APPLICATION NUMBER:

214044Orig1s000

OTHER REVIEW(S)
1 PURPOSE OF MEMORANDUM
On August 13, 2020, the Applicant submitted and we received a revised container label for Qdolo. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine requested that we review the revised labeling (see Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION AND RECOMMENDATION
The Applicant implemented our recommendation and we have no additional recommendations at this time.

APPENDIX A. IMAGE OF CONTAINER LABEL RECEIVED ON AUGUST 13, 2020
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/
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OTTO L TOWNSEND
08/14/2020 04:24:25 PM

MILLIE B SHAH
08/14/2020 04:42:49 PM
Date: July 29, 2020

To: Rigoberto Roca, M.D., Director (Acting)
Division of Anesthesia, Addiction Medicine, and Pain Medicine (DAAP)

Through: Dominic Chiapperino, Ph.D., Director
Silvia Calderon, Ph.D., Senior Pharmacologist
Controlled Substance Staff

From: James M. Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Tramadol HCl Oral Solution. NDA 214-044
Trade Name, dosages, formulations, routes: QDOLLO, Tramadol HCl 25 mg / 5 mL
IND Number: 127,021
Indication(s): In adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate
Sponsor: Athena Biosciences LLC
PDUFA Goal Date: September 1, 2020

Materials Reviewed:
Abuse-related preclinical and clinical data submitted under NDA 214-044.

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I. EXECUTIVE SUMMARY

1. Background

This memorandum responds to a consult request dated December 2, 2019 by the Division of Anesthesia, Addiction Medicine, and Pain Medicine Products (DAAP) to evaluate from a CSS perspective NDA 214-044 for Tramadol HCl Oral Solution 25 mg/5 mL submitted by Athena Bioscience, LLC. The product is under development using the 505(b)(2) pathway with Ultram (Tramadol Hydrochloride Tablets, USP) (NDA 20281) sponsored by Janssen Pharmaceuticals, Inc as the reference product.

This product is a grape flavored solution containing 25 mg/5 mL of tramadol HCl for oral administration. The drug product has the same indication as Ultram (Tramadol Hydrochloride Tablets), namely the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The recommended starting dose is 25 mg (5 mL)/day with subsequent
titration up to a total daily dose of 400 mg in 25 mg (100 mg (20 mL)/day (25 mg (5mL) four times a day).

Tramadol is an analgesic acting via mu-opioid receptors as well as by weak inhibition of re-uptake of norepinephrine and serotonin. Tramadol has been available in the United States in tablet form since 1995. Following approval, Tramadol HCl Oral Solution will be the first liquid oral form of tramadol available in the United States. According to Sponsor, this oral dosage form 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 liquid.

Tramadol is in Schedule IV of the federal Controlled Substances Act (CSA). Once approved Tramadol HCl Oral Solution will also be in Schedule IV. The Schedule IV designation is in the label proposed by Sponsor.

2. Conclusions

1. Tramadol HCl Oral Solution is under development as a 505(b)(2) submission with listed drug Ultram ® (Tramadol Hydrochloride Tablets, USP), under NDA 20281 sponsored by Janssen Pharmaceuticals, Inc.

2. According to Sponsor, Tramadol HCl 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 in swallowing pills, the tablet forms and not the oral solution would be prescribed to them.

3. The abuse of tramadol is predominantly by the oral route of administration. It is expected that Tramadol HCl Oral Solution would have an oral abuse potential similar that of tramadol immediate-release (Ultram) tablets.

4. It is unlikely that Tramadol HCl Oral Solution will be abused by intravenous injection. The concentration (25 mg/5 mL) 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 41st 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 minimized 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.”

3. Recommendations

Based on our findings as captured in the Conclusions section, we recommend the following:

1. 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.” As noted in Section 9.1 the substance tramadol is a Schedule IV drug under the Controlled Substances Act. Placement in Schedule IV is not consistent with a determination that tramadol has a “high potential for abuse.”

II. DISCUSSION

1. Chemistry

1.1 Substance Information

QDOLO Oral Solution is a clear, grape flavored liquid containing 25 mg of tramadol hydrochloride per 5 mL. The chemical name for tramadol hydrochloride is (±)-cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride and is the same as that used in Ultram. Inactive ingredients include citric acid, glycerin, grape flavor, propylene glycol, purified water, sodium benzoate, sodium citrate dihydrate, and sucralose. A quantitative description of the final to-be-marketed formulation is provided in Table 1 below.

Table 1. Quantitative Composition of Tramadol Hydrochloride Oral Solution, 25 mg/5mL

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Weight (mg per 5 mL)</th>
<th>% (w/w)</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol HCl USP</td>
<td>25.000</td>
<td>(b) (4)</td>
<td>Active Ingredient</td>
</tr>
<tr>
<td>Propylene Glycol USP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycerin USP</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
According to Sponsor, the low dosage strength (25 mg/5 mL) is intended to assist with dosage titration.

1.2 Potential Drug Isomers

QDOLO contains tramadol hydrochloride, an opioid agonist. The chemical name for tramadol hydrochloride is (±)cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. Tramadol has two chiral centers, in positions 1 and 2 in the cyclohexanol ring, and therefore four stereoisomers can exist. These stereoisomers can be described as (1R,2R); (1S, 2S), (1R,2S) and (1S,2R). However, commercially available tramadol represents a 1:1 racemic mixture of the (1R,2R) and (1S,2S) stereoisomers, which are also identified as the (+) and (-) stereoisomers respectively. Considering that this pair of enantiomers represent structures that have the hydroxyl group and the diethylamino-methyl group (both groups) either both up or both down in their positions on the cyclohexane ring in its chair conformation, it is said that both groups are in cis-configuration. Tramadol hydrochloride manufactured by exhibits geometrical isomerism.

1.3 In Vitro Manipulation and Extraction Studies for Products with Abuse-Deterrent Features

Tramadol Oral Solution does not have abuse-deterrent properties. Sponsor is not pursuing any abuse-deterrent claims regarding the product. In vitro physical manipulation and chemical extraction studies were not submitted under NDA 214044.

2. Nonclinical Pharmacology

NDA 214044 involves a 505 (b) (2) submission with listed drug Ultram ® (Tramadol Hydrochloride Tablets, USP) via cross reference to NDA 20281 sponsored by Janssen Pharmaceuticals, Inc. As noted under the “Nonclinical Overview” (Module 2.4), “No nonclinical testing was necessary, due to our reliance on the established nonclinical pharmacology profile and the established nonclinical safety and efficacy profile of ULTRAM.” For information on the pharmacology of tramadol, Sponsor relied upon the approved label for Ultram, the Ultram NDA and recent literature.

