 100 mg can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg/day (2.3, 2.4).

Tramadol exerts much if its analgesic effect through a major metabolite. Tramadol is metabolized by the cytochrome P450 (CYP) enzymes CYP2D6 and CYP3A4 to O-desmethyltramadol (M1) and N,O-desmethyltramadol (M5) in the liver. O-Desmethyltramadol (M1) is a more potent compound whose activity is mediated by binding to mu opioid receptors.

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has supported the efficacy of 50 mg/10 mL tramadol oral solution by demonstrating comparable pharmacokinetics in healthy volunteers compared to Ultram, the reference product, for the proposed indication.

The Applicant performed two pharmacokinetic (PK) studies, one under fasted and one under fed conditions, comparing the proposed product to Ultram. Data from these studies shows that the two formulations are bioequivalent. This provided the scientific bridge that is required to support efficacy of the proposed product by using the Agency's prior finding of efficacy for Ultram.

## 1.3. Benefit-Risk Assessment

## Benefit-Risk Integrated Assessment

The proposed product is an oral solution of tramadol, a μ-opioid agonist and a norepinephrine and serotonin re-uptake inhibitor. Tramadol (Ultram) has been marketed for more than 20 years and has a relatively well-characterized safety profile. A liquid formulation of tramadol has never been approved. A liquid formulation could benefit patients who have difficulty swallowing, including those with feeding tubes or who prefer a liquid formulation over a tablet.

The benefit-risk assessment of tramadol oral solution incorporates the components described in the Agency's draftguidance Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework, Guidance for Industry (June 2019). These considerations are summarized here:

A. Benefits to the Patient Using the Drug as Labeled

- Clinical efficacy and safety studies were not conducted. The Applicant performed two pharmacokinetic (PK) studies comparing the proposed product to Ultram, the reference product. Data from these studies showed that the two formulations are bioequivalent. This provided the scientific bridge that that is required to support efficacy of the proposed product by using the Agency's prior finding of efficacy for Ultram.
- The proposed indications for tramadol HCl solution are identical to those for the already-approved Ultram oral tablet. The proposed dosing is consistent with the approved labeled dosage of Ultram oral tablet. Efficacy of tramadol has been established for different types of pain, including incisional and neuropathic pain, both acute and chronic pain, and pain of moderate to severe intensity.
- An oral solution may provide a benefit to patients, including those who are fed through feeding tubes, who cannot swallow a tablet, thereby eliminating the need to crush pills and mix them into a different liquid.
- Efficacy of tramadol oral solution will be studied in children ages 12 to <17 years as part of a Pediatric Research Equity Act Post-Marketing Requirement (PREA PMR).

B. Risks to the Patient Using the Drug as Labeled

- The safety profile of tramadol is relatively well-characterized.
- Adverse events reported in the PK studies, vomiting and epigastric pain, are consistent with the known safety profile of tramadol. No additional safety studies were conducted.
- Tramadol solution is intended for adults only. The packaging specifies "for adults only."
- The FDA Adverse Event Reporting System can adequately monitor for any long-term effects that may occur in a community setting.
- Safety of tramadol oral solution will be studied in children ages 12 to <17 years as part of a Pediatric Research Equity Act Post-Marketing Requirement (PREA PMR).

C. Effectiveness and Safety of the New Drug Relative to Approved Analgesics

- Tramadol oral solution is bioequivalent to Ultram. Tramadol has a relatively well-characterized safety profile.
- There are no data to suggest that tramadol has any advantage over other available approved analgesic drugs.
- Tramadol oral solution may be more convenient for patients who would otherwise require crushing of a tablet into solution, such as those have difficulty swallowing tablets or for patients requiring nasogastric administration of medications.
- Accurate dosing of tramadol oral solution requires use of a proper measuring device, not common household items. Without the use a proper measuring device, the medication may be underdosed or overdosed compared to a tablet.
    - The need for accurate dosing is reflected in the Boxed Warning and Section of the label.

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

- 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). 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.
- As of August 18, 2014, the Drug Enforcement Administration placed tramadol (including its salts, isomers, and salts of isomers) as Schedule IV under the Controlled Substances Act (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 Controlled Substances Act, have a currently accepted medical use in treatment in the United States, 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)].
- Tramadol (HCl) oral solution is expected to have an oral abuse potential similar that of tramadol immediate release (Ultram) tablet.
- Product-specific characteristics
    - This would be the first approved oral solution of tramadol.
    - Tramadol is contraindicated in all children 12 years of age and younger and is also contraindicated in children 12 to 17 years of age who require postoperative pain management following tonsillectomy and/or adenoidectomy.
    - The review team, in consultation with the Division of Epidemiology II, considered whether an oral liquid tramadol product may confer a different public health risk compared to the solid dosage form, the Division of Epidemiology II reviewed all available data. This included a review of data on tramadol pediatric utilization patterns and on the frequency of opioid misuse and nonmedical use by dosage form for consideration of tramadol oral solution. Morphine and oxycodone are available as oral solutions.
    - The review of these data led to the following conclusions:
        - Tramadol is infrequently prescribed to children. The number of pediatric patients 0-17 years prescribed tramadol-containing prescriptions decreased by half from 2015 through 2019. Pediatric specialty prescribers wrote <1% of the total dispensed tramadol-containing prescriptions from U.S. retail pharmacies in 2019. According to the U.S. office-based physician surveys, drug use mentions for tramadol-containing products from 2015 through 2019 aggregated for pediatric patients 0-17 years were too infrequent to provide reliable national estimates of pediatric diagnoses associated with tramadol mentions.
        - Although the data are limited on misuse and nonmedical use of morphine and oxycodone by dosage form, they do suggest that misuse or abuse of an oral liquid opioid may be less than or similar to that of an oral solid product. Cases of misuse or abuse of the oral liquid product by the injection route were minimal.
    - It is expected that tramadol oral solution would have an oral abuse potential similar that of tramadol immediate-release (Ultram) tablets.
    - This product is intended for patients who cannot swallow solid pills. Such limited distribution would likely assist in mitigating abuse of this product. This patient population would also be unlikely to abuse the product.
    - It is unlikely that tramadol oral solution will be abused by intravenous injection for the following reasons:
        - The concentration (25 mg/5mL) is likely too low to support intravenous abuse.

- When tramadol is administered intravenously, production of the metabolite M1, which provides most of the analgesic effect, is minimalized. This is because first-pass metabolism required for the production of M1 is avoided. Therefore, abuse of tramadol intravenously is not an attractive route for abusers.

- The carton of this product will include the words “For Adults only” to reiterate that this solution is not a pediatric formulation.

E. Risk Management

- Tramadol is an opioid and a Schedule IV controlled substance considered to have potential for abuse. If approved, tramadol oral solution will be subject to the Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits outweigh potential risks in the outpatient setting.

## Benefit-Risk Dimensions

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | Pain impacts millions of people and is the most common reason for seeking medical help.<br>Effective pain management leads to faster recovery and fewer complications.<br>Inadequate treatment of pain can have long-term physical and psychological consequences.<br>Pain can significantly impact the functioning and quality of life of the patient. | Inadequate treatment of pain can have long-term physical and psychological consequences. |
| Current Treatment Options | The treatment of pain is generally individualized to achieve the optimal outcome.<br>In some instances, treatment of pain with acetaminophen, nonsteroidal anti-inflammatory drugs, and non-opioid analgesics is inadequate, necessitating an opioid-containing product.<br>A number of tramadol HCl formulations have been approved by FDA for treatment of pain severe enough to require an opioid analgesic.<br>Tramadol oral formulations are available as a tablet and capsule that contain either tramadol alone (under the brand names Ultram and Conzip and multiple generic products) or combinations of tramadol and acetaminophen (under the brand name Ultracet and multiple generic products). | Treatment of pain is an unmet medical need.<br>The proposed product would be the first FDA-approved oral solution dosage for tramadol.<br>There are no data to support a conclusion that tramadol oral solution has an advantage compared to other approved analgesic drugs.<br>Tramadol oral solution would add an option to the existing armamentarium for the treatment of pain severe enough to require an opioid. |
| Benefit | The efficacy of the tramadol (HCl) oral solution is supported by a scientific bridge between the proposed product and the reference product in two pharmacokinetics (PK) studies.<br>The Applicant has relied on the Agency's previous finding of efficacy for Ultram.<br>A liquid formulation of tramadol may be convenient for patients who cannot swallow a tablet or patients who prefer not to take an oral tablet. | The available data provide adequate evidence to support the safety and efficacy of tramadol (HCl) oral solution for the proposed indication. |
| Risk and Risk Management | The Applicant has relied on the Agency's previous finding of safety for Ultram. The PK data demonstrated bioequivalence between tramadol oral solution and tramadol tablet.<br>Safety data from two pharmacokinetic studies for tramadol oral solution did not show any unexpected adverse events given the characterized safety profile of tramadol.<br>Safety data collected in the PK studies are consistent with the established safety profile of tramadol.<br>The abuse potential of tramadol (HCl) oral solution is expected to be like that of tramadol immediate release (Ultram) tablets. | Tramadol has a relatively well-characterized safety profile.<br>Tramadol oral solution has the potential for abuse, misuse, and addiction.<br>Abuse of tramadol oral solution by the intravenous route is unlikely.<br>The FDA Adverse Event Reporting System can adequately monitor for any long-term adverse events that may occur with off-label use of tramadol oral solution.<br>If approved, tramadol (HCl) oral solution will be subject to the Opioid Analgesic Risk Evaluation and Management Strategy to |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | It is unlikely that Tramadol HCL oral solution will be abused by intravenous injection.<br>The concentration (25 mg/5mL) is likely too low to support intravenous abuse and the intravenous route is an uncommon and unattractive route of abuse for tramadol because it avoids first-pass clearance which is required for production of the major metabolite.<br>Tramadol oral solution has not been formulated with any excipients that could influence its abuse-deterrent characteristics.<br>Tramadol oral solution, as an opioid, has all of the risks associated with opioid medications, including abuse, misuse, addiction, and criminal diversion.<br>A safety assessment based on the available data did not raise any new safety concerns. | ensure that its benefits outweigh the potential risks in the outpatient setting.<br>The overall benefit-risk assessment favors approval of this product for the proposed indication. |

