CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217389Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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***

Date of This Review:	May 9, 2024
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 217389
Product Name, Dosage Form, and Strength:	Ohtuvayre (ensifentrine) inhalation suspension, 3 mg/2.5 mL
Applicant Name:	Verona Pharma
FDA Received Date:	May 7, 2024
TTT ID #:	2023-5267-1
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT

1 PURPOSE OF MEMORANDUM

Verona Pharma submitted revised container labels and carton labeling received on May 7, 2024 for Ohtuvayre. The Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised container labels and carton labeling for Ohtuvayre (Appendix A) to determine if they are 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

Regarding the plastic ampules, we note that Verona stated they *"removed all text (including the statement* (b) (4) *from the back side of the ampule. The front side of the ampule contains all required information per 21 CFR 201.10(i)."* after reevaluation of our Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. We find this proposal acceptable from a medication error perspective.

Verona Pharma implemented all of our recommendations and we have no additional recommendations at this time.

5 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Owens, L. Label and Labeling Review for ensifentrine (NDA 217389). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 OCT 30. TTT ID: 2023-5267.

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/

LISSA C PRINGLE-OWENS
05/09/2024 06:19:39 AM

DAMON A BIRKEMEIER
05/09/2024 08:18:27 AM

The Clinical Inspection Summary

Date	May 9, 2024
From	Tina Chang, M.D., Medical Officer Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Alison Lennox, M.D., Clinical Reviewer Robert Lim, M.D., Team Leader, Deputy Director for Safety Banu Karimi-Shah, M.D., Deputy Division Director Linda Ebonine, Senior Regulatory Project Manager Division of Pulmonary, Allergy, and Critical Care (DPACC)
NDA #	217389
Applicant	Verona Pharma
Drug	Ensifentrine
NME (Yes/No)	Yes
Proposed Indication(s)	For the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD)
Consultation Request Date	August 10, 2023
Summary Goal Date	May 26, 2024
Action Goal Date	June 26, 2024
PDUFA Date	June 26, 2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Regina Deckelmann, Thomas Lienert, Jose Diaz, Thomas Siler, and the contract research organization (CRO) (b) (4) were inspected in support of NDA 217389, covering two clinical studies, RPL554-CO-301 and RPL554-CO-302. Based on the inspection results, the studies appear to have been conducted adequately, and the data generated by the clinical investigator sites and submitted by the sponsor appear acceptable in support of this NDA.

II. BACKGROUND

According to the sponsor, ensifentrine is a small molecule selective dual inhibitor of phosphodiesterase 3 and phosphodiesterase 4. The sponsor submitted NDA 217389 for maintenance treatment of patients with chronic obstructive pulmonary disease (COPD). The sponsor submitted two Phase 3 studies, RPL554-CO-301 and RPL554-CO-302, to support this application. The following briefly describes the two protocols:

> **RPL554-CO-301:** "A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ensifentrine Over 24 Weeks (With a 48-Week Safety Subset) in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease."

Protocol RPL554-CO-301 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled safety and efficacy study. The primary objective was to evaluate the efficacy of ensifentrine on lung function compared to placebo over a 12-hour dosing interval in subjects with moderate to severe COPD.

Sites: The study was conducted at a total of 120 study sites randomized study subjects in 12 countries (Bulgaria, Czech Republic, Germany, Greece, Hungary, South Korea, Poland, Romania, Russia, Slovakia, United Kingdom, and United States).

Subjects: A total of 760 subjects were randomized (i.e., 477 subjects who received ensifentrine, 283 who received placebo), and 645 subjects completed Treatment Period (i.e., 400 who received ensifentrine, 245 who received placebo).

