CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216190Orig1s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality

New Drug Application (NDA)
Integrated Quality Assessment

NDA 216190

ONTRALFY
(tizanidine oral solution)

NDA Executive Summary

1. Application/Product Information

NDA Number	216190		
Applicant Name	Fidelity BioPharma		
Drug Product Name	Ontralfy		
Dosage Form	Solution		
Proposed Strength(s)	2 mg/mL		
NDA Classification	Type 3 - New Dosage Form		
Route of Administration	Oral		
Maximum Daily Dose	36 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	(b) (4) of spasticity		
Drug Product Description	Clear, colorless to pale yellow solution with a strawberry flavor.		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	20°C to 25°C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Zhixing Shan	Donna Christner
	Drug Product/ Labeling	Mariappan Chelliah	Martha Heimann
	Manufacturing	Hong Yang	Shujun Chen
	Biopharmaceutics	N/A	N/A
	Microbiology	N/A[a]	N/A

	Other (specify)	N/A	N/A
	RBPM	Erica Keafer	
	ATL	Martha Heimann	
Consults	N/A		

[a] NDA was adequate for Microbiology First Cycle an no new information was submitted.

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

24 months, when stored at controlled room temperature, 20°C to 25°C.

b. Additional Comments for Action

There are no additional comments for the action letter.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The Agency previously issued a Complete Response Letter for NDA 216190, Ontralfy (Tizanidine oral solution) 2 mg/5 mL, related to deficiencies in the drug substance supplier's drug master file (DMF), the potential presence of (b) (4) inadequate information for the drug product manufacturing process, and inadequate information to support the proposed acceptance criterion for (b) (4) a degradation product of (b) (4) (b) (4) (b) (4) .

NDA 216910 was resubmitted on 6/12/2024. Based on our evaluation of the information provided in the resubmission, the applicant provided sufficient information to support an approval recommendation from the product quality perspective. The applicant provided adequate information to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling is adequate to meet the regulatory requirements. Therefore, the Office of Pharmaceutical Quality (OPQ) recommends **APPROVAL** of NDA 216190.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**N/A**
Microbiology	**-**	**Adequate First Cycle**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:
There are no outstanding issues or lifecycle considerations.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
11/7/2024

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/s/

MARTHA R HEIMANN
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Office of Pharmaceutical Quality

New Drug Application (NDA) 216190
Executive Summary – Addendum

This addendum to the Executive Summary for NDA 216190 dated 2/29/2024 reflects the nonclinical determination that the proposed acceptance criterion for (b) (4) a degradation product of the drug product (b) (4) is unacceptable. This does not impact on the previous Office of Pharmaceutical Quality (OPQ) COMPLETE RESPONSE recommendation.

This addendum to the Executive Summary for NDA 216190 dated 2/29/2024 reflects the nonclinical determination that the proposed acceptance criterion for (b) (4) a degradation product of the drug product (b) (4) is unacceptable. This does not impact on the previous Office of Pharmaceutical Quality (OPQ) COMPLETE RESPONSE recommendation.

NDA Executive Summary

1. Application/Product Information

NDA Number	216190		
Applicant Name	Fidelity BioPharma		
Drug Product Name	Ontralfy		
Dosage Form	Solution		
Proposed Strength(s)	2 mg/mL		
NDA Classification	Type 3 - New Dosage Form		
Route of Administration	Oral		
Maximum Daily Dose	36 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	(b) (4) of spasticity		
Drug Product Description	Clear, colorless to pale yellow solution with a strawberry flavor.		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	20°C to 25°C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Zhixing Shan	Donna Christner

	Drug Product/ Labeling	Mariappan Chelliah	Martha Heimann
	Manufacturing	Hong Yang	Shujun Chen
	Biopharmaceutics	N/A	N/A
	Microbiology	George Arhin	Bethanie Lee
	Other (specify)	N/A	N/A
	RBPM	Erica Keafer	
	ATL	Martha Heimann	
Consults	N/A		

2. Final Overall Recommendation - Complete Response

3. Deficiencies

Refer to the integrated quality review dated 2/29/2024 for product quality deficiencies.[1] The deficiency below will be conveyed in the complete response letter as a nonclinical deficiency.

