CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214044Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of New Drugs
Division of Anesthesiology, Addiction Medicine, and Pain Medicine

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NDA #:	**214044**
Product:	QDOLO (tramadol hydrochloride) oral solution
Applicant:	Athena Bioscience, LLC.
FROM:	Mark Liberatore, PharmD, RAC
DATE:	*See electronic signature*

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

Although the use of prescription opioid analgesics has begun to decline since 2012, there is still substantial use of this class of drugs. With that widespread use, a substantial problem persists with the abuse and misuse of prescription opioid products, resulting in serious adverse outcomes such as addiction, unintentional overdose, and death. The spectrum of behaviors contributing to these problems include inappropriate prescribing such as improper dosing, patient selection, and patient counseling as well as inappropriate patient behaviors such as improper use, storage, and disposal of prescription opioid products.

In July 2012, FDA determined that a REMS was required for the group of extended-release and long-acting (ER/LA) opioid analgesic formulations because there was a concern that ER/LA opioid analgesic formulations pose unique risks to patients due to their pharmacokinetic properties, duration of use, and the

amount of active ingredient contained in the drug product in comparison to their immediate-release opioid counterparts. This REMS included a Medication Guide to be dispensed with each ER/LA opioid analgesic prescription and elements to assure safe use that provides for training to be made available to healthcare providers who prescribe ER/LA opioid analgesics. The content of the training was based on the learning objectives established by the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting (ER/LA) Opioid Analgesics.

On September 18, 2018, the Division of Anesthesia, Analgesia, and Addiction Products (*former division name*) approved the Opioid Analgesics REMS which expanded the ER/LA Opioid Analgesics REMS to include IR opioid analgesics used in the outpatient setting. The REMS program required, for the first time, that training be made available to health care providers who are involved in the management of patients with pain (e.g., nurses, pharmacists), and not only to prescribers. Through a revised "Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain", the new REMS also required that the education cover broader information about appropriate pain management, including alternatives to opioids for the treatment of pain.

After consultations with the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for QDOLO (tramadol hydrochloride) to ensure that the benefits of the drug outweigh the risks of adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse.

In reaching this determination, we considered the following:

A. The indications for the IR opioid analgesics products result in use of these products in millions of patients. QDOLO (tramadol hydrochloride) is indicated in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

B. Pain that is severe enough to require an opioid analgesic such as QDOLO (tramadol hydrochloride) is a fairly serious condition, particularly for those patients who have pain due to etiologies that are unlikely to improve and/or for whom alternative treatments are inadequate.

C. The expected benefit of an QDOLO (tramadol hydrochloride) is the analgesic properties that enable the treatment of pain for which other treatments have been inadequate or not tolerated.

D. The expected duration of treatment with QDOLO (tramadol hydrochloride) is generally from days to weeks. Depending on the specific indication, treatment may be longer.

E. The most serious of the known adverse events associated with opioids,

including QDOLO (tramadol hydrochloride), are death, overdose, respiratory depression, CNS depression, abuse, and addiction.

F. QDOLO contains tramadol, which is not a new molecular entity.

In accordance with section 505-1 of the FDCA and under 21 CFR Part 208, FDA has determined that a Medication Guide is required for QDOLO (tramadol hydrochloride). FDA has determined that QDOLO (tramadol hydrochloride) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of QDOLO (tramadol hydrochloride). FDA has determined that QDOLO (tramadol hydrochloride) is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use QDOLO (tramadol hydrochloride).

The elements of the REMS will be a Medication Guide, elements to assure safe use including healthcare providers who prescribe the drug have particular training, and a timetable for submission of assessments of the REMS.

The shared system Opioid Analgesic REMS was approved on September 18, 2018. Upon approval, QDOLO (tramadol hydrochloride) will be joining this shared system REMS.