Study initiation and completion dates: 29 September 2020 (first patient, first visit); 02 December 2022 (last patient, last visit)

Database lock date and study unblinding date of the study: 12 December 2022 (database lock date) and 13 December 2022 (study unblinding date)

Subjects with moderate to severe COPD were to be randomized to ensifentrine or placebo administered via a nebulizer twice daily over 24 weeks (also known as the 24-week stratum) with a subset of subjects treated for 48 weeks (also known as the 48-week stratum). The 24-week stratum was randomized 1:1 to ensifentrine or placebo while the 48-week stratum of subjects were randomized 3:1 ensifentrine or placebo. The dose of ensifentrine was 3 mg twice daily using the inhaled route via a standard jet nebulizer. Moderate to severe COPD was defined as postbronchodilator FEV1 30% – 70% predicted and pre- and post-bronchodilator FEV1/forced vital capacity (FVC) ratio <0.70. All sites were to use standardized spirometry equipment provided by a central vendor, and all spirometry results were read by a blinded central vendor.

Subjects were screened for eligibility, and eligible subjects entered a 28-day run-in period to ensure a stable background maintenance long-acting muscarinic antagonist (LAMA) or long-acting beta agonist (LABA) bronchodilator medication regimen and to collect baseline information on symptoms and rescue medication use. All subjects were provided with rescue albuterol/salbutamol for use as needed during the study. Subjects completing treatment were to complete a follow-up visit within 4 to 10 days of the last scheduled study visit. The 48-week stratum was intended to provide information on the long-term safety of ensifentrine as well as on exacerbation and health care utilization vs placebo. The 3:1 randomization in this subset was intended to minimize the number of subjects randomized to placebo for 48 weeks.

Key inclusion criteria: Male or female subjects 40 to 80 years of age with at least 10 pack-years smoking history and COPD diagnosis as defined by the American Thoracic Society/European Respiratory Society guidelines with symptoms compatible with COPD. Subjects also had to have COPD symptoms with a score of ≥2 on the Modified Medical Research Council Dyspnea Scale. Subjects' severity of COPD had to be pre- and post-albuterol/salbutamol FEV1/FVC ratio of <0.70 and post albuterol/salbutamol FEV1 ≥30 % and

≤70% of predicted normal. Please see protocol for full details pertaining to eligibility criteria.

Primary efficacy endpoint: Change from baseline in average forced expiratory volume in 1 second (FEV_1) area under the curve $(AUC)_{0\text{-}12h}$ post-dose at Week 12.

Protocol RPL554-CO-302: "A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ensifentrine over 24 Weeks in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease."

Protocol RPL554-CO-302 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled safety and efficacy study. The primary objective was to evaluate the efficacy of ensifentrine on lung function compared to placebo over a 12-hour dosing interval in subjects with moderate to severe COPD.

Sites: The study was conducted at total of 130 study sites randomized subjects in 10 countries (Belgium, Bulgaria, Canada, Denmark, Estonia, Hungary, Poland, Slovakia, Spain, and the United States of America).

Subjects: A total of 790 subjects were randomized (i.e., 498 subjects received ensifentrine, 291 received placebo subjects received Placebo, and 611 subjects completed Treatment Period (i.e., 393 who received ensifentrine, 218 who received placebo).

Study initiation and completion Dates: 22 September 2020 (first patient, first visit); 06 July 2022 (last patient, last visit)

Database lock date and study unblinding date of the study: 06 July 2022 (database lock date) and 26 July 2022 (study unblinding date)

The study design, inclusion criteria, and primary efficacy endpoint were similar to study RPL554-CO-301 except that subjects were randomized 5:3 ratio to ensifentrine or placebo over 24 weeks, and there was no 48-week subset of subjects.

III. RESULTS (by site):

1. **Dr. Regina Deckelmann**
   Site #806
   Salvus – Klinische Studien Gmbh
   Diezmannstr. 5
   Leipzig, Germany
   PDUFA Inspection Dates: 11/6/23 – 11/10/23

For Protocol RPL554-CO-301, 35 subjects were screened, 29 subjects were randomized, and 22 subjects completed the study. According to the sponsor's data line listings, two subjects withdrew consent, and one subject withdrew due to not seeing any improvements in his COPD.