## 1.4. Patient Experience Data

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|---|---|---|---|---|
| □ | The patient experience data that was submitted as part of the application include: | | | Section where discussed, if applicable |
| | □ | Clinical outcome assessment (COA) data, such as | | [e.g., Section 6.1 Study Endpoints] |
| | | □ | Patient-reported outcome (PRO) | |
| | | □ | Observer-reported outcome (ObsRO) | |
| | | □ | Clinician-reported outcome (ClinRO) | |
| | | □ | Performance outcome (PerfO) | |
| | □ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | | |
| | □ | Patient-focused drug development or other stakeholder meeting summary reports | | [e.g., Section 2.1 Analysis of Condition] |
| | □ | Observational survey studies designed to capture patient experience data | | |
| | □ | Natural history studies | | |
| | □ | Patient preference studies (e.g., submitted studies or scientific publications) | | |
| | □ | Other: (Please specify) | | |
| □ | Patient experience data that were not submitted in the application, but were considered in this review: | | | |
| | | □ | Input informed from participation in meetings with patient stakeholders | |
| | | □ | Patient-focused drug development or other stakeholder meeting summary reports | [e.g., Current Treatment Options] |
| | | □ | Observational survey studies designed to capture patient experience data | |
| | | □ | Other: (Please specify) | |
| X | Patient experience data was not submitted as part of this application. | | | |

# 2. Therapeutic Context

## 2.1. Analysis of Condition

Pain is the most common reason for seeking medical attention. Pain is defined as a subjective and emotional experience and is a multifactorial medical condition that can occur in a variety of clinical settings, such as trauma, musculoskeletal injury, nerve injury, visceral distention and inflammation, and after surgical procedures. Pain can significantly impact the function and quality of life of a patient. Untreated or inadequately treated pain can result in progression of acute pain to chronic pain, which potentially has long-term physical and psychological consequences.

Because pain is subjective and varies among patients, the treatment approach is generally individualized. The treatment choice will be based on the most favorable benefit-to-risk ratio for the condition being treated. There are multiple therapeutic approaches for acute pain, including pharmacologic and non-pharmacologic modalities.

The pharmacologic options for acute-pain control include multiple classes of medications, such as acetaminophen, nonsteroidal anti-inflammatory drugs, anesthetics (such as lidocaine), anticonvulsants, antidepressants, opioids (tramadol and tapentalol), and combination products containing two or more different medications.

In cases in which non-opioid medications do not adequately control pain, opioid medications with or without a non-opioid can be considered. The choice of opioid is based upon the intensity and duration of the pain, the preferred mode of administration, associated adverse effects, and prior experience. Oral agents are used for moderate-to-severe pain if the patient is able to tolerate oral medication.

## 2.2. Analysis of Current Treatment Options

The tramadol products currently marketed in the United States are oral tablet and capsule formulations that contain either tramadol alone (under the brand names Ultram and Conzip and multiple generic products) or a combination of tramadol and acetaminophen (under the brand name Ultracet and multiple generic products).

The first tramadol product, Ultram, was approved in the United States in March 1995, and is an immediate-release (IR) formulation approved for treatment of moderate to moderately severe pain in adults.

Five other tramadol products have been approved since March 1995:

- Ultracet (NDA 21123), approved in August 2001. This is an IR tramadol and acetaminophen combination product for short-term (≤5 days) management of acute pain.
- Ultram ODT (NDA 21693), approved in May 2005, is an IR orally disintegrated tramadol for moderate to moderately severe pain in adults.

- The first extended-release (ER) tramadol product, Ultram ER tramadol (NDA 21692), was approved in September 2005 for the management of pain severe enough to require daily around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
- Ryzolt (NDA 21745), an ER tramadol tablet product, was approved in December 2008. Ryzolt was approved for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time.
    - Ryzolt differs from Ultram ER in that it has a core (b) (4) and an outer coat (b) (4).
- Conzip (NDA 22370), ER tramadol capsules for oral administration was approved in May 2010. for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

On August 18, 2014, the U.S. Drug Enforcement Administration (DEA) placed tramadol-containing products into Schedule IV of the Controlled Substances Act (CSA). Schedule IV drugs are defined by the DEA as having low potential for abuse and a low risk of dependence. Tramadol in the only opioid analgesic with a Schedule-IV classification that is approved by FDA for the management of pain.

The Applicant anticipated that oral tramadol solution would be used for the treatment of pain in patients who require or prefer a solution rather than a tablet.

# 3. Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

Ultram (NDA 20281) was initially approved by the FDA on March 3, 1995. 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 Applicant is seeking the same indication and the same dosing as Ultram and is relying on FDA's previous findings of safety and effectiveness.

In December 2015, an FDA Advisory Committee was convened to discuss the risks of codeine in children. Following this meeting, the Division of Anesthesia, Analgesia, and Addiction Products and the Division of Pulmonary, Allergy, and Rheumatology Products added a new contraindication to codeine-containing products for all children less than 12 years of age. This contraindication expands on the currently approved contraindication against use for postoperative pain management in children of any age who have undergone tonsillectomy and/or adenoidectomy. Because tramadol follows the same metabolic pathway as codeine, the same contraindication was added to the labeling of tramadol-containing products.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

On November 12, 2019, Athena Bioscience, LLC submitted an NDA seeking approval for tramadol oral solution through the 505(b)(2) regulatory pathway with the proposed proprietary name of QDOLO. The application references the FDA's previous findings on the safety and effectiveness of Ultram. The Applicant also performed two bioavailability studies.

In 2015, (b) (4) submitted a request to a meeting to discuss the development plan for tramadol injection and tramadol oral solution. The Division determined that written responses to the submitted questions would be the most appropriate way for responding to the meeting request.

The responses to the questions were communicated to the Applicant on October 7, 2015. The responses regarding regulatory and clinical issues included:

1. The Division agreed with the 505(b)(2) regulatory pathway for tramadol oral solution as appropriate for the planned NDA relying on the Agency's previous findings of safety and effectiveness for Ultram (NDA 20281), sponsored by Janssen Pharmaceuticals, Inc.
2. The Division advised that a definitive study; i.e., a relative bioavailability study, comparing the proposed product and Ultram tablets will be required to establish a scientific bridge to the reference product. It was further noted that they also must demonstrate that for the oral solution formulation, food has a comparable or smaller effect on the proposed product compared to the listed drug.
3. The Division communicated to the Applicant that an initial Pediatric Study Plan (iPSP) describing how the Applicant plan to fulfill the requirements to conduct a pediatric assessment for the proposed product, under the Pediatric Research Equity Act (PREA). The plan must be agreed upon prior to submission of the NDA.

On February 27, 2018, IND 127021 was submitted. On September 25, 2019 the Division was notified of a change in ownership of the rights and responsibilities for IND 127021 for tramadol oral solution from (b) (4) to Athena Bioscience, LLC.

The Sponsor submitted their IND proposing to evaluate the PK of 50 mg/10 mL oral tramadol solution in healthy volunteers under fasting and fed conditions. The proposed bioavailability studies involved the oral administration of a single dose of tramadol.