Tramadol is long established as an opioid analgesic. The analgesic effect of tramadol is believed to be due to both binding to mu-opioid receptors and weak inhibition of re-uptake of norepinephrine and serotonin. Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite O-desmethyltramadol (ODMT) to mu-opioid receptors. In animal models, ODMT is up to 6 times more potent than tramadol in producing analgesia and 200 times
more potent in mu-opioid binding. Tramadol-induced analgesia is only partially antagonized by the opioid antagonist naloxone in several animal tests. The relative contribution of both tramadol and ODMT to human analgesia is dependent upon the plasma concentrations of each compound. (ODMT is being developed for its analgesic properties under IND [Redacted] (Omitam) by Syntrix Biosystems Inc, with the support of the National Institute on Drug Abuse, NIDA)

2.1 Receptor Binding and Functional Assays

Receptor binding and functional assays were not submitted with this NDA 214-044. As a 505(b)(2) application, Sponsor is relying on results of preclinical studies conducted under the reference drug, Ultram.

2.2 Safety Pharmacology/Metabolites

Studies involving safety pharmacology of metabolites were not conducted under NDA 214-044. Sponsor did note that in animal models, ODMT is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in mu-opioid binding (Preclinical Overview, Module 2.4).

2.3 Findings from Safety Pharmacology and Toxicology Studies

Studies involving safety pharmacology and toxicology were not conducted under NDA 214-044. Safety pharmacology and toxicology of Tramadol Oral Solution is inferred from the safety pharmacology and toxicology conducted on tramadol as found in the Ultram label and NDA submission as well as scientific and medical literature.

2.4 Animal Behavioral Studies

Preclinical behavioral studies, including those examining abuse potential, were not submitted under NDA 214-044.

2.5 Tolerance and Physical Dependence Studies in Animals

No tolerance or physical dependence studies in animals were submitted under NDA 214-044.

3. Clinical Pharmacology

Sponsor conducted two Phase 1 bioequivalence and bioavailability studies but no Phase 2 or Phase 3 studies. These are discussed in section 4 below.
3.1 Absorption, Distribution, Metabolism, Elimination (ADME)

No in vivo studies in animals were conducted using Tramadol Oral Solution. Due to the bioequivalence of Tramadol Oral Solution to Ultram 50 mg tablets, as seen in two Phase I studies conducted by Sponsor, information regarding absorption, distribution, metabolism, and elimination of tramadol were inferred from the approved label for Ultram, the Ultram NDA, and the scientific literature. (Module 2.6.4 of NDA 214-044).

Two Phase 1 pharmacokinetic studies examined the bioequivalence of Tramadol Oral Solution to that of Ultram tablets are discussed under Section 4 of this review.

3.2 Drug/Product Interactions

No drug interactions pertaining to Tramadol Oral Solution were documented in the NDA 214-044 submission. It is expected that any interactions with other drugs would be similar that for Ultram (tramadol HCl tablets) 50 mg.

3.3 Special Considerations

Tramadol Oral Solution, as is the case with Ultram (tramadol HCl tablets) 50 mg, are both intended for oral administration and therefore first pass metabolism of tramadol to N-desmethyltramadol in the liver. Phase 1 clinical study 197/18 demonstrates bioequivalence between the two products with respect to both peak plasma concentrations and time course of tramadol and N-desmethyltramadol in plasma of human subjects.

4. Clinical Studies

NDA 214-044 involves a 505(b)(2) submission with listed drug Ultram ® (Tramadol Hydrochloride Tablets, USP), under NDA 20281 sponsored by Janssen Pharmaceuticals, Inc. No Phase 2 or Phase 3 studies were submitted.

Clinical development program consisted of the two Phase 1 studies listed below.

- **Clinical Study 197/18** entitled “An open label, balanced, randomized, single dose, two treatment, two period, two sequence, crossover oral relative bioavailability study of Tramadol HCl oral solution (50 mg / 10mL) manufactured for [redacted]®, and Ultram® (tramadol HCl tablets)50 mg manufactured for Janssen Pharmaceuticals, Inc., Titusville, New Jersey08560, USA, in healthy adult human subjects under fasting condition.”

- **Clinical Study 198/18** entitled “An open label, balanced, randomized, single dose, three treatment, three period, three sequence, crossover, oral food effect and fed Bioequivalence study of Tramadol HCl oral solution (50 mg/10 mL) manufactured for [redacted]®, and Ultram® (tramadol...
Information on these studies is provided below. The Sponsor’s conclusions are provided; however, the final determination of bioequivalence between Tramadol Oral Solution and Ultram rests with FDA CDER Office of Clinical Pharmacology.

Phase 1 Clinical Study 197/18

Study 197/18, was an open label, balanced, randomized, single dose, two treatment, two period, two sequence, crossover oral relative bioavailability study of Tramadol HCl Oral Solution (25 mg/5 mL) manufactured for USA (QDOLÔ™), and ULTRAM® (Tramadol HCl tablets) 50 mg manufactured for Janssen Pharmaceuticals, Inc., Titusville, New Jersey 08560, USA, in healthy adult human subjects under fasting condition.

Thirty-one subjects completed the study. Specific oral treatments administered under fasted conditions included:

- Tramadol HCl oral solution (50 mg/10 mL) (TEST)
- Ultram 50 mg (REFERENCE)

Both tramadol and O-desmethyltramadol plasma concentrations were determined pre-dose and at selected times post-dosing out to 48 hours. Bioequivalence was established based just on tramadol. Data on O-desmethyltramadol was obtained as “supportive evidence” of bioequivalence.

Pharmacokinetic parameter examined for both substances included the following:

- Cmax = Maximum plasma concentration (ng/mL)
- Tmax = Time to achieve Cmax
- AUCt = Area under the plasma concentration versus time curve out to last time point (t) measured indicative to total drug exposure.
- AUCinfinity = Area under the plasma concentration versus time curve out extrapolated to infinity indicative of total drug exposure.

The pharmacokinetic results for tramadol and O-desmethyltramadol following each treatment are provided in Table 2 below.

Table 2. Summary of Pharmacokinetic Results for Plasma Tramadol and O-Desmethyltramadol

<table>
<thead>
<tr>
<th>Tramadol Plasma PK Parameter</th>
<th>Arithmetic Mean (SD) Tramadol</th>
<th>Arithmetic Mean (SD) O-Desmethyltramadol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol Oral Solution 50 mg</td>
<td>180.20 ± 33.80</td>
<td>47.7739 ± 19.06335</td>
</tr>
<tr>
<td>Ultram Tablet 50 mg</td>
<td>173.51 ± 29.59</td>
<td>46.1375 ± 18.27749</td>
</tr>
<tr>
<td>Mean Cmax (ng/mL)</td>
<td>180.20 ± 33.80</td>
<td>47.7739 ± 19.06335</td>
</tr>
<tr>
<td>Median Tmax (Hours)</td>
<td>1.5 (0.5 – 2.5)</td>
<td>2.0 (0.5 – 5.0)</td>
</tr>
<tr>
<td></td>
<td>1.5 (0.75 – 3.0)</td>
<td>2.25 (1.2 – 10.0)</td>
</tr>
</tbody>
</table>
Ratios of means of each test and reference formulations were estimated using the Least Square Mean for ln-transformed Cmax, AUCt, and AUConf. Bioequivalence was declared if the Test and Reference ratios of the geometric LSMs in the ln-transformed pharmacokinetic parameters and their 90% confidence intervals were within 80%-125% for tramadol.