The information provided is not adequate to support the proposed specification of NMT (b) (4)% for (b) (4) which would result in a maximum daily intake (b) (4)mg) of (b) (4) that exceeds the qualification threshold, as recommended in guidance (ICH Q3B(R2), August 2006). The OECD SIDS Initial Assessment Report on (b) (4) upon which you rely, contains only a summary of the available information on (b) (4) To address this deficiency, you would need to lower the specification consistent with guidance or provide additional data to support the specification of NMT (b) (4)%.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The previous integrated review for NDA 216910, Ontralfy (Tizanidine oral solution) 2 mg/5 mL, recommended a **COMPLETE RESPONSE** due to outstanding issues related to deficiencies in the drug substance supplier's drug master file (DMF), the potential presence of (b) (4) (b) (4) and inadequate information for the manufacturing process. At that time, acceptability of the proposed acceptance criterion for

[1] https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8072c5ab&showAsPdf=true

[redacted] a degradation product from [redacted] was under nonclinical review. The nonclinical reviewer has determined that the proposed level is not adequately supported by the information submitted in the application and recommends a complete response. The drug product recommendation has been updated to reflect the nonclinical recommendation. The OPQ **COMPLETE RESPONSE** recommendation is unchanged.

The overall manufacturing inspection recommendation is approval/withhold for all facilities associated with this application. The proposed labeling and labels have adequate information to meet the regulatory requirements.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Inadequate**
Drug Product	**-**	**Inadequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Inadequate**
Biopharmaceutics	**-**	**N/A**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:
Not applicable.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
March 29, 2024

Martha Heimann

Digitally signed by Martha Heimann
Date: 3/29/2024 11:09:31AM
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NDA 216190
Tizanidine Oral Solution

Addendum to Drug Product Quality Review #1

Recommendation: Inadequate

Product Information	
NDA Number	216190
Assessment Cycle Number	1
Drug Product (DP) Name / Strength	Tizanidine Oral Solution
Route of Administration	Oral
Drug Product Manufacturer	Novitium Pharma LLC
RLD Information (Brand Name of Product, Applicant)	Zanaflex Tablets and Zanaflex Capsules (LEGACY PHARMA USA INC)
RLD/RS Number	NDA 020397 (Zanaflex Tablets) and NDA 021447(Zanaflex Capsules)
Proposed Indication	Management of spasticity

Updated assessment of control for (b) (4) in the drug product specification:

Reviewer's Assessment: *Inadequate*

In the NDA 216190 Drug Product Review, dated 02-06-2024, this reviewer recommended "adequate", but noted that the acceptability of the proposed limit of NMT (b) (4)% for (b) (4) in the drug product specification is under the non-clinical assessment. The non-clinical discipline has now concluded that the Applicant has not adequately justified the proposed limit for this impurity, and they will be including the following deficiency in the CR Letter:

> "The information provided is not adequate to support the proposed specification of NMT (b) (4)% for (b) (4) which would result in a maximum daily intake (b) (4) mg) of (b) (4) that exceeds the qualification threshold,

as recommended in guidance (ICH Q3B(R2), August 2006). The OECD SIDS Initial Assessment Report on [redacted](b) (4) upon which you rely, contains only a summary of the available information on [redacted](b) (4) To address this deficiency, you would need to lower the specification consistent with guidance or provide additional data to support the specification of NMT [redacted](b) (4) . "

Therefore, the drug product specification is now considered not acceptable. **Accordingly, we change our recommendation from "adequate" to "inadequate"**

Note: Because the Drug Substance and Manufacturing disciplines recommended "Inadequate", the OPQ's overall recommendation was "COMPLETE Response" (see NDA 216190 Executive Summary, dated 02/29/2024). Therefore, the "adequate" to "inadequate" change for the Drug Product review does not affect OPQ's overall recommendation.

