DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209229

NDA APPROVAL

US World Meds, LLC
4441 Springdale Rd
Louisville, KY 40241

Attention: Polly F. Eifert
Sr. Regulatory Manager

Dear Ms. Eifert:

Please refer to your New Drug Application (NDA) dated and received September 26, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for LUCEMYRA (lofexidine) tablets, 0.18 mg.

This new drug application provides for the use of LUCEMYRA for the mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the prescribing information, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry, *SPL Standard for Content of Labeling Technical Qs and As*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels, submitted on May 7, 2018, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically

according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 209229**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for > 7 days and < 12 years because necessary studies are impossible or highly impracticable. This is because children in this age range would experience opioid withdrawal due to iatrogenic opioid dependence, and opioids are generally not *abruptly* discontinued in children with iatrogenic opioid dependence.

We are deferring submission of your pediatric studies for ages birth to 7 days (neonates), and 12 to < 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. These required studies are listed below.

3391-1 Conduct a juvenile animal study in rats from post-natal day (PND) 36 to PND 90 to support pediatric drug development in children aged 12 to 17 years. The study will evaluate the effect of the drug on growth and development, specifically, reproductive capacity, bone development, and the central nervous system histopathology and long-term functional effects (learning and memory, motor function. reflexes, and an assessment of social interaction or other higher-cognitive functioning).

The timetable you submitted via email on May 16, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/2018
Study Completion:	03/2019
Final Report Submission:	10/2019

3391-2 Conduct a pharmacokinetic and safety study of lofexidine in adolescents age 12 to 17 years with opioid withdrawal syndrome.

The timetable you submitted via email on May 16, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	05/2019
Study Completion:	05/2021
Final Report Submission:	11/2021

3391-3 Conduct a juvenile toxicology in rats to evaluate the impact of lofexidine on early neuronal development during peak synaptogenesis to support pediatric studies in neonates and children under the age of 3.

The timetable you submitted via email on May 16, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2019
Final Protocol Submission:	02/2020
Study Completion:	09/2020
Final Report Submission:	03/2021

3391-4 Conduct a dose-ranging pharmacokinetic, safety, and efficacy study of lofexidine in neonates with neonatal opioid withdrawal syndrome.

The timetable you submitted via email on May 16, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2021
Final Protocol Submission:	03/2022
Study Completion:	02/2024
Final Report Submission:	08/2024

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of genetic toxicity, impairment of fertility, general toxicity, or adverse effects on development in juvenile animals; it will also not be sufficient to assess a signal of serious hypotension, bradycardia, syncope, hepatotoxicity, or rebound hypertension; or identify potential unexpected serious risks of long-term use of lofexidine in the setting of gradual opioid taper.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

3391-5 Conduct an in vivo comet assay testing lofexidine in the liver and stomach.

The timetable you submitted via email on May 16, 2018, states that you will conduct this study according to the following schedule:

Study Completion:	06/2018
Final Report Submission:	09/2018

3391-6 Conduct a pharmacokinetic study in the rat to characterize the plasma levels of lofexidine and the lofexidine metabolites LADP (N-(2-aminoethyl)-2-(2,6-dichlorophenoxy)propenamide), LDPA (2-(2,6-dichlorophenoxy)propionic acid), and 2,6-DCP (2,6-dichlorophenol) using a validated assay.

The timetable you submitted via email on May 16, 2018, states that you will conduct this study according to the following schedule:

Study Completion:	06/2018
Final Report Submission:	07/2018

3391-7 Conduct a juvenile animal study in rats from PND 7 to 90 to support pediatric drug development in children and neonates. The study will evaluate the effect of the drug on growth and development, specifically, reproductive capacity, bone development, and the central nervous system histopathology and long-term functional effects (learning and memory, motor function. reflexes, and an assessment of social interaction or other higher-cognitive functioning).

The timetable you submitted via email on May 16, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2019
Final Protocol Submission:	06/2019
Study Completion:	06/2020
Final Report Submission:	01/2021

3391-8 Conduct a fertility and early embryonic development study in rats testing lofexidine administration to males and include histopathology of the testes and sperm assessments (count, motility, and morphology).

