CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209229Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
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	209229
PDUFA Goal Date	May 16, 2018
OSE RCM #	2018-749
Reviewer Name(s)	LaShaun Washington-Batts, Pharm.D.
Team Leader	Selena Ready, Pharm.D
Division Director	Cynthia LaCivita, Pharm.D
Review Completion Date	May 10, 2018
Subject	Evaluation of Need for a REMS
Established Name	Lofexidine Hydrochloride
Trade Name	Lucemyra
Name of Applicant	US WorldMeds, LLC
Therapeutic Class	Centrally acting alpha 2 adrenergic agonist
Formulation(s)	0.18 mg tablets
Dosing Regimen	Four 0.18 mg tablets QID; Recommended dose 2.88 mg/Day

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Lucemyra (lofexidine) is necessary to ensure the benefits outweigh its risks. US WorldMeds, LLC (Applicant) submitted a New Drug Application(NDA) 209229 for lofexidine with the proposed indication to mitigate the symptoms associated with opioid withdrawal and facilitate of completion of opioid discontinuation treatment. The risks associated with lofexidine includes hypotension, bradycardia, and orthostatic hypotension at higher doses. The applicant did not submit a REMS with this application but proposed a pharmacovigilance plan.

Lofexidine is a synthetic, non-narcotic, centrally acting alpha-2 adrenergic agonist that reduces the release of norepinephrine from the central nervous system (CNS). The Applicant's proposed indication is to mitigate the symptoms associated with opioid withdrawal and facilitate of completion of opioid discontinuation treatment. Lofexidine centrally suppresses the signs and symptoms of opioid withdrawal which can include: chills, sweating, stomach cramps, muscle pain, tachycardia, and runny nose by reducing noradrenergic hyperactivity when the inhibitory effects of opioids is removed. The product should be used as part of a long-term treatment plan for managing opioid use disorder (OUD) following discontinuation of opioids.

Currently, there are three alpha-2 adrenergic agonists in this class (clonidine, tizanidine, and dexmedetomidine) which have been FDA-approved for various indications such as hypertension (clonidine), attention deficit hyperactivity disorder (ADHD) (clonidine), muscle spasticity (tizanidine), and ICU sedation (dexmedetomidine). None of these products are approved for symptom management for opioid withdrawal, but clonidine has been used off-label for many years.

Lofexidine efficacy and safety in opioid withdrawal management is supported by three clinical studies in adult patients undergoing acute opioid withdrawal from immediate release (IR) opioids. Lofexidine has also been approved for over 25 years in the UK, where lofexidine is prescribed for opioid detoxification. The safety risks identified in the pivotal trials included hypotension, bradycardia, orthostatic hypotension, which were dose-dependent, and QT prolongation. The cardiovascular events are expected events associated with the use of other alpha-2 adrenergic agonists, such as clonidine, which is used as a hypotensive agent in the treatment of hypertension. The proposed labeling for lofexidine includes hypotension and bradycardia, and QT prolongation in the Warnings and Precautions and the Clinical Trials Experience. The proposed label also includes a Patient Package Insert that discusses low blood pressure and slow heart rate.

Based on the available data, DRISK has determined a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with lofexidine use are similar to other alpha-2 agonists in this class. Labeling of the safety concerns will provide healthcare providers who treat OUD with the necessary information to mitigate the risk of cardiovascular events and stresses the importance of patient monitoring. Should DAAAP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Lucemyra (lofexidine) is necessary to ensure the benefits outweigh its risks. US WorldMed, LLC (Applicant) submitted a New Drug Application (NDA) 209229 for lofexidine with the proposed indication for the mitigation of symptoms associated with opioid withdrawal and facilitation of completion of opioid discontinuation treatment. This application is under review in the Division of Anesthesia, Analgesia, and Addiction Products. The applicant did not submit a REMS with this application but proposed a pharmacovigilance plan.

2 Background

2.1 Product Information

Lofexidine is a synthetic, non-narcotic, centrally acting alpha-2 adrenergic agonist that reduces the release of norepinephrine from the central nervous system (CNS). The Applicant's proposed indication is to mitigate the symptoms associated with opioid withdrawal and facilitate of completion of opioid discontinuation treatment. Lofexidine centrally suppresses the signs and symptoms of opioid withdrawal which can include: chills, sweating, stomach cramps, muscle pain, tachycardia, and runny nose by reducing noradrenergic hyperactivity when the inhibitory effects of opioids is removed. The product should be used as part of a long-term treatment plan for managing opioid use disorder (OUD) following discontinuation of opioids.