Mariappan Chelliah

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Date: 3/29/2024 09:24:29AM
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Martha Heimann

Digitally signed by Martha Heimann
Date: 3/29/2024 09:57:21AM
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/s/

MARTHA R HEIMANN
03/29/2024 11:27:42 AM

Office of Pharmaceutical Quality

New Drug Application (NDA)
Integrated Quality Assessment

NDA 216190

ONTRALFY
(tizanidine oral solution)

NDA Executive Summary

1. Application/Product Information

NDA Number	216190		
Applicant Name	Fidelity BioPharma		
Drug Product Name	Ontralfy		
Dosage Form	Solution		
Proposed Strength(s)	2 mg/mL		
NDA Classification	Type 3 - New Dosage Form		
Route of Administration	Oral		
Maximum Daily Dose	36 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	(b) (4) of spasticity		
Drug Product Description	Clear, colorless to pale yellow solution with a strawberry flavor.		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	20°C to 25°C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Zhixing Shan	Donna Christner
	Drug Product/ Labeling	Mariappan Chelliah	Martha Heimann
	Manufacturing	Hong Yang	Shujun Chen
	Biopharmaceutics	N/A	N/A
	Microbiology	George Arhin	Bethanie Lee

	Other (specify)	N/A	N/A
	RBPM	Erica Keafer	
	ATL	Martha Heimann	
Consults	N/A		

2. Final Overall Recommendation - Complete Response

3. Deficiencies

Drug Substance

We acknowledge the response that you provided on February 8, 2024, for the Agency's (b) (4) information request (IR) dated November 29, 2023. While we have not performed an in-depth review, in the response, you stated that there is no potential for the formation of (b) (4) per Sun Pharma's overall review of the synthetic scheme and manufacturing process for the drug substance. However, your conclusion was not made based on a proper application of the (b) (4) guidance.

You determined that the (b) (4) score is not applicable since the (b) (4) and is thus out of scope of (b) (4) Therefore, it requires the use of alternative methods for establishing an AI limit. We recommend that you work with the DMF holder to establish an appropriate AI limit for control of (b) (4) that may be found in the API.

Manufacturing Process:

(b) (4)

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(b) (4)

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends a **COMPLETE RESPONSE** for NDA 216910 for commercialization of Ontralfy (Tizanidine oral solution) 2 mg/5 mL. The applicant has not provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product. As summarized below, the outstanding issues are related deficiencies in the drug substance supplier's drug master file (DMF), the potential presence of (b) (4) and inadequate information for the manufacturing process. The overall manufacturing inspection recommendation is approval/withhold for all facilities associated with this application. The proposed labeling and labels have adequate information to meet the regulatory requirements.

(b) (4)

In an IR sent 11/29/2023, the applicant was asked to assess the risk for formation of (b) (4) (e.g., structure **1** below). In the 2/8/2024 response, the applicant indicated that treatment of tizanidine with a (b) (4) agent did not result in formation of **1** but the (b) (4) **2** and (b) (4) **3** were formed.

(b) (4)

The applicant determined that the (b) (4) (b) (4) score described in the (b) (4) Guidance[1] is not applicable since a (b) (4) group (b) (4) (b) (4) thus out of scope of (b) (4) However, the applicant did not use any alternative methods to establish/propose an acceptable intake limit. The response is deemed inadequate.

(b) (4)

Manufacturing Process

The manufacturing deficiencies listed above were conveyed to the applicant as IRs on 1/12/2024 with a request that they respond by 1/18/2024. The applicant has repeatedly pushed the estimated date for submission of the responses back. As of 2/29/2024 no responses have been received. In the absence of the requested information, the application is deemed inadequate.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Inadequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Inadequate**
Biopharmaceutics	**-**	**N/A**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:
Not applicable.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.
February 29, 2024

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide (OPQ-ALL-WI-0006)

NDA Number	216190
Assessment Cycle Number	1
Drug Product Name	Tizanidine Oral Solution

Assessment Recommendation: Adequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	SDN1, but edited in the SharePoint version
Patient Information	N/A	N/A
Instruction for Use (IFU)	N/A	N/A
Container Labels	Adequate	SDN8.
Carton Labeling	N/A	

Brief Description of Outstanding Issues: None

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
Original, SDN1	05-31-2023	Prescribing Information
Labeling, SDN8	11-13-2023	Carton/container labels