The Food and Drug Administration Modernization Act requires that applicants submit an application for a drug subject to the PREA to submit an iPSP early in the development process. The Applicant submitted their iPSP on February 27, 2018, which included (b) (4) The Division did not agree to (b) (4). On May 16, 2018, in response to the iPSP, the Division communicated the following issues to the Applicant:

1. For patients <12 years of age, it is reasonable to request a partial waiver based on the evidence strongly suggesting that the drug is unsafe.

2. For patients 12 to <17 years of age, studies are needed. Although extrapolation is generally acceptable for pure opioid receptor agonists, the mechanism of action of tramadol includes weak inhibition of reuptake of norepinephrine and serotonin in addition to mu opioid receptor binding. Therefore, evaluation of the PK, safety, and efficacy is needed. In the study, exclude patients who have risk factors that may increase their sensitivity to the respiratory-depressant effect of tramadol—such as obesity, obstructive sleep apnea, and other respiratory conditions—as described in the safety labeling change dated August 29, 2017.

On August 9, 2019, the iPSP, which incorporated modifications of the pediatric study plan in the iPSP, was submitted to the Agency.

August 28, 2019 the Division discussed the pediatric plan with the Pediatric Review Committee and recommended the following:

1. Deferral of pediatric studies for patients ≥12 and <17 years of age until after drug approval and initiation of a clinical trial in adolescents (≥12 and <17 years of age) upon approval
2. Partial waiver for pediatric patients <12 years of age, because tramadol is contraindicated for patients in this age range.

The following estimated timelines are for the planned clinical efficacy and safety studies in pediatric patients 12 to <17 years of age:

- Final Protocol Submission: December 2020
- Study Completion: February 2024
- Final Report Submission: August 2024

### 3.3. Foreign Regulatory Actions and Marketing History

There is no foreign marketing development for oral tramadol solution.

## 4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

### 4.1. Office of Scientific Investigations

The Division of Generic Drug Study Integrity within the Office of Study Integrity and Surveillance inspected the clinical site under the following submissions (ANDA (b) (4), (b) (4), (b) (4), and (b) (4)) in February 2019. Therefore, it was determined that an inspection for the 197/18 and 198/18 PK studies was not warranted at this time.

## 4.2. Product Quality

The Quality Assessment team (Drs. Kelly, Christner, Bow, Pinto, Moore, Waches, Crenshaw, Craig, Lalmansingh, and Amspacher) recommends approval.

According to the team's review, the manufacturing process for this non-sterile oral solution involves (b) (4). The process is relatively simple, and the manufacturing parameters and controls were shown to be adequate to mitigate risks.

The applicant has adequately demonstrated the stability of the drug product over 24 months when stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

## 4.3. Clinical Microbiology

Not applicable because the product is not a therapeutic antimicrobial.

## 4.4. Nonclinical Pharmacology/Toxicology

The nonclinical team (Drs. Emami, Chang, and Mellon) recommends approval with the recommended labeling revisions and a post-marketing requirement for a juvenile animal study.

No nonclinical studies were conducted with the proposed drug product. The Applicant intends to rely on the safety and exposure data of the listed product, Ultram, (NDA 20281, 50 mg oral tablet) and the published literature for tramadol, which includes acute and chronic exposure.

The components of the container closure system are all food contact compliant, therefore extractable/leachable studies are not needed. An extractable study was conducted by the Applicant and no extractables were detected that would pose a safety concern.

To support the Pregnancy and Lactation Labeling Rule (PLLR) sections of labeling, the Applicant provided a review of the nonclinical literature, and the review team searched the literature as well. The nonclinical team agrees with the Applicant to include findings from a published article by Aboulhoda et al. (2018) that demonstrated that tramadol administration at doses at or below the maximum recommended human daily dosage (MRHD) of Tramadol Oral Solution based on body surface area-comparison to pregnant rats from Gestation Day 10 to 21 caused cerebellar cortex structural abnormalities in rat pups examined postnatally. In addition, the literature review identified multiple studies suggesting adverse effects on the male reproductive system consistent with and supportive of the current labeling.

Based on the agreed initial Pediatric Study Plan (iPSP) on September 3, 2019, juvenile animal toxicology studies are planned to address potential acute CNS toxicity. The juvenile animal toxicology studies will be performed concurrently with the planned efficacy, safety, and pharmacokinetic study in pediatric patients 12-17 years of age. The team agrees that these studies may be completed post-approval.

Finally, the Applicant submitted a toxicological risk assessment for intravenous administration (unintended route of abuse) of the drug product formulation components. For each of the

components, the Applicant performed a literature review to determine the information available on its toxicity, calculated a permitted daily exposure, and performed route-to-route extrapolation as necessary to assess its toxicity by the intravenous route. Although the risk assessment provided was informative, the data are not adequate to fully assess the risk of intravenous administration. However, because the review team believes that the likelihood of abuse by the intravenous route is low, more definitive toxicity assessments to inform the potential intravenous risk will not be required.

## 4.5. Clinical Pharmacology

The Clinical Pharmacology team (Drs. Lee and Xu) recommends approval. Refer to their review for the full assessment.

The Applicant conducted two comparable bioavailability studies. One study was done under fasting conditions and the second under fed conditions.

*Study 197/18 (Fasting)*

Study 197/18, considered the "pivotal" bioavailability study, was an open-label, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, crossover oral relative bioavailability study of tramadol oral solution (50 mg/10 mL) and Ultram tramadol tablet (50 mg). Details of the protocol and safety results are described in Section 6 and 8.

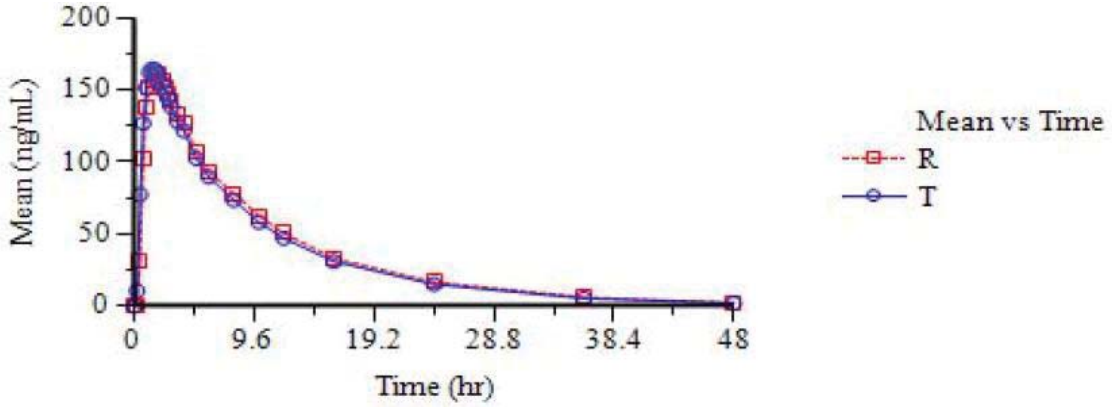
The study involved administration of the following:

- Test product: 50 mg/10 mL tramadol HCl oral solution. Ten milliliters of solution as a single dose for each subject, together with 240±2 mL of water.
- Reference product: 50 mg tramadol HCl tablet (Ultram) as a single dose to each subject, together with 240±2 mL of water.

Figure 1 shows plasma concentration vs time for tramadol (1a) and the metabolite O-Desmethyl tramadol (1b) under fasting conditions (Study 197/18). Table 1 summarizes the PK parameters in this study. These data support the conclusion that the two products are bioequivalent.

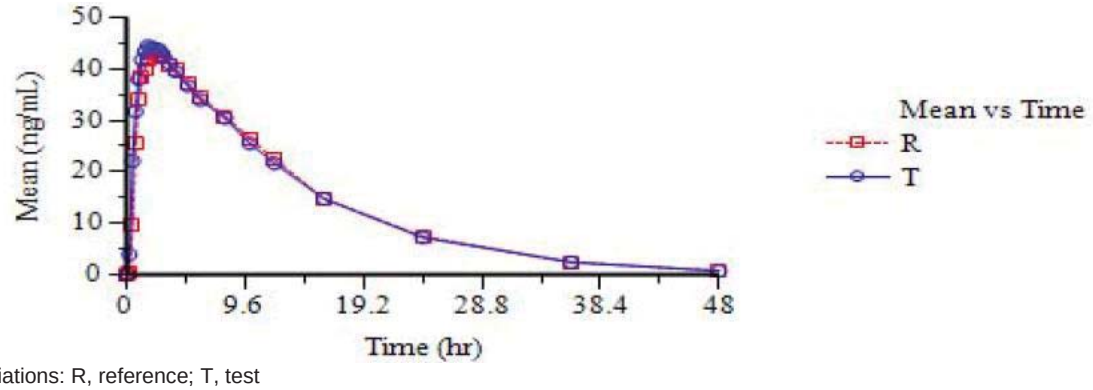
**Figure 1: Mean Tramadol (1a) and M1, O-Desmethyl Tramadol (1b) plasma concentration versus time under fasted conditions (Study 197/18).**