Sponsor findings for this study are noted below.
- With respect to the tramadol plasma parameters of Cmax, AUCt, and AUConf, bioequivalence was established between Tramadol Oral Solution (50 mg/10 mg) (TEST) and Ultram 50 mg thereby establishing bioequivalence under fasted conditions.
- With respect to O-desmethyltramadol plasma parameters for Cmax, AUCt, and AUConf ratios of test to reference were also within the 80% and 125% interval provide “supportive evidence” of bioequivalence.

### Phase 1 Clinical Study 198/18

Study 198/18, was an open label, balanced, randomized, single dose, three treatment, three period, three sequence, crossover, oral food effect and fed bioequivalence study of Tramadol HCl Oral Solution (25 mg/5 mL) manufactured for [QDOLO™](#), and ULTRAM® (Tramadol HCl tablets) 50 mg manufactured for Janssen Pharmaceuticals, Inc., Titusville, New Jersey 08560, USA, in healthy adult human subjects.

Eighteen subjects were randomized and completed the study. Oral treatments administered with 240 mL of water included the following:
- Tramadol oral solution 50 mg/10 mL FED condition
- Tramadol oral solution 50 mg/10 mL FASTED condition
- Ultram tramadol 50 mg tablet FED condition

Both tramadol and O-desmethyltramadol plasma concentrations were determined pre-dose and at selected times post-dosing out to 48 hours. Bioequivalence was established based just on tramadol. Data on O-desmethyltramadol was obtained as “supportive evidence” of bioequivalence.

Pharmacokinetic parameter examined for both substances included the following:
- Cmax = Maximum plasma concentration (ng/mL)
- AUCt = Area under the plasma concentration versus time curve out to last time point (t) measured indicative to total drug exposure.
- AUConf = Area under the plasma concentration versus time curve out extrapolated to infinity indicative of total drug exposure.

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Mean AUC0-t (hr*ng/mL)</th>
<th>Mean AUC0-Inf (hr*ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1623.93 ± 502.43</td>
<td>1658.31 ± 525.97</td>
</tr>
<tr>
<td></td>
<td>1681.64 ± 578.06</td>
<td>1721.47 ± 624.72</td>
</tr>
<tr>
<td></td>
<td>624.11 ± 205.58</td>
<td>638.95 ± 207.13</td>
</tr>
<tr>
<td></td>
<td>624.10 ± 199.82</td>
<td>639.26 ± 198.044</td>
</tr>
</tbody>
</table>

Table 3 below provides the arithmetic means (SD) for pharmacokinetic parameters of plasma tramadol and O-desmethyltramadol following each treatment.
Table 3. Summary of Pharmacokinetic Results for Tramadol and O-Desmethyltramadol. (Data taken from tables 13A, 13B, 13C and 13 D of the clinical study report for study 198/18, report version 00).

<table>
<thead>
<tr>
<th>Tramadol Plasma PK Parameter</th>
<th>Mean (SD) (Exception: Tmax – Median (Range))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tramadol Oral Sol 50 mg/10 mL FED</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>146.22 ± 28.50</td>
</tr>
<tr>
<td>Tmax (Hours)</td>
<td>2.0 (0.5 – 3.5)</td>
</tr>
<tr>
<td>AUC0-t (hr*ng/mL)</td>
<td>1606.04 ± 574.38</td>
</tr>
<tr>
<td>AUC0-Inf (hr*ng/mL)</td>
<td>1635.90 ± 594.44</td>
</tr>
</tbody>
</table>

Ratios of means of each test and reference formulations were estimated using the Least Square Mean for ln-transformed Cmax, AUCt, and AUCinfinity. Bioequivalence was declared if the Test and Reference ratios of the geometric LSMs in the ln-transformed pharmacokinetic parameters and their 90% confidence intervals were within 80%-125% for tramadol. Bioequivalence in the FED state was determined by the comparison of Tramadol Oral Solution 50 mg/10 mL under FED conditions compared to Ultram 50 mg under FED conditions.

The absence of a food effect on bioavailability of Tramadol Oral Solution was established if the 90% confidence intervals (CIs) for the ration of population geometric means between FED and FASTED treatments of Tramadol Oral Solution, based on log-transformed data, were contained in the equivalence limits of 80%-125% for Cmax, AUCt, and AUCinfinity.

Sponsor results are provided below.

- In comparison of Tramadol Oral Solution under FED and FASTED conditions, no food effect was observed in this study.
- With respect to tramadol Cmax, the % ratio of Tramadol Oral Solution Fed Conditon over Ultram FED condition was 78.12 which fell out of the range of 80%-125%, indicating a lack of bioequivalence with respect to tramadol Cmax. Sponsor considered the 1.88% difference (from 80:00) small, suggesting that for Cmax bioequivalence was nearly reached.
- With respect to tramadol AUCt and AUCinfinity bioequivalence was established between FED Tramadol Oral Solution 50 mg/10 mL and FED Ultram 50 mg.
- “Supportive evidence” of bioequivalence between Tramadol Oral Solution 50 mg/10 mL FED and Ultram 50 mg FED was obtained for Cmax, AUCt, and AUCinfinity for plasma O-desmethyltramadol.
The findings provided above for the two clinical studies are those of the Sponsor. The final decision regarding bioavailability and bioequivalence of Tramadol Oral Solution to Ultram 50 mg tablets rests with the Office of Clinical Pharmacology.

4.1 Human Abuse Potential Studies

No human abuse potential studies were submitted under NDA 214-044.

Tramadol Oral Solution is under development via the 505(b)(2) pathway with Ultram as the reference product. Considering the bioequivalence results from studies 197/18 and 198/18 between oral Tramadol Oral Solution 50 mg/10 mL and oral Ultram 50 mg tablets it is probable that both products will have a similar oral abuse potential. On July 2, 2014, tramadol, and therefore Ultram, was placed into Schedule IV of the federal Controlled Substances Act. The Schedule IV designation means that Ultram, containing tramadol, is associated with some abuse potential, although less than schedule II and III controlled substances.

Several completed oral human abuse potential studies found in the medical literature supports an oral abuse potential for tramadol. Babalonis et al. (2013) found that oral doses (tablets) of tramadol (200 mg and 400 mg) given to nine healthy, non-dependent prescription opioid abusers (6 male and 3 female) produced significantly increased ratings, when compared to placebo on subjective measures associated with abuse liability, such as subjective measures of “high,” and “liking” for the drug, and street value estimates. Zacny (2005) gave 22 recreational drug users 50 or 100 mg of oral tramadol (tablets). The 100 mg dose, but not the 50 mg dose, produced subjective measures of “drug liking” and “want to take drug again” that were significantly above that produced by placebo.

4.2 Adverse Event Profile Through all Phases of Development

Clinical development program consisted of two Phase 1 bioequivalence pharmacokinetic studies (Clinical Study 197/18 and Clinical Study 198/18). There were no Phase 2 or Phase 3 clinical studies conducted. Pharmacovigilance database consists entirely of adverse events reported in these two bioequivalence studies.