The dose and duration of lofexidine is proposed as 0.72 mg [4 x 0.18 mg oral tablets, equivalent to 0.8 mg lofexidine hydrochloride (HCl)] given 4 times a day, with an intended daily dose of 2.88 mg (3.2 mg lofexidine HCl), for 7 days. (b) (4) (b) (4) The Applicant proposed that lofexidine will potentially be used in opioid treatment centers, hospitals, and clinics for patients undergoing abrupt opioid withdrawal of immediate-release (IR) opioids.

Lofexidine has been approved in the United Kingdom since 1992, marketed as BritLofex™, at 2.4 mg, prescribed to relieve symptoms in patients undergoing opioid detoxification.[1] Lofexidine is not a member of a class of drugs that requires a REMS and does not have a Boxed Warning in the proposed Prescribing Information (PI). Lofexidine has been granted Fast Track Designation.

2.2 Regulatory History

The following is a summary of the regulatory history for NDA 209229 relevant to this review:

- **12/15/2016**: The Agency granted Fast Track Designation.
- **05/03/2017:** The Applicant submitted a NDA 209229 for lofexidine hydrochloride.
- **07/27/2017**: The Applicant amended their application to request priority review.

- **07/28/2017:** The Applicant submitted a Risk Management (Non-REMS) Pharmacovigilance Plan.
- **03/27/2018:** Advisory Committee Meeting was convened to discuss the clinical relevance of lofexidine in the mitigation of symptoms associated with opioid withdrawal and if lofexidine facilitates the completion of abrupt opioid discontinuation treatment in patients with opioid use disorder. The AC voted 11:1 in favor of approval. A REMS proposal was not discussed at this meeting.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

There are about 36 million people that are affected by opioid abuse and dependence globally. An estimated 4.3 million people in the US suffered from substance use disorders related to prescription pain medications in 2014. The social impact of opioid abuse, dependence, and addiction, are rising substantially. In 2015, there were over 30,000 deaths due to opioid overdose in the US. Economically, the cost of opioid abuse is estimated to be from $53 billion to $72 billion annually, this is comparable to treating chronic diseases such as asthma or HIV.[2]

Opioid use reduces the perception of pain but produces drowsiness, mental confusion, euphoria, nausea, constipation, and, at higher doses, can depress respiration. The use of illegal drugs, such as heroin and prescription opioid pain relievers, such as oxycodone and hydrocodone, can cause serious health effects in those who misuse them. The euphoric response some people experience to opioid medications, cause people to misuse them to try to intensify the experience by injecting or snorting. Using these methods put the user at risk of serious medical complications, including overdose and death.

OUD is a physical dependence to opioids and is an expected physiological response to chronic opioid exposure, associated with a down-regulation of endogenous endorphins and dynorphins. The symptoms of withdrawal include flu-like manifestations, vomiting, diarrhea, abdominal cramping, runny nose/eyes, and feelings of anxiety. Opioid withdrawal symptoms occur both in patients who have been using opioids appropriately, and in patients with OUD.

There are no approved medications for the treatment of OUD. However, methadone and buprenorphine are indicated for opioid dependence/withdrawal. These medications are both controlled substances, have the potential for abuse, and can only be used in licensed addiction-treatment programs. Clonidine and tizanidine are used off-label to decrease anxiety and other signs and symptoms of autonomic overactivity.[3] Table 1 provides a summary of treatment options relevant to the proposed indication for lofexidine.

Table 1: Summary of Treatment Options Relevant to Proposed Indication[3]

Product Name	Relevant Indication	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Methadone	For detoxification treatment of opioid addiction (heroin and other morphine-like drugs)	Oral, 40 mg per day in divided doses, gradual taper	Not described in product label	Respiratory depression, misuse and diversion, QT prolongation	Restricted to use in a certified opioid treatment program or inpatient setting
Buprenorphine/ naloxone	Used off label for withdrawal management	Up to 8/2 mg to 16/4 mg SL per day (Suboxone and its generics), taper	Not approved for withdrawal management	Respiratory depression, misuse and diversion	
Clonidine	Used off label for withdrawal management	75-300 ug tid	Not approved for withdrawal management	Rebound hypertension, hypotension, bradycardia	