**Figure 1a.**




Abbreviations: R, reference; T, test
Source: Adapted from Applicant's submission, NDA 214044 2.7.6: Synopses of Individual Studies

**Figure 1b.**




Abbreviations: R, reference; T, test
Source: Adapted from Applicant's submission, NDA 214044 2.7.6: Synopses of Individual Studies

## Table 1: Summary of Pharmacokinetic Data in Study 197/18

| | Arithmetic Mean ± SD (N = 33) | |
|---|---|---|
| | **Test product (T)** | **Reference product (R)** |
| $^{\#}T_{max}$ (hr) | 1.500 (0.500 – 2.500) | 1.500 (0.750 – 3.000) |
| $C_{max}$ (ng/mL) | 180.2017 ± 33.80524 | 173.5143 ± 29.58931 |
| $AUC_{0-t}$ (hr*ng/mL) | 1623.9252 ± 502.42885 | 1681.6377 ± 578.06464 |
| $AUC_{0-inf}$ (hr*ng/mL) | 1658.3115 ± 525.96905 | 1721.4670 ± 624.71658 |
| $t_{1/2}$ (hr) | 7.6460 ± 1.63351 | 7.6095 ± 1.81820 |
| $K_{el}$ (1/hr) | 0.0951 ± 0.02256 | 0.0959 ± 0.02193 |

Source: Applicant's submission

*Study 198/18 (Food effect study)*

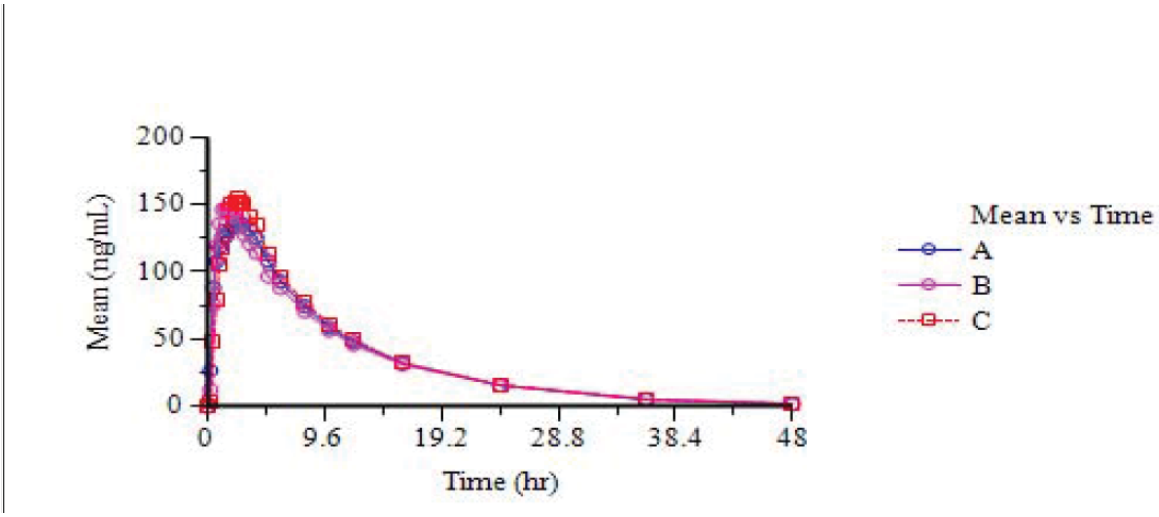
Study 198/18 was an open-label, balanced, randomized, single-dose, three-treatment, three period, three-sequence, crossover, food effect (fed vs. fasting) trial involving three treatment arms:

> Treatment A: Tramadol HCl oral solution (10 mL) as a single dose to each subject (30 minutes after breakfast), together with 240±2 mL of water.
> Treatment B: Tramadol HCl oral solution (10 mL) as a single dose to each subject (at least 10 hours [or overnight] after the last meal), together with 240±2 mL of water.
> Treatment C: Tramadol HCl 50 mg tablet as a single dose to each subject (at least 10 hours [or overnight] after the last meal), together with 240±2 mL of water.

Figure 2 shows mean tramadol (2a) and O-desmethyl tramadol (2b) plasma concentration versus time under fed and fasted conditions (Study 198/18). The study 198/18 demonstrated that no food effect was observed for tramadol HCL oral solution, based on the bioequivalence analysis results.

**Figure 2: Mean plasma concentrations profiles of tramadol (2a) and O-Desmethyl tramadol (2b) plasma concentration versus time under fed and fasted conditions (Study 198/18).**

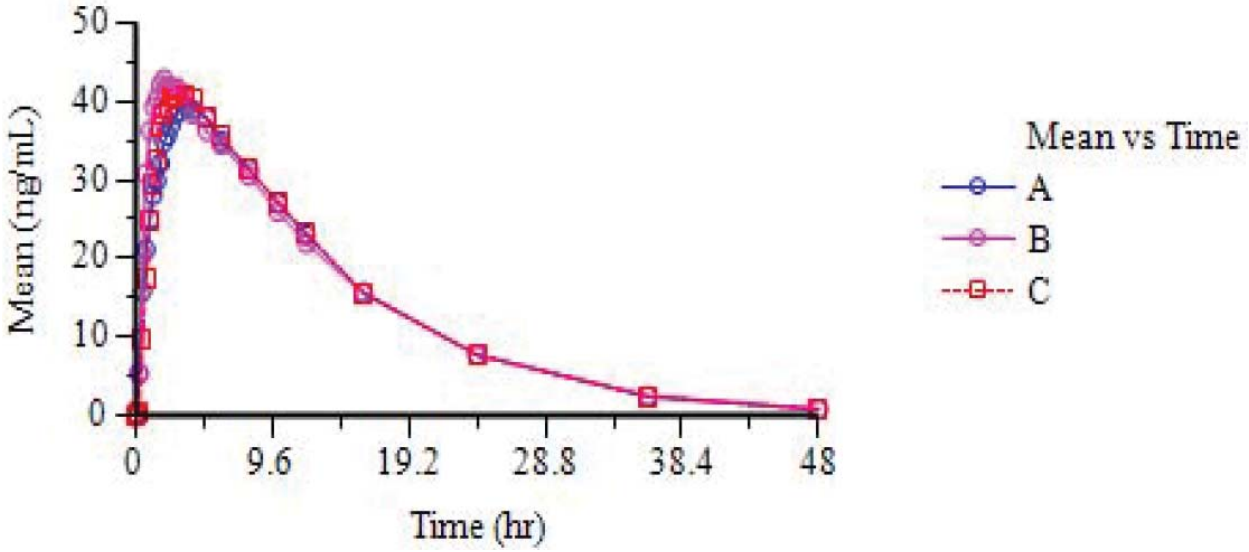
**Figure 2a.**




A: 'Test' Formulation - Tramadol hydrochloride oral solution 5 mg/mL Fed
B: 'Test' Formulation - Tramadol hydrochloride oral solution 5 mg/mL Fasted
C: 'Reference Formulation' - Ultram 50 mg tablet Fed

Source: Adapted from Applicant's submission, NDA 214044, 2.7.6: Synopses of Individual Studies

**Figure 2b.**




A: 'Test' Formulation - Tramadol hydrochloride oral solution 5 mg/mL Fed
B: 'Test' Formulation - Tramadol hydrochloride oral solution 5 mg/mL Fasted
C: 'Reference Formulation' - Ultram 50 mg tablet Fed

Source: Adapted from Applicant's submission, NDA 214044, 2.7.6: Synopses of Individual

# 5. Sources of Clinical Data and Review Strategy

## 5.1. Table of Clinical Studies

The two bioavailability studies performed in support of the NDA are summarized in Table 3.

**Table 1: Clinical Trials Supporting NDA 214044**

| Trial Identity | NCT No. | Trial Design | Regimen/Schedule/Route | Safety Endpoints | Treatment Duration/ Follow Up | No. of Patients Enrolled | Study Population | No. of Centers and Countries |
|---|---|---|---|---|---|---|---|---|
| 197/18 | N/A | Open-label, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, crossover study under fasting conditions | Test drug: Tramadol hydrochloride 25 mg/5 mL oral solution<br>Reference product: Oral solution tramadol HCl (Ultram) 50 mg tablet | No safety endpoints defined | Single dose with a 7-day washout period | N=36 | Healthy adult male volunteers | Trial conducted outside of the United States |
| 198/18 | N/A | Open-label, balanced, randomized, single-dose, three-treatment, three-period, three-sequence, crossover, food-effect study | Test drug: Tramadol hydrochloride 25 mg/5 mL oral solution<br>Reference product: Oral solution tramadol HCl (Ultram) 50 mg tablet | No safety endpoints defined | Three single doses were administered with a 7-day washout period between each dose OR | N=18 | Healthy adult male volunteers | Trial conducted outside of the United States |

Abbreviations: N/A, not applicable; NCT, National Clinical Trial

### 5.2. Review Strategy

The Clinical Review focused on the review of safety data from the two PK studies, lab values and individual case reports.