For both studies, there were no adverse events associated with abuse potential such as euphoria, euphoric mood, elevated mood, mood alteration, feeling drunk, feeling abnormal, mood elevation, sedation, psychotomimetic events, hallucinations (auditory/visual), drug maladministration or derealization. In study 197/18 two adverse events were noted, namely “vomiting” and “epigastric pain”, both following Tramadol Oral Solution. No adverse events were reported under Study 198/18. These studies are briefly discussed below.

Clinical Study 197/18

Clinical study 197/18 was an open label, balanced, randomized, single dose, two treatment, two period, two sequence, crossover oral relative bioavailability study having the objective of comparing the rate
and extent of absorption of Tramadol HCl oral solution (50 mg/10 mL) manufactured for [redacted] against that of Ultram® (tramadol HCl tablets) 50 mg. An additional objective was to assess the safety and tolerability following oral administration of the investigational product. Thirty-one subjects completed the study.

There were two adverse events in total, involving one case of “vomiting” and another of “epigastric pain” both following Tramadol Oral Solution 50 mg dose. One subject reported “vomiting” at 4 hours post-dosing. A second subject reported “epigastric pain” at one-hour post-dosing.

Five subjects withdrew from study 197/18
- Subject number [redacted] was withdrawn from the study due to an adverse event (Vomiting) after the 4-hour post-dose blood collection in period-I.
- Subject number [redacted] was voluntarily withdrawn from the study due to personal reasons during period-II check-in.
- Subject number [redacted] was withdrawn from the study due to an adverse event (Epigastric Pain) after the 1-hour post-dose blood collection in period-I.
- Subject numbers [redacted] & [redacted] were voluntarily withdrawn from the study due to personal reasons after the 28-hour post-dose lunch in period-II.

Clinical Study 198/18

Clinical study 198/18 was an open label, balanced, randomized, single dose, three treatment, three period, three sequence, crossover, oral food effect and fed bioequivalence study in healthy adult human subjects. Eighteen healthy adult subjects were randomized and completed the study. Primary objectives are listed below.
- To evaluate the effect of food on the rate and extent of absorption of Tramadol HCl oral solution (50 mg/10 mL) manufactured for [redacted] in healthy adult human subjects.
- To compare the rate and extent of absorption of Tramadol HCl oral solution (50 mg/10 mL) manufactured for [redacted] and Ultram® (tramadol HCl tablets) 50 mg manufactured for Janssen Pharmaceuticals, Inc., Titusville, New Jersey 08560, USA, in healthy adult human subjects under fed condition.

A secondary objective was to assess the safety and tolerability of Tramadol HCl oral solution (50 mg/10 mL) against Ultram (tramadol HCl tablets) 50 mg.

No adverse events were documented in this study. No subjects withdrew from the study.

4.3 Safety Profile

Safety profile of Tramadol HCl Oral Solution may be similar to that of Ultram (tramadol HCl tablets) 50 mg. Under NDA 214-044, Tramadol HCl Oral Solution is under development utilizing a 505 (b) (2) pathway with Ultram (Tramadol HCl tablets) 50 mg being the reference drug with respect to efficacy and safety. Phase 1 bioequivalence studies demonstrate equivalent between the two products with
respect to maximum tramadol and N-desmethyltramadol plasma concentrations and total exposure. It is likely that both products will have a similar oral abuse potential.

4.4 Evidence of Abuse, Misuse, and Diversion in Clinical Trials

In the two Phase 1 pharmacokinetic studies, dosing was conducted in the clinical setting with supervision of investigators thereby ensuring no opportunity for abuse, misuse, or diversion of the study drugs. There were no Phase 2 or Phase 3 studies conducted as part of the clinical development program.

4.5 Tolerance and Physical Dependence Studies in Humans

No tolerance or physical dependence studies in humans were submitted under NDA 214044. Like other approved mu-opioid analgesics, tramadol produces physical dependence and tolerance from continued use, as described in Ultram labeling.

5. Regulatory Issues and Assessment

Labeling – Language for Section 9 of the Label

As a 505(b)(2) application, the labeling of Tramadol Oral Solution will be similar to the label of the reference drug, namely ULTRAM.

The substance, tramadol, is in Schedule IV of the federal Controlled Substances Act (CSA). Due to the presence of tramadol, Tramadol HCL Oral Solution will also be in Schedule IV. The Schedule IV designation is provided in the Sponsor’s proposed label including under Section 9.

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 would be 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.”

Abuse-Deterrent Claims

As Tramadol HCl Oral Solution is not an abuse-deterrent formulation there are not abuse-deterrent claims regarding the formulation.

Risks Evaluation and Mitigation Strategies (REMS)

Tramadol HCl Oral Solution, as a take home medication, will be required to have a REMs.
FDA Advisory Committee Meeting

According to DAAP, Tramadol HCl Oral Solution will not be the subject of an FDA Advisory Committee.

6. Other Relevant Information

Foreign Labels

Tramadol oral solutions are marketed in other countries. An Internet search revealed Tramadol 100 mg/mL Oral Drops Solution available in the United Kingdom and (b)(4). However, foreign labels or evidence of abuse or misuse was not provided by Sponsor under NDA 214044.

Scientific and Medical Literature (PubMed Search)

Review of the scientific and medical literature did not reveal any evidence of misuse, abuse, or adverse events associated with abuse potential with respect to Tramadol Oral Solutions marketed in other countries.

Periodic Safety Update Reports (PSUR)

Tramadol oral solutions have not previously been marketed in the United States; as such, there are no periodic safety update reports (PSUR).

III. REFERENCES


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

/s/

JAMES M TOLLIVER
07/29/2020 03:20:19 PM

SILVIA N CALDERON
07/29/2020 03:24:41 PM

DOMINIC CHIAPPERINO
07/29/2020 03:44:27 PM
PLLRR Labeling Memorandum

Date: July 24, 2019  Date consulted: December 20, 2019

From: Jane Liedtka, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, DPMH
Lynne P. Yao, MD, OND, Division Director, DPMH

To: Taiye Adedeji, PharmD, Regulatory Project Manager (RPM),
Division of Anesthesiology, Addiction Medicine and
Pain Medicine (DAAP)

Drug: Tramadol HCl oral solution, 25 mg/5 mL.

NDA: 214044

Applicant: Athena Bioscience

Subject: Pregnancy and Lactation Labeling Rule (PLLRR) Conversion
[505(b)2 pathway New Drug Application (NDA)]

Indication: Tramadol HCl oral solution is an opioid agonist indicated in adults for the
management of pain severe enough to require an opioid analgesic and for
which alternative treatments are inadequate.

Limitations of Use
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended
doses (5.1), reserve Tramadol HCl oral solution for use in patients for whom alternative
treatment options [e.g., non-opioid analgesics]:
• Have not been tolerated or are not expected to be tolerated.
• Have not provided adequate analgesia or are not expected to provide adequate analgesia.