Subjects [redacted] (b) (6) and Subject [redacted] (b) (6) (both randomized to placebo) were discontinued due to contracting COVID-19. Subject [redacted] (b) (6) (randomized to ensifentrine) was discontinued due to severe adverse event of metastatic pancreatis adenocarcinoma. Subject [redacted] (b) (6) (randomized to ensifentrine) was discontinued due to a severe COPD exacerbation.

A full audit of the study records for 26 or the 29 randomized subjects was conducted. Records reviewed included, but were not limited to, protocol versions, informed consent forms (ICF), Independent Ethics Committee (IEC) approvals, IRB approval letters, IRB correspondence, financial disclosure reports, eligibility records, randomization records, investigational product accountability records, laboratory sample shipment records, training records, monitoring reports, subject medical records, case report forms, adverse event reports, pulmonary function test results, and source documents for verification of the primary efficacy endpoint. Source records for subjects consisted of paper charts.

The FEV1 values for pre-dose, 30 minutes, 1-, 2-, 4-, 6-, 8-, and 12-hours post-dose at Week 12 in the source documents at the clinical site were compared with the FEV1 values in the subject data line listings submitted by the sponsor to the Agency, and no discrepancies were noted. There was no evidence of underreporting of adverse events.

2. **Dr. Thomas Lienert**
   Site #811
   116 Manning Drive
   Chapel Hill, NC 27599-6117
   PDUFA Inspection Dates: 10/30/23 – 11/3/23

For Protocol RPL554-CO-301, 38 subjects were screened, 23 subjects were randomized, and all 22 subjects completed the study. According to the sponsor's data line listings, Subject [redacted] (b) (6) (randomized to placebo) was discontinued due to a COPD exacerbation.

A full audit of the study records for all 23 randomized subjects was conducted. Records reviewed included, but were not limited to, protocol versions, informed consent forms (ICF), Independent Ethics Committee (IEC) approvals, IRB approval letters, IRB correspondence, financial disclosure reports, eligibility records, randomization records, investigational product accountability records, laboratory sample shipment records, training records, monitoring reports, subject medical records, case report forms, adverse event reports, pulmonary function test results, and source documents for verification of the primary efficacy endpoint. Source records for subjects consisted of paper charts.

The FEV1 values for pre-dose, 30 minutes, 1-, 2-, 4-, 6-, 8-, and 12-hours post-dose at Week 12 in the source documents at the clinical site were compared with the FEV1 values in the subject data line listings submitted by the sponsor to the Agency, and no discrepancies were noted. There was no evidence of underreporting of adverse events.

3. **Dr. Thomas Siler**
   Site #1739
   330 1st Capitol Dr Ste 470
   Saint Charles, MO 63301-2847
   PDUFA Inspection Dates: 12/5/23 – 12/7/23

For Protocol RPL554-CO-302, 27 subjects were screened,19 subjects were randomized, and 17 subjects completed the study. One subject was lost to follow-up. Subject (b) (6) (randomized to ensifentrine) withdrew due to COVID-19 infection.

A full audit of the study records for all 19 randomized subjects was conducted. Records reviewed included, but were not limited to, FDA form 1572s, financial disclosure reports, regulatory records, IRB records, monitoring reports, pharmacy records, case report forms, protocol versions, subject medical records, informed consent forms, investigational product dosing and accountability, adverse event reports, protocol deviations, concomitant medications, and source documents for verification of the primary efficacy endpoint. Source records for subjects consisted of paper charts.

The FEV1 values for pre-dose, 30 minutes, 1-, 2-, 4-, 6-, 8-, and 12-hours post-dose at Week 12 in the source documents at the clinical site were compared with the FEV1 values in the subject data line listings submitted by the sponsor to the Agency, and no discrepancies were noted. There was no evidence of underreporting of adverse events.