## 6. Review of Relevant Individual Trials Used to Support Efficacy

### 6.1. Study 197/18

This study was an open-label, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, crossover oral bioavailability study of tramadol HCl oral solution (50 mg/10 mL) and Ultram, tramadol HCl tablet (50 mg), in healthy adult volunteers.

### 6.1.1. Study Design

**Objectives**

1. To compare the rate and extent of absorption of tramadol HCl oral solution (50 mg/10 mL) and Ultram (50 mg tramadol HCl tablets) in healthy adult volunteers under fasting conditions.
2. To assess the safety and tolerability of the study drug after oral administration.

**Location**

The study was conducted outside of the United States (India).

The intent of the study was to compare formulations, not to assess PK differences for race or sex. If bioequivalence is established in one population, bioequivalence will also apply to other populations. Therefore, the population for this study is acceptable.

**Population**

The study involved 36 healthy adult volunteers 18 to 45 years of age.

**Key Inclusion and Exclusion Criteria**

Healthy volunteers, age 18 to 45, were enrolled. Potential subjects were excluded if they used a alcohol in the past year or had a history of smoking (more than 10 cigarettes a day), were hypotensive or hypertensive (systolic <90 or >140 mmHg or diastolic <60 or >90 mmHg), bradycardic or tachycardic (<50 or >100 beats/minute), used any xanthine-containing food, beverage, or grapefruit 48 hours prior to the study, used any prescribed medications or over-the-counter (OTC) medications 2 months prior to the study, or were pregnant, currently breast-feeding, or likely to become pregnant during the study.

**Trial Design**

The trial was designed to enroll thirty-six subjects in this open-label, balanced, randomized, two-treatment, two-period, two-sequence, crossover, single-dose, oral bioavailability study in healthy adults under fasting conditions. Subjects were monitored starting 11 hours before administration of the drug followed by drug administration for up to 48 hours post-dose, including an at least 7-day washout period between the treatments (Table 2).

**Table 2: Treatment Schedule**

| | |
|---|---|
| **Test Product (T)** | |
| Name of the product | Tramadol HCl oral solution |
| Dose | 50 mg/10 mL |
| Dosing schedule | 10 mL of solution as a single dose to each subject |
| Route/mode of administration | Orally with 240±2 mL of water |
| Treatment period | Single dose in the study per randomization schedule |
| **Reference Product ®** | |
| Name of the product | Ultram (tramadol HCl tablets) |
| Dose | 50 mg |
| Dosing schedule | One tablet as a single dose to each subject |
| Route/mode of administration | Orally with 240±2 mL of water |
| Treatment period | Single dose in the study per randomization schedule |

Dosing will occur on 1 day in each period (including a gap of at least 7 days between two successive treatment schedules).
Reference product: After overnight fasting for at least 10 hours, one tablet of reference product ®, together with 240±2 mL of water, will be administered to the subject.
Test product: 10 mL of test product (T) will be administered orally to the subject in a 10 mL syringe. After the subject swallows the test product, the syringe is rinsed two to three times with an adequate amount of water from the given 240±2 mL, and the subject swallows the rinse. Compliance with dosing is assessed by evaluation of the oral cavity immediately after introducing the drug.

## Procedures/Assessment

The frequency and timing of assessments, laboratory tests and blood samples were adequate.

All participants underwent screening, including a physical examination, electrocardiogram, laboratory tests, urine tests, and chest X-ray. Screening took place within 28 days before the start day of the study. The assessments performed in the study are listed in Table 3.

**Table 3: Schedule of Assessments**

| | Screening ('-28' days to day '-1') | Period I and II | | | |
|---|---|---|---|---|---|
| | | Day '-1' | Day 1 | Day 2 | Day 3 |
| Informed consent (Study) | X | - | - | - | - |
| Demography | X | - | - | - | - |
| Electrocardiogram | X | - | - | - | - |
| Chest X-Ray* (P/A view) | X | - | - | - | - |
| Blood sample for Hematology | X | - | - | - | X[1] |
| Blood sample for Biochemistry | X | - | - | - | X[1] |
| Blood sample for serological examination | X | - | - | - | - |
| Urine analysis | X | - | - | - | - |
| Urine sample for drugs of abuse | - | X | - | - | - |
| Pregnancy Test | - | X[2] | - | - | - |
| Alcohol breath test | - | X | - | - | - |
| Evaluation of inclusion/exclusion criteria | X[3] | X[3] | - | - | - |
| Dispensing | - | X | - | - | - |
| Dosing | - | - | X | - | - |
| Blood samples for Pharmacokinetics | - | - | X | X | X |
| Vital signs measurement# | X | X | X | X | X |
| Diet schedule | - | X | X | X | - |
| Adverse Events monitoring | - | X | X | X | X |

Source: Protocol synopsis, IND 127021

**Study Withdrawal Criteria**

A subject could be withdrawn for the following:

- Subjects who wish to withdraw consent
- Subjects not compliant with the study protocol
- Subjects who experienced emesis during or before two-times median Tmax
- Subjects who experienced any significant adverse effect
- Subjects who received any concomitant medication that could interfere with the PK of the study drug
- Subjects with a positive result on a breath alcohol test
- Subjects who missed three consecutive blood tests

**Study Restrictions**

Subjects were instructed to:

- Not take any prescription medication 2 weeks prior to the study and any OTC, herbal medications 1 week prior to the study
- Not be on any unusual diet (for example, a low-salt diet) for at least 3 weeks prior to enrollment in the study
- Abstain from consuming any alcoholic beverages 48 hours prior to enrollment in the study

**Statistical Analysis**

An analysis of variance model was used to analyze the PK parameters $C_{max}$, area under the concentration-time curve from time zero to time *t* ($AUC_{0-t}$), and area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$). Statistical analysis will be performed using the SAS® package, version 6.3 or higher (SAS Institute, Inc.).

**Protocol Amendments**

Several information Request letters with clarifying questions, most of which related to CMC, were sent to the Applicant. There was no significant study modification or amendment submitted that would affect the safety measurements and assessments.

### 6.1.2. Study Results

**Compliance with Good Clinical Practices**

The Applicant stated that all studies were conducted in accordance with the guidelines for Good Clinical Practices and the Declaration of Helsinki and in compliance with FDA regulations for informed consent and protection of patient rights as described in 21 CFR parts 50, 56, and 312. The Applicant also states that the studies were approved by the appropriate Institutional Review Boards/Independent Ethics Committees and that all studies underwent regular monitoring by the Applicant or an appointed Contract Research Organization.

**Financial Disclosure**

The Applicant submitted Form FDA 3454 "Certification: Financial Interests and Arrangements of Clinical Investigator", certifying that they had no financial interests or arrangements to disclose. A total of eight investigators was listed in both studies.

**Patient Disposition**

In Study 197/18, 31 volunteers between 18-45 years of age completed the study. Three subjects were withdrawn from the study for personal reasons, and two subjects were withdrawn from the study due to adverse events (vomiting and epigastric pain).

**Protocol Violations/Deviations**

There were no protocol deviations.

**Demographic Characteristics**

All subjects in Study 197/18 were Asian men with a mean age of 31.4 years, a mean weight of 64.3 kilograms, and a mean BMI of 23.1**.** If bioequivalence is established in one population, bioequivalence will also apply to other populations. Therefore, the population for this study is acceptable.

## 6.2. Study 198/18

This was an open-label, balanced, randomized, single-dose, three-treatment, three-period, three-sequence, crossover, oral food-effect bioequivalence study of tramadol HCl oral solution (50 mg/10 mL) and Ultram (tramadol HCl tablets) 50 mg in healthy adult human subjects.

### 6.2.1. Study Design

**Objectives**

The primary objectives of the study were:

- To evaluate the effect of food on the rate and extent of absorption of tramadol HCl oral solution (50 mg/10 mL) in healthy adult human subjects.
- To compare the rate and extent of absorption of tramadol HCl oral solution (50 mg/10 mL) and Ultram (tramadol HCl tablets) 50 mg in healthy adult human subjects under fed conditions.

The secondary objective was to assess the safety and tolerability of the study drug following oral administration.

**Location**

The study was conducted in India. The intent of the study was to compare formulations, not to assess PK differences for race or sex. If bioequivalence is established in one population, bioequivalence will also apply to other populations. Therefore, the population for this study is acceptable.