4 Benefit Assessment[4,5,6]

This NDA is supported by two pivotal studies, USWM-LXI-3003-1[6] and USWM-LXI-3002. The objective of study USWM-LXI-3003-1 (LXI-3003-1) was to evaluate the efficacy, safety, and dose-response of lofexidine in reducing withdrawal symptoms and facilitating completion of opioid discontinuation treatment in patients undergoing withdrawal from short-acting opioids. LXI-3003-1 was divided into two parts, based on the opioid withdrawal period. Part 1 (n=603) was a randomized, double-blind, placebo controlled, parallel-group study that evaluated opioid dependent adults (male n=427; female n=176) undergoing abrupt withdrawal from short-acting opioids in an inpatient setting on Days 1 to 7 of the opioid withdrawal period. Lofexidine doses in Part 1 were 2.4 mg/day (n=230), 3.2 mg/day (n=222) or placebo (n=151). Part 2 (n=83) of LXI-3003-1 was an optional open-label inpatient/outpatient treatment continuation conducted on Days 8-14 of the opioid withdrawal treatment period. Lofexidine doses in Part 2 were variable, not to exceed 3.2 mg/day. The concomitant medications allowed in both parts of the study were aluminum hydroxide, magnesia, simethicone, bismuth sulfate, acetaminophen, zolpidem. The primary efficacy endpoint for LXI-3003-1 Part 1 was total scores from the Short Opiate Withdrawal Scale-Gossop (SOWS-Gossop), a 10-item questionnaire developed to evaluate opioid withdrawal symptom severity. The patients rated their withdrawal symptoms as 0 (none), 1 (mild), 2 (moderate), or 3 (severe) to each item on the questionnaire and their scores were tallied to a total sum. The secondary endpoint was the number of study completers, defined as the number of patients who received at least one dose of study drug on Day 7 and completed the post-dose SOWS-Gossop on Day 7. Based on the results of LXI-3003-1, lofexidine demonstrated better efficacy than placebo for reducing

opioid withdrawal symptoms in patients undergoing abrupt withdrawal from short-acting opioids and resulted in a greater percentage of patients completing withdrawal.

The primary objective of study USWM-LXI-3002 (LXI-3002) was to evaluate the efficacy of lofexidine in reducing withdrawal symptoms in patients undergoing opioid withdrawal management. LXI-3002 was a randomized, double-blind, placebo controlled, parallel-group study (n=264) that evaluated opioid dependent adults (male n=200; female n=64) undergoing abrupt withdrawal from short-acting opioids in an inpatient setting on Days 1-7 of the opioid withdrawal period. (Subjects with a dependence on or use of long-acting opioids were excluded to minimize the variability in the timing of withdrawal symptoms and concerns about potential QTc prolongation.) On Days 1-5, study patients received lofexidine 3.2 mg/day (n=134) or placebo (n=130). On Days 6-7, all study patients received placebo. Study primary efficacy endpoints were SOWS-Gossop scores on Day 3 and the time-to-dropout. The secondary endpoints included the daily mean Sows-Gossop scores, proportion of completers, and proportion and daily mean of subjects requiring any concomitant medications for withdrawal symptoms. Based on the results of LXI-3002, lofexidine demonstrated better efficacy than placebo for reducing opioid withdrawal symptoms in patients undergoing abrupt withdrawal from short-acting opioids.

Studies LXI-3001, LXI-3002, and LXI-3003-1 provided safety data for treatment-emergent serious adverse events (SAEs). The clinically significant treatment-emergent SAEs included hypotension ((b) (4) %), bradycardia ((b) (4) %), and orthostatic hypotension ((b) (4) %), which appeared to be dose dependent. A small number of subjects experienced syncope (0.9%) and the incidence of dose holds for symptomatic hypotension or bradycardia criteria was higher in the 3.2 mg group compared to the 2.4 mg group. Blood pressure elevations with discontinuation of lofexidine were noted to be above normal and above pre-treatment values. This elevation was noted to peak on Day 2 after discontinuation, and were observed after abrupt discontinuation and after a two-day dose reduction.

5 Risk Assessment & Safe-Use Conditions[5,6]

The safety risks identified in the pivotal trials included hypotension, bradycardia, and orthostatic hypotension, which were dose-dependent (higher in the 3.2 mg/day group as compared to the 2.4 mg/day group.) Of note, these events occurred at greater incidence in women than men at the 3.2 mg dose. These cardiovascular events are expected events associated with the use of other alpha-2 adrenergic agonists, such as clonidine, which is used as a hypotensive agent in the treatment of hypertension. Hypertension is one of the symptoms of opioid withdrawal that typically begins in the first 24 hours and thus, stimulating the alpha-adrenoreceptors in the brain stem results in decreases in heart rate, and blood pressure. Clonidine lists these specific cardiovascular events in the Adverse Reactions Section of the approved PI. The proposed labeling for lofexidine includes hypotension and bradycardia in the Warnings and Precautions and the Clinical Trials Experience. The proposed label also includes a Patient Package Insert that discusses low blood pressure and slow heart rate.