Materials Reviewed
• Sponsor’s submitted background package for NDA 214044, submitted on November 1, 2019.
• DPMH consult review of Ultram (tramadol), NDA 20281. Miriam Dinatale, D.O. October 13, 2015, DARRTS Reference ID 3829377\(^1\).
• DPMH consult review of Ultram (tramadol), NDA 20281. TSI 1418. Miriam Dinatale, D.O. February 13, 2017, DARRTS Reference ID 4055175\(^2\).

Consult Question:
Please 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.

INTRODUCTION AND BACKGROUND
• On November 1, 2019, the applicant, Athena Bioscience, submitted a new drug application via 505(b)2 pathway for the same indications, dosage, and administration as for the Reference Listed Drug (RLD) - ULTRAM. ULTRAM, NDA 20281 was first approved in the US in March of 1995.
• DAAP consulted DPMH on December 20, 2019 to provide input for appropriate labeling of the pregnancy and lactation sections of tramadol HCl oral solution, 25 mg/5 mL to comply with the PLLR format.
• Labeling for the RLD, ULTRAM\(^\circ\) was reviewed for PLLR conversion by DPMH in 2015 (see above referenced DPMH review dated October 13, 2015\(^3\)).
• Revisions to the Lactation subsection, 8.2 were proposed by DPMH in the review referenced above dated February 13, 2017.

Current State of the Labeling for the RLD-Ultram (tramadol)
• The most recently revised labeling for Ultram, dated October 7, 2019 is in Physicians Labeling Rule (PLR) format and complies with PLLR regulations.
• “Boxed Warnings” for Ultram include
  ○ Addiction
  ○ Abuse, and misuse

\(^1\) DPMH consult review of Ultram (tramadol), NDA 20281 was part of the materials reviewed, but was not relied upon for the purposes of the recommendations.
\(^2\) DPMH consult review of Ultram (tramadol), NDA 20281, TSI 1418, was part of the materials reviewed,
The following Contraindications appear in the 2019 Ultram label

- Children younger than 12 years of age
- Postoperative management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy
- Significant respiratory depression
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected gastrointestinal obstruction, including paralytic ileus
- Hypersensitivity to tramadol, any other component of this product or opioids
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days

“Warnings and Precautions” in the 2019 Ultram label include

- Serotonin Syndrome: May be life-threatening. Can occur with use of tramadol alone, with concomitant use of serotonergic drugs, with drugs that impair metabolism of serotonin or tramadol.
- Risk of Seizure: Can occur at the recommended dose of tramadol. Concomitant use with other drugs may increase seizure risk. Risk may increase in patients with epilepsy, a history of seizures, and in patients with a recognized risk for seizures.
- Risk of Suicide: Do not prescribe for suicidal or addiction-prone patients.
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off the opioid.
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration.
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of ULTRAM in patients with circulatory shock.
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of ULTRAM in patients with impaired consciousness or coma.

Under Section 8.1 Pregnancy, the PLLR converted Ultram label notes, under “Risk Summary”

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. Available data with ULTRAM in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage.

In animal reproduction studies, tramadol administration during organogenesis decreased fetal weights and reduced ossification in mice, rats, and rabbits at 1.4, 0.6, and 3.6 times the maximum recommended human daily dosage (MRHD). Tramadol decreased pup body weight and increased pup mortality at 1.2 and 1.9 times the MRHD [see Data]. Based on animal data, advise pregnant women of the potential risk to a fetus.
The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

- Under Section 8.1 Pregnancy, under subheading “Fetal/Neonatal Adverse Reactions” there is a “Clinical Considerations” that states
  Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in respiratory depression and physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

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

  Neonatal seizures, neonatal withdrawal syndrome, fetal death and still birth have been reported during post-marketing.

- Under Section 8.1 Pregnancy, under subheading “Labor or Delivery” there is a “Clinical Considerations” that states
  Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. ULTRAM is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including ULTRAM, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

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

  The effect of ULTRAM, if any, on the later growth, development, and functional maturation of the child is unknown.

Data

Animal Data

Tramadol has been shown to be embryotoxic and fetotoxic in mice, (120 mg/kg), rats (25 mg/kg) and rabbits (75 mg/kg) at maternally toxic dosages but was not teratogenic at these dose levels. These doses on a mg/m² basis are 1.4, 0.6, and 3.6 times the maximum recommended human daily dosage (MRHD) for mouse, rat and rabbit, respectively.
No drug-related teratogenic effects were observed in progeny of mice (up to 140 mg/kg), rats (up to 80 mg/kg) or rabbits (up to 300 mg/kg) treated with tramadol by various routes. Embryo and fetal toxicity consisted primarily of decreased fetal weights, decreased skeletal ossification and increased supernumerary ribs at maternally toxic dose levels. Transient delays in developmental or behavioral parameters were also seen in pups from rat dams allowed to deliver. Embryo and fetal lethality were reported only in one rabbit study at 300 mg/kg, a dose that would cause extreme maternal toxicity in the rabbit. The dosages listed for mouse, rat and rabbit are 1.7, 1.9 and 14.6 times the MRHD, respectively.

Tramadol was evaluated in pre- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg (1.2 times the MRHD) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (1.9 times the MRHD).

- Under Section 8.2 Lactation, under subheading “Risk Summary” the Ultram labeling states

  ULTRAM is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied.

Tramadol and its metabolite, O-desmethyltramadol (M1), are present in human milk. There is no information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. The M1 metabolite is more potent than tramadol in mu opioid receptor binding [see Clinical Pharmacology (12)]. Published studies have reported tramadol and M1 in colostrum with administration of tramadol to nursing mothers in the early post-partum period. Women who are ultra-rapid metabolizers of tramadol may have higher than expected serum levels of M1, potentially leading to higher levels of M1 in breast milk that can be dangerous in their breastfed infants. In women with normal tramadol metabolism, the amount of tramadol secreted into human milk is low and dose-dependent. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with ULTRAM [see Warnings and Precautions (5.4)].

- Under Section 8.2 Lactation, there is a “Clinical Considerations” that states

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

- Under Section 8.2 Lactation, there is a “Data” subsection that states
Following a single IV 100 mg dose of tramadol, the cumulative excretion in breast milk within 16 hours post dose was 100 mcg of tramadol (0.1% of the maternal dose) and 27 mcg of M1.

- Under Section 8.3 Females and Males of Reproductive Potential there is a subheading “Infertility” that states
  Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see Adverse Reactions (6.2)].

- Under Section 17 Patient Counseling Information there are the following subheadings and additional comments
  
  **Pregnancy**
  *Neonatal Opioid Withdrawal Syndrome*
  Inform female patients of reproductive potential that prolonged use of ULTRAM during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated and that the patient should inform their healthcare provider if they have used opioids at any time during their pregnancy, especially near the time of birth. [see Warnings and Precautions (5.5); Use in Special Populations (8.1)].

  **Embryo-Fetal Toxicity**
  Inform female patients of reproductive potential that ULTRAM may cause fetal harm and to inform the healthcare provider of a known or suspected pregnancy [see Use in Special Populations (8.1)].