4. **Dr. Jose Diaz**
   Site #1733
   1038 W North Blvd Ste 101
   Leesburg, FL 34748-5077
   PDUFA Inspection Dates: 10/30/23 – 11/3/23

For Protocol RPL554-CO-302, 20 subjects were screened, 10 subjects were randomized, and seven subjects completed the study. Two subjects withdrew consent. Subject (b) (6) (randomized to placebo) was discontinued due to septic shock resulting in death from a Clostridium difficile infection.

A full audit of the study records for 20 screened subjects was conducted. Records reviewed included, but were not limited to, regulatory records, financial disclosures, FDA form 1572s. delegation of authority logs, monitoring logs, training documents, and study drug kit accountability records, protocol versions, IRB submissions and approvals, informed consent forms, case report forms, subject medical records, adverse events reports, and source documents for verification of the primary efficacy endpoint. Source records for subjects consisted of paper charts.

The FEV1 values for pre-dose, 30 minutes, 1-, 2-, 4-, 6-, 8-, and 12-hours post-dose at Week 12 in the source documents at the clinical site were compared with the FEV1 values in the subject data line listings submitted by the sponsor to the Agency, and no discrepancies were

noted. There was no evidence of underreporting of adverse events.

5. (b) (4)

This inspection covered the responsibilities transferred from the sponsor to the contract research organization (CRO), (b) (4) related to Protocols RPL554-CO-301 and RPL554-CO-302. The primary responsibilities transferred to (b) (4) included identifying qualified investigators and sites, clinical monitoring, data management, maintaining the electronic trial master file (eTMF), site training, and safety management.

Documents reviewed included, but were not limited to, transfer of regulatory obligation (TORO), study specific SOPs, official contract between the CRO and sponsor, clinical monitoring plan, monitoring reports, correspondence, clinical research associates (CRA) training records, site certification, monitoring of clinical investigator sites, financial disclosures of clinical investigators, IRB approvals, and organization and personnel, training of personnel, selection of monitors, quality assurance, and data management.

The inspection found that three sites #1768, #1741, #1721 were terminated due to GCP noncompliance. Subject data from sites #1721 (14 screened, 13 randomized) and #1768 (88 screened, 77 randomized) were removed from the primary efficacy analysis for study RPL554-CO-301. Subject data from site #1741 (22 subjects screened, 18 randomized) was removed from the primary efficacy analysis for study RPL554-CO-302. No specific information was provided in the inspection report. The inspection found the site monitoring and general oversight by the CRO to be adequate. No significant GCP issues were found.

{See appended electronic signature page}

Suyoung Tina Chang, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader

Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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CONCURRENCE:

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Jenn Sellers, M.D., Ph.D.
Branch Chief
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Office of Scientific Investigations

CC:

Central Doc. Rm.
Review Division /Division Director/
Review Division /Medical Team Leader/
Review Division /Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/
OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
OSI/DCCE/GCP Reviewer/
OSI/ GCP Program Analysts/
OSI/Database PM/

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/s/

SUYOUNG T CHANG
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PHILLIP D KRONSTEIN
05/09/2024 02:50:13 PM

JENN W SELLERS
05/09/2024 03:01:45 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: March 29, 2024

To: Linda Ebonine, PA-C, Regulatory Project Manager, Division of Pulmonology, Allergy, and Critical Care (DPACC)

Alison Lennox, MD, Medical Officer, DPACC

Jessica Lee, Associate Director for Labeling, DPACC

From: Taylor Burnett Mmagu, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for Ohtuvayre (ensifentrine) inhalation suspension, for oral inhalation use (Ohtuvayre)

NDA: 217389

Background:

In response to DPACC's consult request dated July 17, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for Ohtuvayre.

PI/PPI/IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on March 13, 2024, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI/IFU, and comments were sent under separate cover on March 28, 2024.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on June 23, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Taylor Burnett Mmagu at 240-402-1349 or taylor.burnettmmagu@fda.hhs.gov.