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/s/

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

Application Type	NDA
Application Number	214044
PDUFA Goal Date	September 1, 2020
OSE RCM #	2019-2450
Reviewer Name	Somya Dunn, MD
Team Leader	Carolyn Tieu, PharmD, MPH
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	September 1, 2020
Subject	Evaluation of REMS Submission
Established Name	tramadol hydrochloride
Trade Name	Qdolo
Name of Applicant	Athena Bioscience, LLC
Therapeutic Class	Opioid
Formulation(s)	25 mg/5 mL oral solution
Dosing Regimen	Starting dose: 25 mg (5 mL)/day, titrated in 25 mg (5 mL) increments as separate doses every 3 days to reach 100 mg (20 mL)/day (four times a day). Thereafter: total daily dose may be increased by 50 mg (10 mL) as tolerated every 3 days to reach 200 mg (40 mL)/day (four times a day). After titration: 50 mg (10 mL) to 100 mg (20 mL) administered as needed for pain every 4 to 6 hours not to exceed 400 mg (80 mL)/day.

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EXECUTIVE SUMMARY

This review evaluates the risk evaluation and mitigation strategy (REMS) submitted for tramadol hydrochloride oral solution (Qdolo) to ensure the benefits outweigh its risks. Athena Bioscience, LLC (Athena) submitted a New Drug Application (NDA) 214044 for Qdolo with the proposed indication for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate in adults.

The Agency has determined that a REMS is necessary for opioid analgesics that are intended to be used in the outpatient setting to ensure the benefits of the drug outweigh the risks of adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse. Qdolo is an opioid analgesic expected to be used in an outpatient setting and therefore a REMS is needed in order to be approved.

Athena submitted a Letter of Authorization (LOA) cross-referencing the approved Opioid Analgesic REMS. This REMS includes all opioids intended for use in the outpatient setting, which are not covered by another REMS, and mitigates the risks of serious adverse outcomes from addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse. The Opioid Analgesic REMS has a Type V Drug Master File (DMF),[a] DMF (b) (4), that contains the REMS Document, appended materials, and supporting document approved by the Agency on September 18, 2018. Therefore, the REMS for Qdolo is acceptable.

1 Introduction

This review evaluates the risk evaluation and mitigation strategy (REMS) submitted for tramadol hydrochloride oral solution (Qdolo) to ensure the benefits outweigh its risks. Athena Bioscience, LLC (the Applicant or Athena) submitted a New Drug Application (NDA) 214044 for Qdolo with the proposed indication for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate in adults. This NDA is under review in the Division of Anesthesia and Analgesia Products (DAAP).

The Agency has determined that a REMS is necessary for opioid analgesics that are intended to be used in the outpatient setting that are not already covered by another REMS program. The OA REMS is to ensure the benefits of the drug outweigh the risks of adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse. Qdolo is an opioid analgesic expected to be used in an outpatient setting; therefore, a REMS is needed in order for this product to be approved. Athena was authorized by the Drug Master File Holder (DMF) (b) (4) to cross-reference the approved Opioid Analgesic (OA) REMS. This Letter of Authorization (LOA) allows Athena to reference the REMS Document, appended materials, and

[a] Before the Agency can review the DMF information in support of an NDA, the DMF holder must also submit a duplicate LOA permitting FDA to reference the DMF. The applicant referencing a DMF is required to include a copy of the DMF holder's LOA in their NDA.

supporting document for the shared system OA REMS (DMF (b) (4)). The OA REMS is comprised of members collectively called the REMS Program Companies (RPC). The OA REMS includes elements to assure safe use (ETASU) and a timetable for submission of assessments and Medication Guides are product specific.

2 Background

2.1 Product Information

This application is for a non-new molecular entitity submitted via a 505(b)(2) regulatory pathway. The reference listed drug (RLD) for Qdolo is Ultram (tramadol hydrochloride tablets). Ultram was originally approved in March 1995 under NDA 20281 as an immediate-release formulation. Tramadol is a centrally-acting synthetic opioid analgesic and is indicated for the management of moderate to moderately severe pain in adults. The opioid activity in tramadol is due to the parent compound and its metabolite (M1). Human analgesia is dependent upon the plasma concentrations of each compound.