**Population**

The study intended to enroll 18 healthy male adult volunteers 18 to 45 years of age.

**Key Inclusion/Exclusion Criteria**

Criteria were similar to those described above for Study 197/18.

**Trial Design**

The trial was designed as an open-label, balanced, randomized, single-dose, three-treatment, three-period stud. The subjects were to be randomly assigned to Treatment A (Table 4) or Treatment B (Table 5). Treatment A was a 50 mg/mL oral solution of tramadol HCI under fed conditions. Treatment B was a 50 mg/mL oral solution of tramadol HCI under fasting conditions. The subjects were monitored from 11 hours before administration of the drug, followed by drug administration for up to 48 hours post-dose, including an at least 7-day washout period between the treatments.

After overnight fasting (at least 10 hours), a high-fat, high-calorie breakfast was served 30 minutes prior to administration of 10 mL of oral tramadol followed by 240±2 mL of water. The breakfast contained approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively. After the subject swallowed the study drug, the drug

dispensing container was rinsed with water two to three times, and the remaining water was given to the patient.

**Table 4: Treatment A**

| | |
|---|---|
| Name of the product | Tramadol HCl oral solution |
| Dose | 50 mg/10 mL |
| Dosing schedule | 10 mL of solution as a single dose to each subject |
| Condition | Fed |
| Route/mode of administration | Orally with 240±2 mL of water |
| Treatment period | Single dose in the study per randomization schedule |

After overnight fasting for at least 10 hours, 10 mL of oral tramadol HCI, together with 240±2 mL of water, were given to the subject. After the subject swallowed the study drug, the drug-dispensing container was rinsed with water two to three times, and the remaining water was given to the patient.

Compliance with dosing was assessed by checking the oral cavity after administration of the study drug.

**Table 5: Treatment B**

| | |
|---|---|
| Name of the product | Tramadol HCl oral solution |
| Dose | 50 mg/10 mL |
| Dosing schedule | 10 mL of solution as a single dose to each subject |
| Condition | Fasting |
| Route/mode of administration | Orally with 240±2 mL of water |
| Treatment period | Single dose in the study per randomization schedule |

A total of 24 (1 × 5 mL) of blood samples will be collected from each subject in each study group.

**Procedures/Assessment**

The frequency and timing of assessments, laboratory tests and blood samples were adequate.

All participants underwent screening, including a physical examination, electrocardiogram, laboratory tests, urine tests, and chest X-ray. Screening took place within 28 days before the start day of the study. The assessments performed in the study are listed in Table 3.

Vitals signs—seated blood pressure, radial pulse, and oral temperature—will be measured at the screening visit, before dosing, and 1, 3, 6, 12, and 24 hours after dosing. Vital signs could be measured at any point during the study if necessary.

**Study Withdrawal Criteria**

Criteria were the same as described in Study 197/18.

**Study Restrictions**

Subjects were instructed to:

- Not take any prescription medication from 2 weeks prior to the study and any OTC, herbal medications from 1 week prior to the study
- Not be on an unusual diet (e.g., a low-salt diet) for at least 3 weeks prior to enrollment in the study.
- Abstain from consuming any alcoholic beverages 48 hours prior to enrolment. They will not be permitted to consume any xanthine-containing food and/or beverages (including coffee, tea, chocolate, and cola drinks) cigarettes, tobacco, grapefruit and/or grapefruit juice from 48 hours prior to study initiation until the end of the study.

**Statistical Analysis**

An analysis of variance model was used to analyze the PK parameters $C_{max}$, $AUC_{0-t}$, and $AUC_{0-\infty}$. Statistical analysis will be performed using the SAS® package, version 6.3 or higher (SAS Institute, Inc.).

**Protocol Amendments**

Several Information Request letters with clarifying questions, most of which related to CMC, were sent to the Applicant. There was no significant study modification or amendment submitted that would affect the safety measurements or assessments.

### 6.2.2. Study Results

**Compliance with Good Clinical Practices**

The Applicant stated that all studies were conducted in accordance with the guidelines for Good Clinical Practices and the Declaration of Helsinki and in compliance with FDA regulations for informed consent and protection of patient rights as described in 21 CFR parts 50, 56, and 312. The Applicant also states that the studies were approved by the appropriate Institutional Review Boards/Independent Ethics Committees and that all studies underwent regular monitoring by the Applicant or an appointed Contract Research Organization.

**Financial Disclosure**

The Applicant submitted Form FDA 3454 “Certification: Financial Interests and Arrangements of Clinical Investigator”, certifying that they had no financial interests or arrangements to disclose. A total of eight investigators was listed in both studies.

**Patient Disposition**

All subjects completed the study.

**Protocol Violations/Deviations**

There were no protocol deviations.

**Demographic Characteristics**

All subjects in study 198/18 were Asian men with a mean age of 33.9 years, a mean weight of 68.2 kilograms, and a mean BMI of 23.8. If bioequivalence is established in one population, bioequivalence will also apply to other populations. Therefore, the population for this study is acceptable.

# 7. Integrated Review of Effectiveness

Efficacy of this product was established by demonstrating bioequivalence of oral tramadol solution and Ultram, the reference drug.

The applicant will be required to support the efficacy of tramadol oral solution in pediatric patients 12 to <17 years of age. Studies involving pediatric patients 12 to <17 years of age are deferred until drug approval. For pediatric patients from birth to <12 years of age, a partial waiver was accepted based on the justification that such studies are impossible or highly impractical to conduct.

# 8. Review of Safety

The only new safety data in this application are those generated from healthy volunteers in pharmacokinetic studies. There were no dedicated safety studies. In addition, the Office of Surveillance and Epidemiology was consulted to provide current information on tramadol pediatric utilization patterns and the frequency of opioid misuse and nonmedical use by dosage form for consideration regarding the tramadol oral solution. Refer to Section 8.9.3 for more details.

## 8.1. Safety Review Approach

The safety data consist of pooled data from PK studies 197/18 and 198/18.

## 8.2. Review of the Safety Database

### 8.2.1. Overall Exposure

Overall, 54 subjects were exposed to tramadol oral solution 50 mg/10 mL in the two PK studies. In Study 197/18, 5 of the 36 subjects dropped out, 2 of whom were included in the analysis,

because blood samples were collected and available. In Study 198/18, 18 subjects were exposed to the study drug and all completed the study.

### 8.2.2. Relevant Characteristics of the Safety Population

Healthy Indian men were enrolled in the two PK studies. The intent of the study was to compare formulations, not to assess PK differences for race or sex. If bioequivalence is established in one population, bioequivalence will also apply to other populations. Therefore, the population for this study is acceptable.

### 8.2.3. Adequacy of the Safety Database

The safety population consisted of randomized healthy adult population who received a single dose of the study drug. Because the Applicant is using the 505(b)(2) pathway and relying on the Agency's previous findings for Ultram, the 54 subjects exposed to the 50 mg/10 mL tramadol oral solution in the two PK studies are adequate for this safety evaluation.

## 8.3. Adequacy of the Applicant's Clinical Safety Assessments

### 8.3.1. Issues Regarding Data Integrity and Submission Quality

All data and documents in this application were electronically submitted following the guidance for electronic submission. The documents were organized in electronic Common Technical Document format. The overall quality of the submission was adequate. The organization of and the ability to navigate the NDA were acceptable.

### 8.3.2. Categorization of Adverse Events

All adverse events were consistent with the known safety profile of tramadol.

### 8.3.3. Routine Clinical Tests

The clinical laboratory assessments in study 197/18 and study 198/18 consisted of hematology, chemistry, serology, urinalysis, electrocardiogram, and chest X-ray at the screening. Blood hematology and biochemistry were also performed at the final study visit. Drug and alcohol tests, and pregnancy testing were performed at the first study visit. Blood sampling for PK analysis was performed in both study 197/18 and study 198/18.

## 8.4. Safety Results

### 8.4.1. Deaths and Serious Adverse Events

No deaths or serious adverse events were reported in either study.

### 8.4.2. Dropouts and/or Discontinuations Caused by Adverse Effects

There were five study discontinuations in study 197/18. Two of the five subjects discontinued the study because of adverse events: 1) vomiting, which resolved without intervention 2) pain, which was resolved after administration of 40 mg of pantoprazole.

Three subjects ( (b) (6) discontinued the study for personal reasons.
There were no discontinuations or dropouts in study 198/18.

### 8.4.3. Significant Adverse Events

There were no significant adverse events in study 197/18 or in study 198/18.

### 8.4.4. Treatment-Emergent Adverse Events and Adverse Reactions

The two adverse events in study 197/18 are described in 8.4.3.

There are no new safety signals for 50 mg/10 mL tramadol oral solution or new findings that alter the known benefit-risk profile for tramadol.

