CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217389Orig1s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality

New Drug Application (NDA) 217389
Integrated Quality Assessment

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 217389
Assessment #1

Drug Product Name	Ensifentrine Inhalation Suspension
Dosage Form	Inhalation Suspension
Strength	3 mg/2.5 mL
Route of Administration	Oral inhalation
Rx/OTC Dispensed	Rx
Applicant	Verona Pharma, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original (SD 1)	6/26/2023	All
Amendment (SD 2)	7/19/2023	Manufacturing
Amendment (SD 3)	7/21/2023	Manufacturing
Amendment (SD 6)	9/15/2023	Manufacturing/Drug Product/Microbiology
Amendment (SD 9)	10/2/2023	Drug Product
Amendment (SD 14)	11/13/2023	Manufacturing/Microbiology
Amendment (SD-18)	2/6/2024	Manufacturing
Amendment (SD-20)	2/23/2024	Labeling

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Sharon Kelly	Lawrence Perez
Drug Product	Craig M. Bertha	Nina Ni
Manufacturing	Ju Du	Shu-Wei Yang
Microbiology	Koushik Paul	Jesse Wells
Biopharmaceutics	N/A	N/A

Regulatory Business Process Manager	Emma Gimose	
Application Technical Lead	Craig M. Bertha	
Laboratory (OTR)	N/A	
Environmental	N/A	

Table of Content Links

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	Adequate	N/A	(b) (4)
(b) (4)	III			Adequate	6/30/2011	

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	133146	For (b) (4) of patients with chronic obstructive pulmonary disease (COPD)
IND	(b) (4)	

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other				

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

N/A – All deficiencies have been resolved[1], thus, the application is recommended for approval.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The drug product ensifentrine inhalation suspension is to be used for [redacted] (b) (4) of patients with chronic obstructive pulmonary disease (COPD). The route of administration (RoA) is oral inhalation so patients are expected to use a CDRH cleared general nebulizers to administer the drug product. The drug product is sterile as per 21 CFR 200.51. The drug product is formulated as a suspension and the drug substance is [redacted] (b) (4). In addition, as COPD patients' lungs are compromised, there is an increased focus on ensuring that the levels impurities and leachables are adequately controlled to levels that are acceptable to the pharmacology/toxicology team.

Proposed Indication(s) including Intended Patient Population	Maintenance treatment of patients with chronic obstructive pulmonary disease (COPD)
Duration of Treatment	Chronic
Maximum Daily Dose	6 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The application includes an adequately detailed description of the [redacted] (b) (4) ensifentrine, [redacted] (b) (4)

[1]The labeling review decision is pending for this IQA due to ongoing negotiations with the applicant. There are only minor labeling deficiencies from the CMC perspective and we expect the applicant will accept our recommendations. Refer to the CMC sections of the final approved labeling.

administration. All process steps and conditions, test requirements, and other relevant parameters are controlled within predetermined criteria and ranges defined in the master batch records and analytical test procedures. The applicant has sufficiently characterized the structure of ensifentrine by standard spectroscopic techniques. The drug substance specification includes appropriate quality attributes, as well as a test with acceptance criterion for particle size. Analyses data for drug substance batches met the specification acceptance criteria and support the conclusion that sufficient controls are established for the manufacturing process. The application includes (b) (4)