On November 1, 2019 Athena Bioscience, LLC submitted NDA 214044 for Qdolo, 25 mg/5 mL, pursuant to Section (505)b(2) of the Federal Food, Drug, and Cosmetic Act. Qdolo is intended for dosing every 4 to 6 hours (up to a maximum of 400 mg/day) 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 efficacy. Qdolo is a opioid anagelsic and like all opioids, it carries serious risks of abuse, misuse, and potential for overdose which may result in death.

2.2 Regulatory History

The following is a summary of the regulatory history for NDA 214044 relevant to this review:

- March 3, 1995: Tramadol was initially approved by the FDA under the trade name Ultram (NDA 20281).
- August 18, 2014: DEA placed all tramadol products and tramadol-containing products into Schedule IV of the Controlled Substances Act.[1]
- September 18, 2018: The Extended-Release/Long-Acting (ER/LA) REMS was modified to the OA REMS. This modification incorporated all of the tramadol-containing products and in addition, included the following changes:

    1. Include IR opioid analgesics intended for use in an outpatient setting

    2. Ensure that training is made available to healthcare providers involved in the treatment and monitoring of patients with pain (including nurses and pharmacists)

    3. Implement an updated FDA Blueprint (this was renamed the *Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain*) which requires the education to cover broad information about appropriate pain management

- November 1, 2019: Athena submitted an NDA seeking approval for tramadol oral solution through the 505(b)(2) regulatory pathway. The proposed labeling contained references to the OA REMS.
- June 3, 2020: The Agency sent an information request (IR) to the Applicant stating that since Tramadol Hydrochloride Oral Solution is an opioid analgesic expected to be used in an outpatient setting, it will need a REMS in order to be approved. In order for the Agency to review information in the DMF in support of the NDA, an LOA would be needed indicating that the Applicant had joined the OA REMS.
- June 9, 2020: The Applicant sent a response to the IR stating that they reached out to the RPC regarding joining the shared system and a Confidential Disclosure Agreement (CDA) had been fully executed with the RPC General Counsel for participation in the shared REMS system.
- June 25, 2020: The Applicant submitted the LOA indicating that they are authorized by the DMF Holder (b) (4) to crossreference the OA REMS.

3 Benefit Assessment

The efficacy of the tramadol oral solution is supported by a scientific bridge between the proposed product and the reference product, Ultram, in two pharmacokinetic (PK) studies. The Applicant proposed indication and dosing for Qdolo is the same as the approved Ultram oral tablet. The clinical program was supported by PK data that demonstrated comparable exposure and bioequivalence between tramadol oral solution and tramadol 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.

One of the two studies, 197/18 is considered as a pivotal study and was an open-label, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, crossover fasted oral relative bioavailability trial of tramadol HCl oral solution (25 mg/5 mL) and Ultram tramadol tablet (50 mg). The other PK study was 198/18, an open-label, balanced, randomized, single-dose, three-treatment, three-period, three-sequence, crossover, food effect (fed vs. fasting) trial. The results showed that tramadol oral solution 50 mg/10 mL met the bioequivalence criteria for both the area under the concentration-time curve (AUC) and maximum concentration (C_{max}) under the fasting conditions and food effect statistical analysis. Under fed conditions, there was a slight different in tramadol Cmax between the two products. This slight difference was not deemed to be clinically significant since the two products are bioequivalent under fasted conditions and there is no food effect observed.[2]

Due to the bioequivalence of Qdolo and the Ultram tablet, and the very similar PK profiles, a scientific bridge has been created which enables use of the Agency's prior efficacy findings for Ultram.[3]

4 Risk Assessment & Safe-Use Conditions

The safety population in the Qdolo pivotal trials consisted of 54 randomized healthy male adults who received a single dose of the study drug. There were no deaths, serious adverse events or significant adverse events in the clinical program. There were two treatment-emergent adverse events in study 197/18 of patients with vomiting and epigastric pain. Overall, Qdolo has a favorable adverse event

profile and is well-tolerated, with nausea and vomiting being the most frequently reported adverse effects. Review of the available safety data for Qdolo showed its safety profile to be comparable to that of tramadol tablets, the approved reference listed drug Ultram.