16 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

TAYLOR B BURNETT MMAGU
03/29/2024 04:46:47 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	March 28, 2024
To:	Linda Ebonine, PA-C Senior Regulatory Project Manager **Division of Pulmonology, Allergy, and Critical Care (DPACC)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Taylor Burnett Mmagu, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	OHTUVAYRE (ensifentrine)
Dosage Form and Route:	inhalation suspension, for oral inhalation
Application Type/Number:	NDA 217389
Applicant:	Verona Pharma

1 INTRODUCTION

On June 23, 2023, Verona Pharma submitted for the Agency's review an original New Drug Application (NDA) 217389 for their product OHTUVAYRE (ensifentrine) inhalation suspension, for oral inhalation. The proposed indication for OHTUVAYRE (ensifentrine) is the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

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 Pulmonary, Allergy, and Critical Care (DPACC) on July 17, 2023, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) amd Instructions for Use (IFU) for OHTUVAYRE (ensifentrine) inhalation suspension, for oral inhalation.

2 MATERIAL REVIEWED

- Draft OHTUVAYRE (ensifentrine) PPI and IFU received on June 23, 2023, received by DMPP and OPDP on March 13, 2024.
- Draft OHTUVAYRE (ensifentrine) Prescribing Information (PI) received on June 23, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 13, 2024.

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. In our review of the PPI and IFU the target reading level is at or below an 8th grade 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. We reformatted the PPI and IFU document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU is consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI and IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFU meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)

4 CONCLUSIONS

The PPI and IFU are 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 PPI and IFU 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 PPI and IFU.

Please let us know if you have any questions.

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/s/

KELLY D JACKSON
03/28/2024 02:34:02 PM

TAYLOR B BURNETT MMAGU
03/28/2024 02:57:42 PM

MARCIA B WILLIAMS
03/28/2024 03:04:04 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: February 9, 2024

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Team Lead, Cardiac Safety IRT, DCN

To: Linda Ebonine
Senior Regulatory Health Project Manager, DPACC

Subject: QT Consult to NDA # 217389 (SDN #0001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 12/22/2023 regarding the Review Division's QT related question. We reviewed the following materials:

- Previous IRT review(s) for IND # 133146 dated 07/17/2023 in DARRTS;
- Annotated product label (NDA 217389 / 001 ; link)

1 Responses for the Sponsor

Consult request: DPACC would like to request a consult from the QT-IRT team regarding the QT labeling language submitted by Verona Pharma in their original NDA submission for ensifentrine (QT language is in subsection 12.2)"

IRT's response: We have the following labeling recommendations which are based on our previous assessment (IND # 133146 dated 07/17/2023 in DARRTS) that concluded "*no significant QTcF prolongation effect of ensifentrine was detected in the QT assessment*".

Below are proposed edits to the label submitted to NDA 217389 / 001(link) from the CS-IRT. Our changes are highlighted (addition, ~~deletion~~).

12.2 Pharmacodynamics
Cardiac Electrophysiology

~~*QTc interval prolongation was studied in a randomized, double-blind, placebo- and positive-controlled, 4-period crossover study in 32 healthy subjects.*~~ (b) (4) [redacted] *At 3 times the maximum recommended dose, clinically significant QTc interval prolongation was not observed.*
Reviewer's comment: We propose to use labeling language for this product consistent with the "QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry" draft guidance (link).

2 BACKGROUND

Ensifentrine inhalation suspension ((also referred to as RPL554, VMX554, or VRP554) is being developed by Verona Pharma for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD) and has been submitted to the Agency for approval on 26th June 2023.

CS-IRT team was earlier consulted for cardiac safety study. Submitted TQT study was assessed, and the review team concluded that ensifentrine did not prolong the QTcF interval (IND# (b) (4) [redacted]

Briefly, ensifentrine did not prolong the QTcF interval in the TQT study assessment (see Table 1 for overall results). The clinical study RPL554-CV-101 was a phase 1, randomized, double blind, placebo- and moxifloxacin controlled, 4-period crossover study to evaluate the effect of ensifentrine on 12-lead electrocardiogram parameters in healthy adult subjects. The highest dose (9 mg single dose) provided 1.4-fold high clinical exposure. Data were analyzed using exposure response analysis as the primary analysis, which did not suggest that ensifentrine is associated with significant QTc prolonging effect. The findings of the primary analysis were further supported by the lack of QTc prolongation in by-time analysis and categorical analysis.