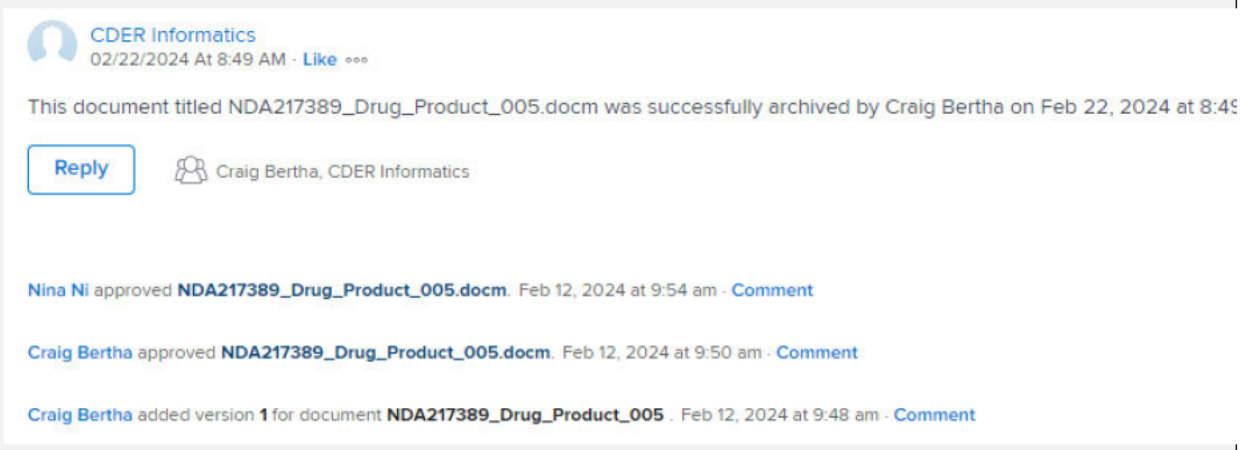
Drug Product: Adequate

The ensifentrine inhalation suspension drug product is formulated with compendial grade excipients, and there is one strength. It is intended to be dosed by patients using general-use jet nebulizers. It is noted that sodium chloride is the only excipient that has been used in products for oral inhalation at levels that exceed that in the drug product formulation. (b) (4) of the drug product formulation is tightly controlled and the pH (b) (4) (b) (4) technology is used to package the solution formulation and the control strategy for (b) (4) was found to be adequate. The drug product specification is in line with the recommendations in Agency guidance,[2] and the acceptance criteria are reflective of the data provided. The associated analytical methods appear to be validated such that they are suitable for regulatory purposes. The stability data provided for the drug product support a **36 month shelf-life**. There were no significant changes on stability when drug product was stored at 25°C/60%RH for up to 36 months and 40°C/75%RH for 6 months. The product will be labeled to be stored at USP Controlled Room Temperature.

NOTE: Due to a problem with the archiving feature of Panorama, the drug product review chapter was not converted to pdf and did not include electronic signatures,

[2] *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products, CMC Documentation*, available at https://www.fda.gov/media/70857/download.

however, the system does show that the review was approved by the drug product reviewer and Branch Chief, as shown below:



In order to meet the IQA review goal date, the Word file was manually converted to pdf and is included in this IQA.

Labeling: Inadequate

See footnote 1 and refer to the labeling chapter. Note that the applicant was asked (via the late cycle meeting comments) to include the name of the manufacturer, packer, or distributor, on the immediate container (ampule), as per 21 CFR 201.10(h)(2). The amendment SD-20 dated 2/23/2024 includes the revised immediate container that is engraved with "Mfg for Verona" (distributor). Other minor labeling/label revisions will be addressed during labeling negotiations. See the labeling chapter for details.

Manufacturing: Adequate

Ensifentrine inhalation suspension drug product (3 mg/2.5 ml=1.2 mg/ml), is a yellow to pale-yellow suspension filled into a unit dose low density polyethylene (LDPE) plastic ampule, and is intended to be dosed with standard jet nebulizers. The DS is (b) (4) The manufacturing process (b) (4) Three registration stability batches are provided (21N36, 21M74, and 21MA9). The manufacturing

process and scale, equipment, process parameters, and in-process controls are same for the registration batches and commercial baches. The drug substance and drug product manufacturing sites have been reviewed and found acceptable based on inspection history and district review recommendations. The facilities with analytical functions have also been found to be adequate.

Biopharmaceutics: N/A

Microbiology (if applicable): Adequate

As the ensifentrine has very low water solubility and is formulated as a suspension for inhalation, the manufacturing process (b) (4)

Risk Assessment - Refer to the Drug Product chapter of the IQA

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

N/A

2. Drug Substance Deficiencies

N/A

3. Drug Product Deficiencies

N/A

4. Labeling Deficiencies

Refer to the labeling review chapter of the IQA.