Although tramadol has a lower risk of respiratory depression compared to other opioids, such as morphine and oxycodone with similar analgesic efficacy, as an opioid, it still carries the risks associated with opioid medications, including abuse, misuse, addiction, and diversion. The approved product, Ultram, has warnings consistent with other opioids; labeling includes a boxed warning for addiction, abuse, misuse, respiratory depression, accidental ingestion, neonatal opioid withdrawal syndrome, interactions with drugs affecting cytochrome P450 isoenzymes and concomitant use with benzodiazepines and other CNS depressants. Qdolo labeling will also contain these box warnings.

Ultram and other opioids intended for use in the outpatient setting have a REMS in place to ensure that the benefits outweigh the risks of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse.

5 Risk Management Activities Proposed by the Applicant

5.1 Review of Applicant's Proposed REMS

On June 25, 2020, the Applicant submitted an LOA which gives them right of reference to the approved OA REMS in DMF (b) (4). The OA REMS is an educational effort and one of a number of national efforts that are designed to address the epidemic of prescription opioid abuse. The goal of the OA REMS is to educate prescribers and other healthcare providers (including pharmacists and nurses) on the treatment and monitoring of patients with pain. The education provided through the REMS program is based on the FDA Blueprint. Through better education, the healthcare team will have an improved understanding of how to manage pain and the role of opioid analgesics along with nonpharmacologic and non-opioid analgesics in pain management. The education will also provide information about the risks of opioids and use of other therapies which is intended to assist healthcare providers in reducing adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse. The REMS will accomplish this goal by:

1. Ensuring that training based on the FDA Blueprint is effective in educating prescribers and other healthcare providers involved in the treatment and monitoring of patients in pain (including pharmacists and nurses) about recommended pain management practices and appropriate use of opioid analgesics.
2. Informing patients about their roles and responsibilities regarding their pain treatment plan, including the risks of opioid analgesics and how to use and store them safely, as outlined in the Medication Guides and Patient Counseling Guide for opioid analgesics.

The OA REMS elements consists of a Medication Guide, and elements to assure safe use. The REMS elements to assure safe requirements state that the Opioid Analgesic Applicants must make training available to healthcare providers who prescribe and are involved in the treatment and monitoring of patients who receive opioid analgesics. The training must include all the educational elements detailed

in the FDA Blueprint. The OA REMS also consists of Healthcare Provider and Professional Society Licensing Board Letters and a Patient Counseling Guide.

The timetable for submission of assessments for the OA REMS requires the NDA Applicants to submit REMS Assessments reports at 6 months, 12 months, and annually thereafter from the date of the approval of the REMS (09/18/2018).

6 Conclusion & Recommendations

The Agency has determined that a REMS is necessary for opioid analgesics that are intended to be used in the outpatient setting to ensure the benefits of the drug outweigh the risks of adverse outcomes of addiction, unintentional overdose, and death resulting from inappropriate prescribing, abuse, and misuse. Qdolo is an opioid analgesic expected to be used in an outpatient setting and will require a REMS. The Applicant submitted a LOA cross-referencing the approved OA REMS. The approved OA REMS include the REMS Document, appended materials, and supporting document. Therefore, the REMS for Qdolo is acceptable.

Should DAAP have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

6.1 REFERENCES

[1] Federal Register /Vol. 79, No. 127 /Wednesday, July 2, 2014 /Rules and Regulations.

[2] Lee, D. Clinical Pharmacology Review for Qdolo, June 20, 2020.

[3] Khachikyan, Izabella. DAAP Clinical Review for Qdolo NDA 214044, darrted 9/1/2020.

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