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

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

**DATA REVIEW**

DPMH has completed multiple tramadol reviews including DPMH consult review of Ultram (tramadol), NDA 20281 dated October 13, 20151, and previously reviewed literature see the above DPMH reviews.
Pregnancy

Applicant’s Review of Literature
According to the Applicant, literature searches were conducted on PubMed from 01/01/1995 to the present. A total of 43 publications were identified and were reviewed by the applicant. Only one of these was considered relevant by the applicant to PLLR and is summarized below.

- Yefet et al. described a randomized, controlled trial using two modes of oral analgesia administration for the treatment of post-caesarean pain in the first 48 h following surgery: on-demand versus fixed time interval administration. Patients were randomly assigned to receive predetermined combinations of tramadol, paracetamol and diclofenac either following patient demand or at predetermined 6-h intervals for the first 48 h. The ‘fixed time interval’ group, compared with the ‘on-demand’ group, had lower mean pain score, higher satisfaction rate, more breastfeeds and less use of supplemental formulas. The number of times that drugs were given was slightly higher in the ‘fixed time interval’ group without an increase in maternal adverse effects, which were mild. No adverse effects were reported for the neonates.

Applicant Review of Pharmacovigilance Database (PVDB)
No pregnancies were identified in the sponsor’s PVDB.

DPMH’s Review of the Literature
DPMH conducted a search of published literature in PubMed using the search terms “Tramadol and pregnancy,” “Tramadol and pregnant women,” “Tramadol and pregnancy and birth defects,” “Tramadol and pregnancy and congenital malformations,” “Tramadol and pregnancy and stillbirth,” “Tramadol and spontaneous abortion” and “Tramadol and pregnancy and miscarriage” for the time period January 2020 through the present. No new relevant articles were identified.

Lactation

Applicant’s Review of the Literature
According to the Applicant, literature searches were conducted on PubMed from 01/01/1995 to the present. No new relevant publications were identified regarding lactation.

DPMH’s Review of Literature
DPMH conducted a search of published literature in PubMed using the search “tramadol and lactation” and “tramadol and breastfeeding” for the time period January 2020 through the present. No new relevant publications were identified.

Females and Males of Reproductive Potential

Applicant Review of the Literature
According to the Applicant, literature searches were conducted on PubMed from 01/01/1995 to the present. No new relevant publications were identified regarding fertility.

DPMH Review of the Literature
DPMH reviewed tramadol and effects on fertility in the published literature in PubMed using the search terms “tramadol and fertility” and “tramadol and infertility” for the time period January 2020 through the present. No new relevant publications were identified.

RECOMMENDATIONS
DPMH does not recommend revisions to the PLLR labeling for tramadol proposed in previous DPMH reviews.

DPMH Proposed Tramadol HCl oral solution Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

------------------USE IN SPECIFIC POPULATIONS------------------
• Pregnancy: May cause fetal harm (8.1).
• Lactation: Breastfeeding not recommended (8.2).

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. Available data with Tramadol HCl oral solution in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage.

In animal reproduction studies, tramadol administration during organogenesis decreased fetal weights and reduced ossification in mice, rats, and rabbits at 1.4, 0.6, and 3.6 times the maximum recommended human daily dosage (MRHD). Tramadol decreased pup body weight and increased pup mortality at 1.2 and 1.9 times the MRHD [see Data]. Based on animal data, advise pregnant women of the potential risk to a fetus.

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

Clinical Considerations
Fetal/Neonatal Adverse Reactions

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

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

Neonatal seizures, neonatal withdrawal syndrome, fetal death and still birth have been reported during post-marketing.

Labor or Delivery

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

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

The effect of Tramadol HCl oral solution, if any, on the later growth, development, and functional maturation of the child is unknown.

Data

Animal Data

Tramadol has been shown to be embryotoxic and fetotoxic in mice, (120 mg/kg), rats (25 mg/kg) and rabbits (75 mg/kg) at maternally toxic dosages, but was not teratogenic at these dose levels. These doses on a mg/m² basis are 1.4, 0.6, and 3.6 times the maximum recommended human daily dosage (MRHD) for mouse, rat and rabbit, respectively.
No drug-related teratogenic effects were observed in progeny of mice (up to 140 mg/kg), rats (up to 80 mg/kg) or rabbits (up to 300 mg/kg) treated with tramadol by various routes. Embryo and fetal toxicity consisted primarily of decreased fetal weights, decreased skeletal ossification and increased supernumerary ribs at maternally toxic dose levels. Transient delays in developmental or behavioral parameters were also seen in pups from rat dams allowed to deliver. Embryo and fetal lethality were reported only in one rabbit study at 300 mg/kg, a dose that would cause extreme maternal toxicity in the rabbit. The dosages listed for mouse, rat and rabbit are 1.7, 1.9 and 14.6 times the MRHD, respectively.

Tramadol was evaluated in pre- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg (1.2 times the MRHD) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (1.9 times the MRHD).

8.2 Lactation
Risk Summary
ULTRAM is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied.

Tramadol and its metabolite, O-desmethyldtramadol (M1), are present in human milk. There is no information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. The M1 metabolite is more potent than tramadol in mu opioid receptor binding [see Clinical Pharmacology (12)]. Published studies have reported tramadol and M1 in colostrum with administration of tramadol to nursing mothers in the early post-partum period. Women who are ultra-rapid metabolizers of tramadol may have higher than expected serum levels of M1, potentially leading to higher levels of M1 in breast milk that can be dangerous in their breastfed infants. In women with normal tramadol metabolism, the amount of tramadol secreted into human milk is low and dose-dependent. Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with ULTRAM [see Warnings and Precautions (5.4)].

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

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

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

17 Patient Counseling Information

Pregnancy

*Neonatal Opioid Withdrawal Syndrome*
Inform female patients of reproductive potential that prolonged use of ULTRAM during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated and that the patient should inform their healthcare provider if they have used opioids at any time during their pregnancy, especially near the time of birth. [see Warnings and Precautions (5.5); Use in Special Populations (8.1)].

*Embryo-Fetal Toxicity*
Inform female patients of reproductive potential that ULTRAM may cause fetal harm and to inform the healthcare provider of a known or suspected pregnancy [see Use in Special Populations (8.1)].

Lactation
Advise women that breastfeeding is not recommended during treatment with ULTRAM [see Warnings and Precautions (5.4); Use in Special Populations (8.2)].

Infertility
Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible [see Use in Special Populations (8.3)].
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/[s/]

JANE E LIEDTKA
07/24/2020 12:19:22 PM

LYNNE P YAO
07/27/2020 01:50:48 PM
PATIENT LABELING REVIEW

Date: July 24, 2020

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

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

From: Morgan Walker, PharmD, MBA, CPH
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Koung Lee, RPh, MSHS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

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

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

Application Type/Number: NDA 214044

Applicant: Athena Bioscience
1 INTRODUCTION

On November 1, 2019, Athena Bioscience submitted for the Agency’s review a New Drug Application (NDA) 214044 for TRADENAME (tramadol hydrochloride) oral solution. The proposed indication is in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) on February 7, 2020 for DMPP and OPDP to review the Applicant’s proposed Medication Guide (MG) for TRADENAME (tramadol hydrochloride) oral solution.