5. Manufacturing Deficiencies

N/A

6. Biopharmaceutics Deficiencies

N/A

7. Microbiology Deficiencies

N/A

8. Other Deficiencies *(Specify discipline, such as Environmental)*

N/A

Application Technical Lead Name and Date:
Craig M. Bertha, 2/27/2024

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CHAPTER VII: MICROBIOLOGY

IQA ANDA Assessment Guide Reference

Product Information	Ensifentrine inhalation suspension is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).
NDA Number	217389
Assessment Cycle Number	MR01
Drug Product Name / Strength	Ensifentrine Oral Inhalation, 3mg/2.5mL, single dose.
Route of Administration	Oral Inhalation Suspension.
Applicant Name	Verona Pharma, Inc.
Manufacturing Site	(b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Theme:

☐ N/A	☐ Depyrogenation Validation Data
☒ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: *view justification statements found at:* **Justification Statements**

N/A
Other (Requires Division Director Approval) – *Assessor writes-in justification here if "other" selected as theme.*

Assessment Summary: (b) (4)

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
eCTD Seq #0001	06/26/2023
eCTD Seq #0002	07/19/2023
eCTD Seq #0006	09/15/2023

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The submission is **Recommended** for approval on the basis of sterility assurance.

Concise Description of Outstanding Issues: None.

Supporting Documents: [redacted].doc, dated 7/31/2018 and [redacted].doc, dated 11/21/2019, [redacted].doc, dated 10/02/2017.

Select Number of Approved Comparability Protocols: 0

S Drug Substance- Not Applicable

P.1 Description of the Composition of the Drug Product

- **Description of the Composition of the Drug Product**
  (*3.2. P.1. description-and-composition.pdf)*

Ensifentrine inhalation suspension is a yellow to pale-yellow suspension filled into a unit dose low density polyethylene (LDPE) plastic ampule. The drug product is supplied as a [redacted] mL (minimum fill volume), sterile, aqueous suspension packaged in unit-dose in LDPE ampules. Each ampule delivers 2.5mL of 1.2 mg/mL Ensifentrine suspension. Each single ampule is overwrapped in [redacted] foil laminate. The composition is provided below:

Table 2: Quantitative Composition of Ensifentrine Inhalation Suspension (3 mg/2.5 mL)

Components	Reference to Standards	Function	Quantity	
			mg/mL	mg/ampule[b]
Ensifentrine	Internal specification 3.2.S.4.1	Active ingredient		(b) (4)
Sodium chloride	USP			(b) (4)
Monobasic sodium phosphate (b) (4)	USP			
Dibasic sodium phosphate (b) (4)	USP			
Polysorbate 20 (b) (4)	USP-NF			
Sorbitan monolaurate (b) (4)	USP-NF			
Water for Injection	USP			

a. The drug concentration indicated is the targeted nominal assay value in the formulated product. A small manufacturing overage is used to account for mechanical process losses (3.2.P.3.2).
b. Based on deliverable volume of 2.5 mL; to achieve this deliverable volume the target fill volume is (b) (4) mL (3.2.P.2.3).

- **Description of container closure system –**

Ensifentrine inhalation suspension is filled and sealed in labeled LDPE ampules. As the primary container/closure system, the ampules are prepared by (b) (4) technology. The following container-closure systems are used for the production:

Components	Description/product code	Manufacturer	DMF
Low Density Polyethylene (b) (4)	(b) (4) single dose, LDPE ampules. Product code: (b) (4)	(b) (4)	
(b) (4) Foil Laminate	(b) (4) foil pouch Product code: (b) (4)		

Reviewer's Assessment: Based on the above information the reviewer has concluded that the applicant has provided adequate description of the drug product composition and the container closure system designed to maintain product sterility.

Acceptable

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes:

Container/Closure and Package Integrity

(3.2.P.3.5 process-validation-1.pdf, see page 21/26)

The following information request was conveyed to the applicant regarding the container closure integrity testing.