### 8.4.5. Laboratory Findings

The Applicant did not report any abnormal laboratory values.

### 8.4.6. Vital Signs

The Applicant did not report any clinically significant changes from baseline in any vital signs for both studies.

## 8.5. Specific Safety Studies/Clinical Trials

No additional safety studies or updates were submitted for review.

## 8.6. Additional Safety Explorations

### 8.6.1. Human Carcinogenicity or Tumor Development

There are no new animal or laboratory studies with Tramadol oral solution to evaluate carcinogenicity or tumor development. The Applicant is relying upon the carcinogenicity data in the referenced product label. The proposed labeling is identical to the referenced product labeling.

### 8.6.2. Human Reproduction and Pregnancy

There are no data for use of Tramadol oral solution in pregnant or lactating women. The Division consulted Division of Pediatric and Maternal Health (DPMH) to review the clinical pregnancy and lactation sections of the proposed product label, assess the adequacy of the assessment of available clinical information to inform these sections and provide comments.

Based on the available information, DPMH did not recommend revisions to the PLLR labeling for tramadol proposed in the current label.

### 8.6.3. Pediatrics and Assessment of Effects on Growth

The effects of tramadol on growth, development, and functional maturation of the child is unknown. Refer to Section 3.2 for details of required pediatric studies.

### 8.6.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Tramadol is currently Schedule IV controlled substances under the Controlled Substance Act. Tramadol is an opioid and is considered a substance with a potential for abuse, misuse, addiction, and criminal diversion.

The Controlled Substance Staff (Drs. Tolliver, Calderon, and Chiapperino) recommend approval. Refer to their review for details. They conclude the following:

1. Considering the bioequivalence results from studies 197/18 and 198/18 between Tramadol oral solution 50 mg/10mL and oral Ultram 50 mg, both products will likely have a similar oral abuse potential.
2. The abuse of tramadol is predominantly by the oral route of administration.
3. Tramadol oral solution is particularly intended for patients who cannot swallow solid pills, including patients who are fed through feeding tubes, thereby eliminating the need to crush pills and mix them into a different liquid. Such limited distribution would likely assist in mitigating abuse of this product. This patient population would also be unlikely to abuse the product. It seems probable that within the normal patient population, namely those without problems is swallowing pills, the tablet forms and not the oral solution would be prescribed to them.
4. It is unlikely that Tramadol HCL oral solution will be abused by intravenous injection. The concentration (25 mg/5mL) is likely too low to support intravenous abuse. In addition, based on an examination of the scientific and medical literature, tramadol appears not to be abused by intravenous injection. This perception is supported by the following statement taken from a 2018 report entitled “Critical Review Report” from the 41th Expert Committee on Drug Dependence of the World Health Organization: *“It has been generally accepted that parentally administered tramadol is less likely to be identified as an opioid because M1 production is minimalized since first-pass metabolism is avoided. Hence the abuse of tramadol is much reduced through intravenous administration when compared to ingestion.”*
5. Tramadol Oral Solution will be controlled in Schedule IV of the federal Controlled Substances Act due to containing the Schedule IV substance tramadol, as reflected in Section 9.1 of the Sponsor’s proposed label.
6. As a 505(b)(2) application, Sponsor has proposed using the language for Section 9 of the currently approved labeling for Ultram Tablets in Section 9 of the labeling for Tramadol Oral Solution. While Section 9.1 of the label for Ultram makes clear that tramadol is in Schedule IV of the Controlled Substances Act, there is also language in Section 9.2 describing Ultram as “a substance with a high potential for abuse similar to that of other

opioids." This last statement is in keeping with Schedule II controlled substances but is not consistent with the level of abuse potential of a Schedule IV drug under the Controlled Substances Act. Section 9.2 of the Ultram label and of the proposed label for Tramadol Oral Solution needs to be amended by removing the statement of "a substance with a high potential for abuse similar that of other opioids" and adding "a substance having a potential for abuse."

## 8.7. Safety in the Postmarket Setting

### 8.7.1. Safety Concerns Identified Through Postmarket Experience

Tramadol has been widely marketed worldwide for more than 20 years with a well-known safety profile. The safety of tramadol has been under regular review through pharmacovigilance.

### 8.7.2. Expectations on Safety in the Postmarket Setting

Tramadol has all risks associated with opioid medications, including abuse, misuse, addiction, and criminal diversion.

There are no specific characteristics of Tramadol that would be expected to increase or decrease the risks of misuse, abuse, opioid use disorder, and related adverse outcomes. However, given that Tramadol is an opioid-containing product, the risks of unintended use of Tramadol should be evaluated.

If approved, tramadol oral solution (NDA 214044), 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.

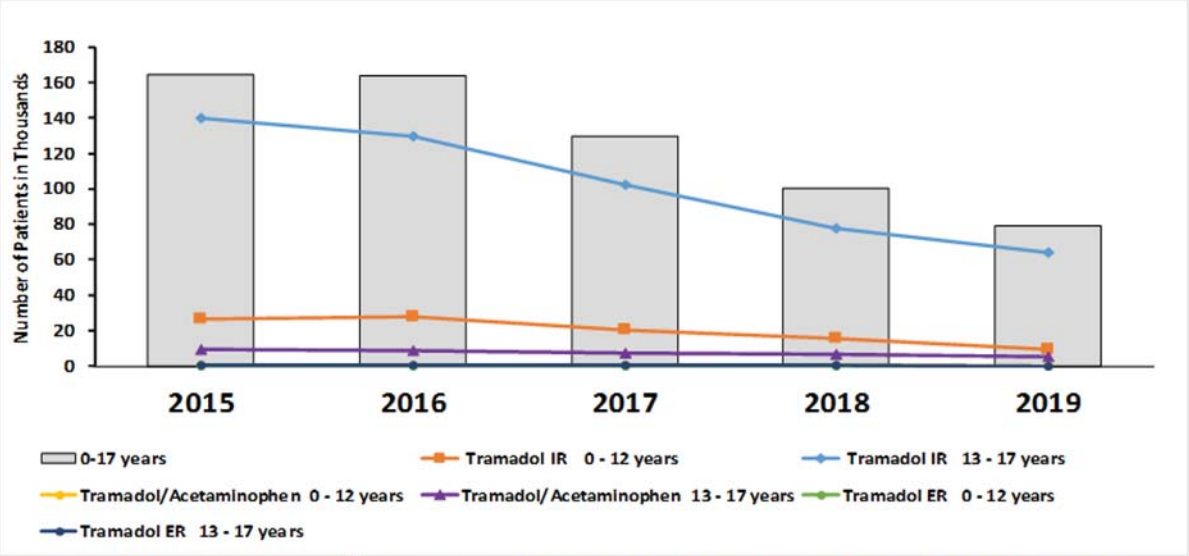
Tramadol oral solution is intended for adults. To understand whether there is a potential concern that prescribers may mistakenly believe that an oral solution is intended for pediatric patients, the Division asked the Division of Epidemiology II (DEPI) to provide current information on tramadol pediatric utilization patterns and the frequency of opioid misuse and nonmedical use by dosage form for consideration regarding the tramadol oral solution (NDA 214044). In addition, the Division asked DEPI to provide data on abuse and misuse of oral solution dosage forms of opioid analgesics.

DEPI submitted a comprehensive review of the use, misuse, nonmedical use, and related adverse outcomes associated with tramadol and other selected opioid analgesics in recent years. According to U.S. office-based physician surveys, drug-use mentions for tramadol-

containing products from 2015 to 2019 for pediatric patients 0 to 17 years of age were too infrequent to provide reliable national estimates of pediatric diagnoses associated with tramadol. DEPI found limited data on the misuse and nonmedical use of morphine and oxycodone by dosage form. The number of pediatric patients (0 to 17 years of age) prescribed tramadol-containing medications decreased from an estimated 2.7 million in 2015 to 1.5 million in 2019, a 46% decrease. The highest proportion of tramadol-containing product use by pediatric patients was among those 13 to 17 years of age. Pediatric utilization of tramadol-containing products decreased by 52% from 2015 to 2019.

Tramadol IR in pediatric patients ages 13-17 years accounted for the highest proportion of tramadol use at 81%, followed by tramadol IR in pediatric patients ages 0-12 years at 12% and tramadol/acetaminophen in pediatric patients ages 13-17 at 7% in 2019 (as illustrated in Figure 3). Use of the tramadol ER formulation was negligible in pediatric patients.