Table 1: Summary of findings from TQT study submitted and reviewed under IND # 133146 dated 07/17/2023 in DARRTS.

<table>
<tr><td>QT assessment pathway</td><td>☒ Thorough QT study
☐ Substitute for thorough QT study (5.1)
☐ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings</td><td>• High clinical exposure scenario is defined as subjects with moderate hepatic impairment who take ensifentrine at the dose of 3 mg BID via inhaled administration, with Cmax as 1725 pg/mL (section 3.1).
• In the TQT study, the exposure multiple was 1.4x high clinical exposure scenario.
<table>
<tr><th>ECG parameter</th><th>Treatment</th><th>Concentration</th><th>ΔΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>ΔΔQTcF</td><td>3 mg BID, inhaled administration in moderate hepatic impairment subjects</td><td>1725 pg/mL</td><td>3.8</td><td>(0.8 to 6.9)</td></tr>
<tr><td>ΔΔQTcF</td><td>3 mg BID, inhaled administration</td><td>750 pg/mL</td><td>1.8</td><td>(0.7 to 3)</td></tr>
</table></td></tr>
<tr><td>In vitro findings</td><td rowspan="2">A nonclinical integrated risk assessment was not performed.</td></tr>
<tr><td>In vivo findings</td></tr>
</table>

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

ELIFORD N KITABI
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SATISH SHARAN
02/09/2024 02:43:16 PM

CHRISTINE E GARNETT
02/12/2024 07:31:18 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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***

Date of This Review:	October 30, 2023
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 217389
Product Name, Dosage Form, and Strength:	ensifentrine inhalation suspension, 3 mg/2.5 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Verona Pharma
FDA Received Date:	June 26, 20223
TTT ID #:	2023-5267
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for ensifentrine inhalation suspension, the Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the proposed ensifentrine prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

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

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

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Verona Pharma.

4 RECOMMEDATIONS FOR DIVISION OF PULMONOLOGY, ALLERGY, AND CRITICAL CARE (DPACC)

Table 2. Identified Issues and Recommendations for Division of Pulmonology, Allergy, and Critical Care (DPACC)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	As currently presented in the Dosage and administration section, [redacted] (b) (4)	Expressing the units in this manner may lead to confusion and drug errors.	We recommend revising the statement to read: [redacted] (b) (4)
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	This section contains the following statement: [redacted] (b) (4)	Post-marketing reports have shown that negative statements (e.g., Not for) may have the opposite of the intended meaning because the word “not” can be overlooked and misinterpreted as an affirmative action.	We recommend deleting this statement from this section.
2.	This section contains the following statement: [redacted] (b) (4)	This statement is unrelated to [redacted] (b) (4)	We recommend relocating this statement to a more appropriate section.
Full Prescribing Information – Section 17 Patient Counseling			
1.	Section 17 begins with information of “Not for treatment of Acute Symptoms”	Post-marketing reports have shown that negative statements (e.g., Not for) may have the opposite of	We recommend leading with the most important and product relevant information. If included, this information

Table 2. Identified Issues and Recommendations for Division of Pulmonology, Allergy, and Critical Care (DPACC)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		the intended meaning because the word “not” can be overlooked and misinterpreted as an affirmative action.	should reference the warnings and precaution section and revised into affirmative language.