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Jesse Wells

Digitally signed by Jesse Wells
Date: 11/09/2023 08:47:27AM
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Koushik Paul

Digitally signed by Koushik Paul
Date: 11/09/2023 08:48:13AM
GUID: 5600522e0069b02f59c7bd85b6b54742

CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Start Applicant Material

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

(b) (4)

End Applicant Material

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	The labeling includes an appropriate statement that the patient should shake the ampule vigorously before opening and transferring the formulation to the jet nebulizer.
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the	N/A	

patient and healthcare practitioner(s) who administer the drug		
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Start Applicant Material

3 DOSAGE FORMS AND STRENGTHS

Inhalation suspension: 3 mg of ensifentrine in 2.5 mL of sterile, yellow to pale yellow, aqueous suspension in unit-dose ampules.

End Applicant Material

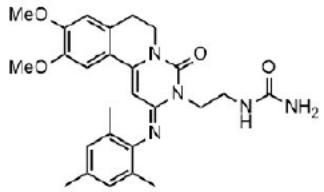
Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Inadequate	Revise the wording to indicate that the unit-dose ampules are low-density polyethylene.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 11 (DESCRIPTION)

Start Applicant Material

11 DESCRIPTION

TRADENAME is a sterile, yellow to pale yellow aqueous suspension of ensifentrine. Ensifentrine, the active component of TRADENAME, is a [redacted] (b) (4) inhibitor of phosphodiesterases 3 and 4 (PDE3 and PDE4). The chemical name for ensifentrine is *N*-(2-{(2*E*)-9,10-dimethoxy-4-oxo-2-[(2,4,6-trimethylphenyl)imino]-6,7-dihydro-2*H*-pyrimido[6,1-*a*]isoquinolin-3(4*H*)-yl}ethyl)urea; its structural formula is:



Ensifentrine has a molecular weight of 477.56 and its empirical formula is $C_{26}H_{31}N_5O_4$. Ensifentrine is a yellow to pale yellow crystalline powder which is practically insoluble in water.

TRADENAME is supplied as 2.5 mL of sterile ensifentrine (1.2 mg/mL) suspension packaged in a unit-dose low-density polyethylene ampule overwrapped in a sealed foil pouch. Each single-dose ampule contains 3 mg ensifentrine suspended in a pH 6.7 aqueous solution containing sodium chloride, monobasic sodium phosphate [redacted] (b) (4) dibasic sodium phosphate [redacted] (b) (4) polysorbate 20, sorbitan monolaurate and water for injection.

The ampule containing TRADENAME should be shaken vigorously to ensure complete resuspension of the active ingredient immediately prior to administration by nebulization. Like all other nebulized treatments, the amount delivered to the lungs will depend on patient factors, the nebulization system used, and compressor performance.

Using the PARI LC Sprint® jet nebulizer attached to a PARI Vios Pro® compressor under in vitro conditions, the mean delivered dose from the mouthpiece was approximately 933 micrograms (31% of label claim) at a mean flow rate of approximately 5 liters per minute. The mean nebulization time was approximately 7 minutes. TRADENAME should only be administered via a standard jet nebulizer connected to an air compressor with an adequate airflow and equipped with a mouthpiece.

End Applicant Material

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	
Dosage form(s) and route(s) of administration	Inadequate	Revise the section to include the route of administration. Also list the dosage form as "inhalation suspension."
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Inadequate	Revise the labeling such that the inactive ingredients are listed in alphabetical order. Use USP/NF names for monobasic sodium phosphate and dibasic sodium phosphate, i.e., remove (b) (4)
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	Adequate	
Pharmacological/Therapeutic class	Adequate	
Chemical name, structural formula, molecular weight	Inadequate	Revise the molecular weight to 477.57 g/mole (as listed in USAN)
If radioactive, statement of important nuclear characteristics.	Adequate	
Other important chemical or physical properties (such as pKa or pH)	Inadequate	The pH of the suspension formulation is indicated. However, the Agency recommends that the delivered dose and description of particle/droplet size distributions that could be expected from an identified nebulizer under specific and defined operating conditions should be provided. Although the former is provided, the latter is not. It will be recommended that the applicant include the fine particle dose as well (defined as ≤ 5 mcm).

2. Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	

Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”)	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling	Assessor's Comments

	(choose "Adequate", "Inadequate", or "N/A")	(If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.
Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Start Applicant Material

Manufactured for:
Verona Pharma, Inc.
Raleigh, NC 27617

End Applicant Material

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Inadequate	The address of the distributor should also include the street address, city, State, and ZIP Code.

2.0 PATIENT LABELING

Start Applicant Material

Inactive ingredients: sodium chloride, monobasic sodium phosphate (b) (4) dibasic sodium phosphate (b) (4) polysorbate 20, sorbitan monolaurate and water for injection.

Manufactured for:
Verona Pharma, Inc.
Raleigh, NC, 27617

End Applicant Material

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	
Special preparation instructions (if applicable)	Adequate	
Storage and handling information (if applicable)	Adequate	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	Inadequate	Revise the labeling such that the inactive ingredients are listed in alphabetical order. Use USP/NF names for monobasic sodium phosphate and dibasic sodium phosphate, i.e., remove (b) (4)
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Inadequate	The address of the distributor should also include the street address, city, State, and ZIP Code.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CONTAINER AND CARTON LABELING

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

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	Note that the font size of "inhalation suspension" is just over half the size of the "Tradename."
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Inadequate	Although the dosage form is not an injection, the inactive ingredient information is on the proposed pouch label. Revise the labeling such that the inactive ingredients are listed in alphabetical order. Use USP/NF names for monobasic sodium phosphate and dibasic sodium phosphate, i.e., remove (b) (4)
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Inadequate	The address of the distributor should also include the street address, city, State, and ZIP Code.
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Inadequate	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	Adequate	The pouch label also includes important instructions for the patient that the ampule should be shaken vigorously until the contents are mixed.

Assessment of Carton and Container Labeling: ***Inadequate.*** The container "label" can be considered to be a "small label" as per 21 CFR 201.10(h)(2). The small label does not include the name of the distributor as required by that regulation.

3. ITEMS FOR ADDITIONAL ASSESSMENT

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See Carton/Container Labeling Specific Resources for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these as deficiencies in this section.

Deficiencies:

1. Revise the ampule labeling to include the name of the manufacturer, packer, or distributor, as per regulation 21 CFR 201.10(h)(2).
2. Revise the DOSAGE FORMS AND STRENGTHS section of the package insert to indicate that the unit-dose ampules are low-density polyethylene.
3. Revise the DESCRIPTION section of the package insert:
    a. To include the route of administration and dosage form.

b. Such that the inactive ingredients are listed in alphabetical order. Use USP/NF names for monobasic sodium phosphate and dibasic sodium phosphate, i.e., remove (b) (4)
c. Such that the drug molecular weight is 477.57 g/mole (as listed in USAN).
d. To include a description of the particle/droplet size distributions that could be expected from the identified nebulizer under specific and defined operating conditions, e.g., fine particle dose defined as ≤ 5 mcm.

4. Revise all labeling that lists the distributor such that it includes the address of the distributor, i.e., the street address, city, State, and ZIP Code.
5. Revise the patient labeling and pouch label as per comment 3.b above.

Overall Assessment and Recommendation:

The above deficiencies will be forwarded to the applicant during labeling negotiations with DPACC.

Primary Labeling Assessor Name and Date:
Craig M. Bertha, 08/07/2023
Secondary Assessor Name and Date (and Secondary Summary, as needed):
Julia Pinto, 08/11/2023

Craig Bertha

Digitally signed by Craig Bertha
Date: 2/22/2024 12:36:00PM
GUID: 50841a65000098a9383c817879a6a84d

Julia Pinto

Digitally signed by Julia Pinto
Date: 2/22/2024 02:39:32PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

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/

CRAIG M BERTHA
02/29/2024 12:13:50 PM