2 MATERIAL REVIEWED

- Draft TRADENAME (tramadol hydrochloride) oral solution MG received on November 1, 2019, and received by DMPP and OPDP on July 14, 2020.
- Draft TRADENAME (tramadol hydrochloride) oral solution Prescribing Information (PI) received on November 1, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 14, 2020.

3 REVIEW METHODS

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

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

In our collaborative review of the MG we:

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

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.

- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.
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/s/

MORGAN A WALKER
07/24/2020 12:33:57 PM

KOUNG U LEE
07/24/2020 12:43:14 PM

LASHAWN M GRIFFITHS
07/24/2020 12:45:29 PM
In response to DAAP’s consult request dated February 7, 2020, OPDP has reviewed the proposed product labeling (PI), Medication Guide/ and container labeling for the original NDA/BLA submission for QDOLO™ (tramadol hydrochloride) oral solution, C-IV.

**Labeling:** OPDP’s comments on the proposed labeling are based on the draft labeling received by electronic mail from DAAP on July 14, 2020 and are provided below.

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

**Container Labeling:** OPDP has reviewed the attached proposed container labeling submitted by the Sponsor to the electronic document room on June 16, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Koung Lee at (240) 402-8686 or Koung.lee@fda.hhs.gov.
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/s/

KOUNG U LEE
07/22/2020 02:38:52 PM
MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: June 4, 2020
Requesting Office or Division: Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number: NDA 214044
Product Name and Strength: Qdolo (tramadol hydrochloride) 25 mg/ 5 ml
Applicant/Sponsor Name: Athena Bioscience, LLC
OSE RCM #: 2019-2275-2
DMEPA Safety Evaluator: Zahra Farshneshani, PharmD
DMEPA Team Leader: Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM
The Applicant submitted a revised container label received on June 1, 2020 for Qdolo. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container label for Qdolo (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.a

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

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JUNE 1, 2020
Container labels
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/s/

ZAHRA FARSHNESHANI
06/04/2020 08:47:04 AM

OTTO L TOWNSEND
06/04/2020 12:45:46 PM
1 PURPOSE OF MEMORANDUM
The Applicant submitted a revised container label received on April 23, 2020 for Qdolo. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container label for Qdolo (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.a

2 CONCLUSION AND RECOMMENDATION
The revised container label is unacceptable from a medication error perspective. We provide our rationale and recommendations below in Table 1 for DAAP and Table 2 for Athena. We recommend Athena implement our recommendation prior to approval of NDA 214044:

<table>
<thead>
<tr>
<th>Identified Issue</th>
<th>Rationale for Concern</th>
<th>Recommendation</th>
</tr>
</thead>
</table>

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Table 1. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

<table>
<thead>
<tr>
<th>Identified Issue</th>
<th>Rationale for Concern</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Container Label</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. We note that the established name is presented as (b) (4) on the container label.</td>
<td>We confirmed with the Office of Product Quality (OPQ) that the established name for this product is “Tramadol Hydrochloride”.</td>
<td>We defer to OPQ to communicate this finding and recommendation to change the established name from (b) (4) to “Tramadol Hydrochloride” on the container label to the applicant.</td>
</tr>
</tbody>
</table>

Table 2. Identified Issue and Recommendation for Athena Bioscience, LLC (entire table to be conveyed to Applicant)

<table>
<thead>
<tr>
<th>IDENTIFIED ISSUE</th>
<th>RATIONALE FOR CONCERN</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Container Label</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. We acknowledge that you have modified the Principal Display Panel to present the product name, tramadol, with Tall Man Lettering (TML). However, we note that you have not altered the presentation of the product name to incorporate TML on the entire label.</td>
<td>TML in all instances may contribute to labeling differentiation with trazodone by minimizing the risk of product name confusion. All instances of the product name, tramadol, should be presented using TML on the container label.</td>
<td>To further address the risk of product name confusion between your tramadol product and marketed trazodone products, we recommend, tramadol, be presented using TML (i.e., traMAldol) on the entire container label for Qdolo (i.e., the content statement).</td>
</tr>
</tbody>
</table>
APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON APRIL 23, 2020

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

/s/

ZAHRA FARSHNESHANI
05/04/2020 03:48:43 PM

OTTO L TOWNSEND
05/05/2020 09:01:55 AM
## LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

<table>
<thead>
<tr>
<th>Date of This Review:</th>
<th>April 20, 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requesting Office or Division:</td>
<td>Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)</td>
</tr>
<tr>
<td>Application Type and Number:</td>
<td>NDA 214044</td>
</tr>
<tr>
<td>Product Name and Strength:</td>
<td>Qdolo (tramadol hydrochloride oral solution), 25 mg/ 5 ml</td>
</tr>
<tr>
<td>Product Type:</td>
<td>Single Ingredient Product</td>
</tr>
<tr>
<td>Rx or OTC:</td>
<td>Prescription (Rx)</td>
</tr>
<tr>
<td>Applicant/Sponsor Name:</td>
<td>Athena Bioscience, LLC</td>
</tr>
<tr>
<td>FDA Received Date:</td>
<td>November 1, 2019, February 18, 2020, April 13, 2020</td>
</tr>
<tr>
<td>OSE RCM #:</td>
<td>2019-2275</td>
</tr>
<tr>
<td>DMEPA Safety Evaluator:</td>
<td>Zahra Farshneshani, PharmD</td>
</tr>
<tr>
<td>DMEPA Team Leader:</td>
<td>Otto L. Townsend, PharmD</td>
</tr>
</tbody>
</table>
1 **REASON FOR REVIEW**

As part of the approval process for Qdolo (tramadol hydrochloride oral solution), the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the proposed Qdolo prescribing information (PI) and container label for areas of vulnerability that may lead to medication errors.

2 **BACKGROUND**

NDA 214044 is a 505(b)(2) NDA and the listed drug product is Ultram (tramadol hydrochloride tablets), NDA 020281. The proposed product would be the first FDA-approved oral solution dosage form for tramadol.