The timetable you submitted via email on May 16, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2018
Final Protocol Submission:	03/2019
Study Completion:	03/2020
Final Report Submission:	09/2020

3391-9 Conduct a 90-day GLP repeat-dose toxicology study in the rat testing lofexidine HCl to establish a NOAEL to support clinical studies that are longer than 14 days in duration. To avoid the potential confounding impact of C_{max}-induced fluctuations in physiology, which could impact the NOAEL, dose the animals several times a day, as feasible, to mimic the clinical setting.

The timetable you submitted via email on May 16, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	08/2018
Final Protocol Submission:	12/2018
Study Completion:	09/2019
Final Report Submission:	01/2020

3391-10 Conduct a dose-ranging pharmacokinetic and safety study of lofexidine in children age 6 to 17 years with iatrogenic opioid withdrawal; the pharmacokinetic component of the study is limited to children aged 6 to 12 years old.

The timetable you submitted via email on May 16, 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	10/2021
Study Completion:	10/2023
Final Report Submission:	04/2024

3391-11 Conduct a dose-ranging pharmacokinetic and safety study of lofexidine in children age >7 days to 6 years with iatrogenic opioid withdrawal.

The timetable you submitted via email on May 16, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	04/2021
Final Protocol Submission:	04/2022
Study Completion:	04/2024
Final Report Submission:	10/2024

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of serious hypotension, bradycardia, syncope, hepatotoxicity, or rebound hypertension; or identify potential unexpected serious risks of long-term use of lofexidine in the setting of gradual opioid taper.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

3391-12 Conduct a randomized, controlled clinical trial to assess the safety and efficacy of lofexidine for use beyond 14 days duration in the setting of gradual opioid taper. The safety evaluation must include the following:

a. adequate assessment of and monitoring for drug-induced liver injury
b. adequate assessment of and monitoring for blood pressure increases upon discontinuing lofexidine.

The timetable you submitted via email on May 16, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	11/2018
Final Protocol Submission:	02/2020
Study Completion:	02/2022
Final Report Submission:	09/2023

The pediatric trials below will not be initiated until after the trial in adults (3391-12) has been completed.

3391-13 Conduct a safety and efficacy study of lofexidine in children and adolescents age 6 to 17 years with iatrogenic opioid withdrawal.

The timetable you submitted via email on May 16, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2023
Final Protocol Submission:	02/2024
Study Completion:	02/2027
Final Report Submission:	08/2027

3391-14 Conduct a safety and efficacy study of lofexidine in subjects age > 7 days to 6 years with iatrogenic opioid withdrawal.

The timetable you submitted vial email on May 16, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	08/2023
Final Protocol Submission:	08/2024
Study Completion:	08/2027
Final Report Submission:	08/2028

Submit clinical protocol(s) to your IND 047857 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital

letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

We remind you of your postmarketing commitment:

3391-15 Due to the concern about product quality (specifically, tablet integrity, i.e., tablets becoming tacky and sticking together), provide reports twice yearly (semi-annually) of these product quality complaints, any adverse events or medication errors associated with or suspected to be associated with product quality, and any patient or provider complaints regarding product quality. After three years of submitting semiannual reports, submit a comprehensive discussion of the reports of these product quality issues; any adverse events or medication errors associated with or suspected to be associated with product quality; and any patient or provider complaints regarding product quality; and provide an explanation of how you addressed those adverse events.

First semiannual report – Year 1:	12/28/2018
Second semiannual report – Year 1:	06/14/2019
First semiannual report – Year 2:	12/27/2019
Second semiannual report – Year 2:	06/12/2020
First semiannual report – Year 3:	12/25/2020
Final semiannual report submission – Year 3:	06/11/2021

Under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

EXPIRY DATING PERIOD

A 36-month expiry dating period is granted for LUCEMYRA (lofexidine) tablets, in 36- and 96-count bottles with (b) (4) desiccant, when stored at 25°C (77°F) with excursions permitted from 15° and 30°C (59° and 86°F).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Kimberly Compton, Senior Regulatory Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Mary T. Thanh Hai, MD
Acting Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY A COMPTON
05/16/2018

MARY T THANH HAI
05/16/2018