5 RECOMMENDATIONS FOR VERONA PHARMA

Table 3. Identified Issues and Recommendations for Verona Pharma (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The terminology within the statement of dosage (e.g. ‘Dosage: (b) (4) [redacted] is inconsistent with the terminology in the Prescribing Information.	To ensure consistency with the terminology in the Prescribing Information.	We recommend revising the statement of dosage to read, “Dosage: see Prescribing Information.”
Container Label(s)			
1.	On the ampule, the warning statement, (b) (4) [redacted] is expressed as a negative statement.	Post-marketing reports have shown that negative statements (e.g., Not for) may have the opposite of the intended meaning because the word “not” can be overlooked and misinterpreted as an affirmative action.	We recommend deleting the negative statement, (b) (4) [redacted] See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
2.	The ampule is missing the name of manufacturer, packer, or distributor of the drug	The name of manufacturer, packer, or distributor is part of the minimum information that is required to be on	Add the name of manufacturer, packer, or distributor of the drug on the

Table 3. Identified Issues and Recommendations for Verona Pharma (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		small labels [(e.g., ampules)] and is important for product distinction.	container label in accordance with 21 CFR 201.10(i). In addition, See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).
3.	The word (b) (4) is located on the foil label	Decreases readability and white space.	Revise the statement from (b) (4) "1 unit-dose ampule'
4.	Bolded font is over utilized throughout the foil label.	The overuse of bolded font decreases the importance of important information (e.g. storage)	Remove the bolded font from the Contents and dosage statements. Ensure that only the most important storage information is bolded.
5.	Ensure the linear barcode is scannable.	The position and placement of surround information may obscure the scan-ability of barcodes.	Ensure the linear barcode on the container label is orientated to improve the scannability of the barcode.
Carton Labeling			
1.	As currently presented, the proprietary name is denoted by the placeholder "Tradename".	We are unable to assess the prominence and readability of the intended presentation of the proprietary name.	Once you have a conditionally acceptable proprietary name, we recommend replacing the placeholder "Tradename" with the conditionally acceptable proprietary name and use the intend-to-market presentation of the proprietary name (font, color, etc.) so that we may adequately evaluate your labels and labeling.
2.	As currently presented, the route of administration is located on two lines.	Decreases readability.	Revise the route of administration so that it fits on one line. (e.g. for oral inhalation only)

Table 3. Identified Issues and Recommendations for Verona Pharma (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	The word (b) (4) is located on the carton labeling.	Decreases readability and white space.	Revise the statement from (b) (4) to read “60 unit-dose ampules”.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for ensifentrine that Verona Pharma submitted on June 26, 2023.

Table 4. Relevant Product Information for ensifentrine	
Initial Approval Date	N/A
Active Ingredient	ensifentrine
Indication	the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).
Route of Administration	Oral inhalation
Dosage Form	Inhalation suspension
Strength	3 mg/2.5 mL
Dose and Frequency	One (b)(4) mg ampule (2.5 mL) twice daily
How Supplied	as a 3 mg/2.5 mL sterile aqueous suspension in a unit-dose low-density polyethylene ampule. Each ampule is overwrapped in a sealed foil pouch and supplied in cartons containing 60 individually pouched unit-dose ampules.
Storage	protective foil pouch at controlled room temperature (68°F to 77°F [20°C to 25°C], excursions permitted from 59ºF to 86ºF [15ºC to 30ºC])

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,[a] along with postmarket medication error experiences with similar products, we reviewed the following ensifentrine labels and labeling submitted by Verona Pharma.

- Container label(s) received on June 26, 2023
- Carton labeling received on June 26, 2023
- Professional Sample Container label(s) received on June 26, 2023
- Professional Sample Carton Labeling received on June 26, 2023
- Instructions for Use received on June 26, 2023, available from \\CDSESUB1\EVSPROD\nda217389\0001\m1\us\114-labeling\114a-draft-label\instructions-for-use.pdf
- Prescribing Information and Patient Information (Image not shown) received on June 26, 2023, available from \\CDSESUB1\EVSPROD\nda217389\0001\m1\us\114-labeling\114a-draft-label\ensifentrine-uspi.pdf and \\CDSESUB1\EVSPROD\nda217389\0001\m1\us\114-labeling\114a-draft-label\patient-information-leaflet.pdf

F.2 Label and Labeling Images

Container label(s)

5 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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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