3 **MATERIALS REVIEWED**

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>B- N/A</td>
</tr>
<tr>
<td>ISMP Newsletters*</td>
<td>C- N/A</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)*</td>
<td>D- N/A</td>
</tr>
<tr>
<td>Other</td>
<td>E- N/A</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>F</td>
</tr>
</tbody>
</table>

N/A = not applicable for this review

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

4 **FINDINGS AND RECOMMENDATIONS**

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI) and container labels, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.
<table>
<thead>
<tr>
<th>Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IDENTIFIED ISSUE</strong></td>
</tr>
<tr>
<td>Prescribing Information – General Issues</td>
</tr>
<tr>
<td>1. The proprietary name, QDOLO, has been found conditionally acceptable.</td>
</tr>
<tr>
<td>Full Prescribing Information – Section 2 Dosage and Administration</td>
</tr>
<tr>
<td>1. Dosage is listed in milligram (mg) followed by volume in milliliters (mL). For example, 25 mg (5 mL).</td>
</tr>
<tr>
<td>Full Prescribing Information – Section 17 Patient Counseling</td>
</tr>
<tr>
<td>1. This product is a liquid dosage form. However, Section 17, does not contain instructions for the healthcare provider (HCP) 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.</td>
</tr>
</tbody>
</table>

\(^a\) Harris, D. FDA Communication: Proprietary Name Request Conditionally Acceptable for Qdolo. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 16. NDA 214044.
### Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

<table>
<thead>
<tr>
<th>IDENTIFIED ISSUE</th>
<th>RATIONALE FOR CONCERN</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Also, add similar instructions for the patient in the Medication Guide. For example, under “How should I take...?” section add, “Use an oral dosing syringe or other dosing device that measures in milliliters (mL) to correctly measure your dose. Ask your pharmacist for an oral dosing syringe if you do not have one.” However, we defer to the Division of Medical Policy Programs, Patient Labeling Team (PLT) for appropriate patient friendly language.</td>
</tr>
</tbody>
</table>

### Table 3. Identified Issues and Recommendations for Athena Bioscience, LLC (entire table to be conveyed to Applicant)

<table>
<thead>
<tr>
<th>IDENTIFIED ISSUE</th>
<th>RATIONALE FOR CONCERN</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Container Label</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. The product name, tramadol, is on the FDA List of Established Drug Names Recommended to Use Tall Man Lettering (TML).\(^b\)

The product name, tramadol has been confused with the product name, trazodone due to orthographic similarity and similar product characteristics such as dose (e.g., 50 mg). The use of tall man lettering and other labeling differentiation

To address the risk of product name confusion between your tramadol product and marketed trazodone products, we recommend, tramadol, be presented using tall man lettering (i.e., traMADol HCL) on the container label for Qdolo.

Table 3. Identified Issues and Recommendations for Athena Bioscience, LLC (entire table to be conveyed to Applicant)

<table>
<thead>
<tr>
<th>IDENTIFIED ISSUE</th>
<th>RATIONALE FOR CONCERN</th>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>strategies can be employed to address the risk of product name confusion.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. The statement “For Oral Administration Only” or “For Oral Use Only” is not present on the container labeling.</td>
<td>Post-marketing experiences has indicated that wrong route of administration errors have occurred when oral liquid products have been inadvertently administered as injections.</td>
<td>To minimize the risk of wrong route of administration medication errors, consider adding the statement, “For Oral Administration Only” to the principal display panel.</td>
</tr>
</tbody>
</table>

5 CONCLUSION

Our evaluation of the proposed Qdolo prescribing information (PI) and container labels identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Athena Bioscience, LLC so that recommendations are implemented prior to approval of this NDA.

---

Table 4 presents relevant product information for Qdolo that Athena Bioscience, LLC submitted on February 18, 2020 and the listed drug (LD), Ultram.

<table>
<thead>
<tr>
<th>Table 4. Relevant Product Information for Listed Drug and Qdolo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product Name</strong></td>
</tr>
<tr>
<td><strong>Initial Approval Date</strong></td>
</tr>
<tr>
<td><strong>Active Ingredient</strong></td>
</tr>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
</tr>
<tr>
<td><strong>Dosage Form</strong></td>
</tr>
<tr>
<td><strong>Strength</strong></td>
</tr>
<tr>
<td><strong>Dose and Frequency</strong></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
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.

Conversion from ULTRAM to Extended-Release Tramadol
The relative bioavailability of ULTRAM compared to extended-release tramadol is unknown, so conversion to extended-release formulations must be accompanied by close observation for signs of excessive sedation and respiratory depression.

Dosage Modification in Patients with Hepatic Impairment
The recommended dose for adult patients with severe hepatic impairment is 50 mg every 12 hours.

Dosage Modification in Patients with Renal Impairment
In all patients with creatinine clearance less than 30 mL/min, it is recommended that the dosing interval of ULTRAM be increased to 12 hours, with a maximum daily dose of 200 mg. Since only 7% of an administered dose is removed by hemodialysis, dialysis titration, TRAMADOL HYDROCHLORIDE ORAL SOLUTION 50 mg (10 mL) to 100 mg (20 mL) can be administered as needed for pain relief every 4 to 6 hours not to exceed 400 mg (80 mL)/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, TRAMADOL HYDROCHLORIDE ORAL SOLUTION 50 mg (10 mL) to 100 mg (20 mL) can be administered as needed for pain relief every four to six hours, not to exceed 400 mg (80 mL)/day.

Conversion from TRAMADOL HYDROCHLORIDE ORAL SOLUTION to Extended-Release Tramadol
The relative bioavailability of TRAMADOL HYDROCHLORIDE ORAL SOLUTION compared to extended-release tramadol is unknown, so conversion to extended-release formulations must be accompanied by close observation for signs of excessive sedation and respiratory depression.

Dosage Modification in Patients with Hepatic Impairment
The recommended dose for adult patients with severe hepatic impairment is 50 mg every 12 hours.

Dosage Modification in Patients with Renal Impairment
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patients can receive their regular dose on the day of dialysis. Dosage Modification in Geriatric Patients Do not exceed a total dose of 300 mg/day in patients over 75 years old.

hepatic impairment is 50 mg (10 mL) every 12 hours.

Dosage Modification in Patients with Renal Impairment

In all patients with creatinine clearance less than 30 mL/min, it is recommended that the dosing interval of TRAMADOL HYDROCHLORIDE ORAL SOLUTION be increased to 12 hours, with a maximum daily dose of 200 mg (40 mL). Since only 7% of an administered dose is removed by hemodialysis, dialysis patients can receive their regular dose on the day of dialysis.

Dosage Modification in Geriatric Patients

Do not exceed a total dose of 300 mg (60 mL)/day in patients over 75 years old.

### How Supplied

<table>
<thead>
<tr>
<th>How Supplied</th>
<th>Bottle of 100 tablets: NDC 50458-659-60</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A clear, grape flavored liquid containing tramadol HCl, 25 mg per (5 mL). Supplied in 16 oz bottles, NDC 71511-301-16</td>
</tr>
</tbody>
</table>

### Storage

<table>
<thead>
<tr>
<th>Storage</th>
<th>Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Store ULTRAM securely and dispose of properly.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dispense in a tight container. Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Store TRAMADOL HYDROCHLORIDE ORAL SOLUTION securely and dispose of properly.</td>
</tr>
<tr>
<td>Container Closure</td>
<td>16 oz white rectangular multiple unit bottle sealed with a white child-resistant closure.</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>white bottles with child-resistant closure.</td>
</tr>
</tbody>
</table>
APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Qdolo labels and labeling submitted by Athena Bioscience, LLC.

- Container label received on April 13, 2020
- Medication Guide received on February 18, 2020
- Prescribing Information (Image not shown) received on February 18, 2020

F.2 Label and Labeling Images

Container label

April 13, 2020

\[\text{(b)(4)}\]

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

/s/

ZAHRA FARSHNESHANI
04/20/2020 03:48:43 PM

OTTO L TOWNSEND
04/20/2020 04:28:26 PM