**Figure 2: National Estimated Number of Pediatric Patients* (0 to 17 Years of Age) Who Received Prescriptions Dispensed for Tramadol-Containing Products, Stratified by Patient Age and Drug Formulation, From U.S. Outpatient Retail Pharmacies**, 2015 to 2019**




Data Source: IQVIA Total Patient Tracker™. 2015-2019. File: Total 2020-362 2015-19 by Age.3-6-20 no vet.xlsx. Data extracted March 2019.
*Note: Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients age 0-17 years include patients less than 18 years of age (17 years and 11 months).
**There was a change in the underlying data and methodology of the proprietary database, IQVIA NPA, to manage prescription claims that are voided and/or reversed. Because TPT patient data are derived from NPA prescription data, projected patient 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 the 2016 and 2017 patient estimates who received prescriptions dispensed from the retail pharmacies; any changes over time must be interpreted in the context of the changes in the underlying data and methodology.
Abbreviations: ER, extended release; IR, intermediate release; NPA (National Prescription Audit) TPT, Total Patient Tracker
Source: Integrated review of epidemiology and drug utilization

Investigation of the potential abuse and misuse of oral solution dosage forms of opioid analgesics relied on the epidemiologic data for morphine and oxycodone. Oral liquid products represented approximately 7% of prescription morphine-containing products and 1% of prescriptions for oxycodone-containing products in outpatient retail pharmacies. By applying the results of this analysis of misuse or abuse of morphine and oxycodone to tramadol, it was concluded that the frequency of misuse or abuse of an oral liquid product may be less than or similar to that of an oral solid product.

Regarding routes of misuse or abuse, the oral route was the most commonly reported for misuse/abuse involving morphine and oxycodone, and solid dosage forms were reportedly involved more frequently than liquid dosage forms.

Refer to the integrated review of epidemiology and drug utilization (Drs. Wittayanukorn, Ibrahim, Rodin, and Staffa).

### 8.7.3. Additional Safety Issues From Other Disciplines

Conclusions from the Controlled Substance Staff are discussed in Section 8.8.4.

## 8.8. Integrated Assessment of Safety

A review of the limited safety data from studies 197/18 and 198/18 revealed no unexpected safety signal with the use of 50 mg/10 mL tramadol oral solution.

It is unlikely that this product will be injected. The solution is of relatively low concentration and tramadol requires first-pass metabolism for generation of the potent metabolite, making it an unattractive route of abuse.

Tramadol use in children is infrequent. In order to minimize the risk of prescribing this oral solution to pediatric patients, the container specifies that this product is for adults only.

Epidemiologic data do not support higher rates of misuse and abuse of oral opioid solutions compared to tablets forms. Therefore, it is not expected that this product will be less safe than what is currently available.

This product will be subject to the Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits outweigh potential risks in the outpatient setting.

# 9. Advisory Committee Meeting and Other External Consultations

Section 106 of the Comprehensive Addiction and Recovery Act of 2016 (Pub. Law 114-198) provides that, prior to the approval of a new drug that is an opioid, the Secretary of Health and Human Services shall refer the application to an FDA advisory committee to seek recommendations from such advisory committee. However, no such referral is required if the Secretary finds that such a referral is not in the interest of public health and not necessary based on a review of the relevant scientific information, and submits a notice containing the rationale for such findings to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives.

We have determined that referral of this application to an Advisory Committee would not be in the interest of public health and is not necessary based on a review of the relevant scientific information. First, clinical safety and efficacy information are not required to support approval

of the product because pharmacokinetic studies were conducted to bridge to the Agency's findings of efficacy and safety for Ultram. No independent advice from outside experts is needed regarding the pharmacokinetic information submitted in the application. The proposed indication and dosing are the same as the reference product, Ultram.

Furthermore, the Division recently received the committee's input on another tramadol-containing product. The postmarket data on misuse and abuse of tramadol products were presented to a joint meeting of the AADPAC and DRISK committees on January 15, 2020. The committees opined on the available data and the potential public health impact of the introduction of a new tramadol-containing product to the market based on these data. There are no additional data in the present application that would inform further discussion of the public health impact of the product.

We will submit the required notice to the relevant Congressional committees following approval of the application.

# 10. Labeling Recommendations

## 10.1. Prescription Drug Labeling

The Division of Medical Error Prevention and Analysis (DMEPA) and the Division of Pediatric and Maternal Health (DPMH) were consulted regarding the proposed labeling (i.e., pregnancy and lactation labeling rule, PLLR).

On December 20, 2019, the Division consulted the Division of Pediatric and Maternal Health (DPMH) to provide input for appropriate labeling of the pregnancy and lactation sections of tramadol HCL oral solution, 50 mg/10 mL to comply with the PLLR format. DPMH conducted a search of published literature in PubMed on "Tramadol and fertility, pregnancy, and lactation" using appropriate search terms. No new relevant publications were identified. DPMH did not recommend revisions to the PLLR labeling for the proposed 50 mg/10mL oral tramadol solution.

On April 20, 2020 DMEPA provided recommendations for the proposed labeling, based on their review. The DMEPA evaluation of the proposed QDOLO (tramadol oral solution) PI and container labels identified areas of vulnerability that may lead to medication errors. A summary of the identified concerns and proposed recommendations is provided in Table 8.

On August 12, 2020, the Division communicated via email to the Applicant recommendation on inclusion of a warning statement on the container label to address the risk of medication errors (e.g., dispensing and administration) associated with Qdolo in children. The Division recommended inclusion of a statement, such as, "WARNING: For Adults Only. See Prescribing information for details" to the principal panel of the container label for Qdolo. On August 13, 2020, the Applicant submitted a revised container label for Qdolo and implemented the recommendations requested by the Division. The Division had no additional recommendations.

**Table 6: Identified Issues and Recommendations**

| Issue | Concern | Recommendation |
|---|---|---|
| The proprietary name, QDOLO is generally acceptable | A proprietary name review has been conducted and the name has been found conditionally acceptable | The proprietary name QDOLO should be included in the prescribing information |
| Dosage is listed in milligrams (mg) followed by volume in milliliters (mL). For example, 25 mg (5 mL) | The dose in mg and in mL could be easily confused and misinterpreted. There is a risk of an overdose or underdose error if the dose was prescribed in mL but dispensed in mg or vice versa | To minimize the risk of wrong dose medication errors, remove the dose as expressed by volume from the dosage and administration section |
| This product is a liquid dosage form. However, Section 17, does not contain instructions for the healthcare provider to instruct patients, or their caregivers, to use an oral dosing syringe or other oral dosing device with metric units of measurements to measure their dose | An oral dosing syringe or other oral dosing device with metric units of measurement more accurately measures drug volumes and may decrease the risk of wrong-dose error, particularly when measuring smaller doses | Add to Section 17 instructions to the healthcare provider to advise the patient to use an oral dosing device to measure QDOLO |
| The product name, tramadol, is on the FDA List of Established Drug Names Recommended to Use Tall-Man Lettering (TML) | The product name, tramadol, has been confused with the product name, trazodone, because of their orthographic similarity and similar characteristics, such as dose (e.g., 50 mg). The use of TML, and other labeling differentiation strategies, can be employed to address the risk of product name confusion | To address the risk of product name confusion between your tramadol product and marketed trazodone products, we recommend tramadol be presented using TML (i.e., traMADol HCl) on the container label for QDOLO |
| The statement “For Oral Administration Only” or “For Oral Use Only” is not present on the container labeling | Postmarketing experience has indicated that wrong-route-of-administration errors have occurred when oral liquid products have been inadvertently administered as injections | To minimize the risk of wrong-route-of-administration medication errors, consider adding the statement, “For Oral Administration Only” to the principal display panel |

# 11. Risk Evaluation and Mitigation Strategies

Tramadol, being an opioid, has all of the risks associated with opioid medications, including abuse, misuse, and addiction. If approved, tramadol oral solution (NDA 214044) must be included in the Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of the drug outweigh the risk of adverse events (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. The Opioid Analgesic REMS was initially approved as the Extended-Release and Long-Acting REMS in July 2012 and was expanded in September 2018 to include all application holders of immediate-release 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. Postmarketing Requirements and Commitments

Post marketing requirements include the following:

- A juvenile animal study to evaluate the potential for acute CNS toxicity and neurodevelopmental adverse effects of tramadol in developmental ages equivalent to the target adolescent age range.
- A pediatric study evaluating the effectiveness, safety, and pharmacokinetic profile of Tramadol oral solution in pediatric patients 12 to less than 17 years of age (excluding setting of tonsillectomy and/or adenoidectomy). Refer to section 3.2. Summary of Presubmission/Submission Regulatory Activity for more details.

# 13. Appendices

## 13.1. Financial Disclosure

The Applicant submitted Form FDA 3454 “Certification: Financial Interests and Arrangements of Clinical Investigator”, which certified that they had no financial interest or arrangement with clinical investigators that could affect the outcome of the studies as defined in 21 CFR 54.2(a). Also, none of the listed investigators was a recipient of other significant payments, as defined in 21 CFR 54.2(f).

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

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