An additional safety risk identified in the pivotal trials was QT prolongation. However, the degree of QT prolongation was not clinically significant at concentrations expected with the proposed dosing and the changes were generally observed on the first days of treatment and returned towards baseline over the

course of treatment. The proposed labeling includes QT prolongation in the Warnings and Precautions Section.

6 Expected Postmarket Use

Lofexidine will likely be used to manage opioid withdrawal symptoms in any treatment setting, inpatient or outpatient. The severity of dependence and withdrawal symptoms may determine where patients may receive treatment. Those addicted to prescription and non-prescription opioid products, are potential candidates for lofexidine.

7 Risk Management Activities Proposed by the Applicant

The applicant did not submit a REMS with this application but proposed a pharmacovigilance plan.

8 Discussion of Need for a REMS

Lofexidine is a centrally acting alpha 2 adrenergic agonist with a proposed indication to mitigate the symptoms associated with opioid withdrawal and facilitate completion of opioid discontinuation treatment. Currently, there are three alpha 2 adrenergic agonists in this class (clonidine, tizanidine, and dexmedetomidine) which have been FDA-approved for various indications such as hypertension (clonidine), attention deficit hyperactivity disorder (ADHD) (clonidine), muscle spasticity (tizanidine), and ICU sedation (dexmedetomidine). None of these products are approved for symptom management for opioid withdrawal, but clonidine has been used off-label for many years.

Lofexidine efficacy and safety in opioid withdrawal management is supported by three clinical studies in adult patients undergoing acute opioid withdrawal from IR opioids. Lofexidine has also been approved for over 25 years in the UK, where lofexidine is prescribed for opioid detoxification. In addition, there are various published data comparing lofexidine and clonidine, which share similar side effect profiles, that concludes that in the treatment of opioid withdrawal lofexidine has a better benefit-risk profile than clonidine. Per the FDA-approved labeling, other drug products in this class have similar cardiovascular adverse events as lofexidine and these have been mitigated with labeling. The currently approved alpha-2 adrenergic agonists do not have a REMS.

The cardiovascular risks associated with lofexidine, including hypotention, bradycardia, orthostatic hypotension, and QT prolongation are listed in the Warnings and Precautions of the proposed labeling. The Applicant has provided specific information on how to prevent adverse events from occurring in specific patient populations, including patients with renal and hepatic impairment, poor CYP2D6 Metabolizers, and co-morbid dependencies. They specify the drug interactions of lofexidine with methadone and naltrexone. Based on the listed Warning and Precautions in the labeling, similar chemical properties to clonidine, proposed pharmacovigilance activities, and clinical safety data, DRISK has determined that a REMS is not necessary to ensure the benefits of lofexidine outweigh its risks.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with lofexidine use are similar to other alpha-2 agonists in this class. Labeling of the safety concerns will provide healthcare providers who treat OUD with the necessary information to mitigate the risk of cardiovascular events and stresses the importance of patient monitoring.

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

10 Appendices

10.1 References

1. FDA Briefing Document, Meeting of Psychopharmacologic Drugs Advisory Committee March 27, 2018
2. Substance Abuse and Mental Health Services Administration, https://www.samhsa.gov/disorders/substance-use; updated October 27, 2015
3. Kahn A, Mumford JP, Rogers GA, Beckford H, Double-blind study of lofexidine and clonidine in the detoxification of opiate addicts in hospital. Drug Alcohol Depen 1997:44:57-61.
4. US WorldMeds, LLC Lucymra (lofexidine HCL), Module 2.5 Clinical Overview.
5. US WorldMeds, LLC Lucymra (lofexidine HCL), Module 2.7.3 Summary of Clinical Efficacy
6. US WorldMeds, LLC Lucymra (lofexidine HCL), Module 2.7.4 Summary of Clinical Safety
7. Study registration for USWM-LXI-3003-1, https://clinicaltrials.gov/ct2/show/NCT01863186

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/s/

LASHAUN WASHINGTON-BATTS
05/10/2018

CYNTHIA L LACIVITA
05/10/2018