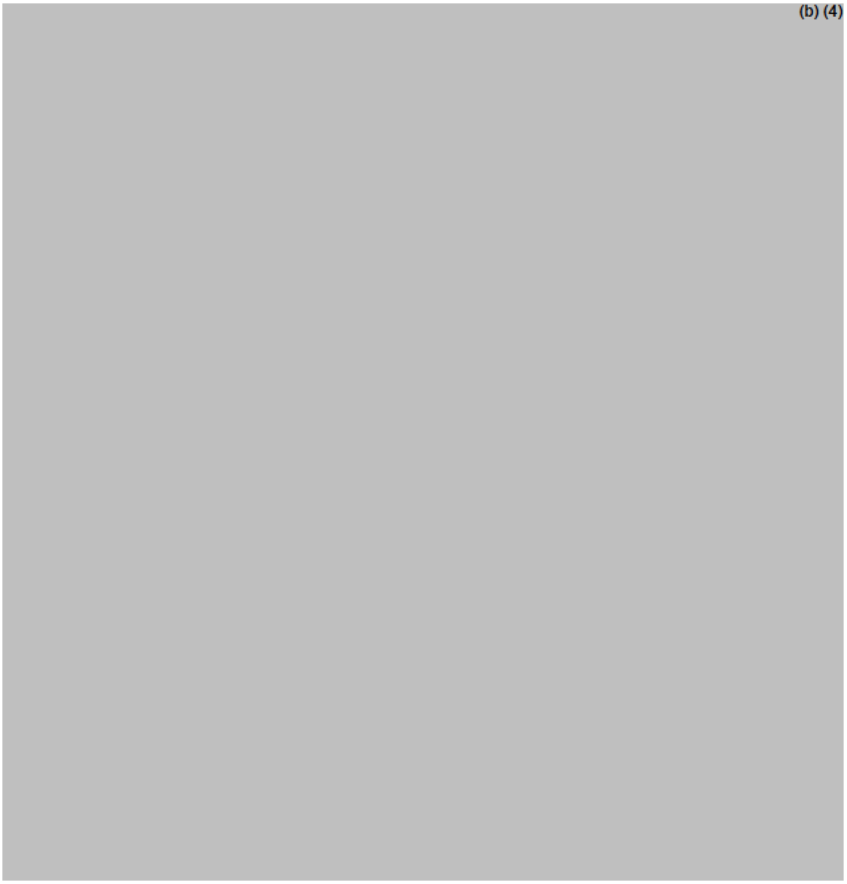
1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

copy of proposed text:



Item	Item 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[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	
Route(s) of administration	Adequate	
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		

[2] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)

[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

Item	Item 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 form(s)[4] and strength(s) in metric system[5]	Adequate	
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).[6]	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	N/A	
For injectable drug products for parenteral 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.[8]	N/A	

Assessment: *Adequate*

When the PI becomes available, we will edit to make sure that the strength is stated in terms of the active moiety (i.e., tizanidine).

[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline
[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>
[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1
[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

copy of proposed text: Not applicable for this product

Item	Item 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 and/or soft food[10], 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).	N/A	
For parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*[11]	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] Note the labeling requirement may be applicable	N/A	USP monograph exists only for tizanidine tablets.

[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)
[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments
[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition

Item	Item 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)
to another section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
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	

Assessment: *Adequate*

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

copy of proposed text:

(b) (4)

Item	Item 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 (e.g., Tablets: 10 mg	Adequate	

[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

Item	Item 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)
of drug-x hydrochloride). No equivalency statement.		
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.	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 parenteral 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 (see USP <659>).	N/A	

Assessment: *Adequate*

When the PI becomes available, we will edit to state that the strength basis is per tizanidine.

1.2.3 Section 11 (DESCRIPTION)[14]

copy of proposed text:

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)

Item	Item 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)[15] [§ 201.57(c)(12)(i)(A)].	Adequate	
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	
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	Adequate	

[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

Item	Item 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)
of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].		
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Adequate	
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. [§ 201.100(b)(5)(iii)].	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

Item	Item 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)
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	
For oral prescription drug products, include gluten statement[19] (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").	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 2).	N/A	USP monograph exists only for tizanidine tablets.

Assessment: *Adequate*

When the PI opens for edit, it will be edited to address the deficiencies cited above.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

copy of proposed text:

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)
[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

(b) (4)

Item	Item 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) [§ 201.57(c)(17)].	Adequate	
Strength(s) in metric system. [§ 201.57(c)(17)(i)] 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. No equivalency statement.	Adequate	
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	

Item	Item 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 injectable drug products for parenteral 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 (see USP <659>).	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." [§ 201.57(c)(17)(iv)]	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	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."*[21]	N/A	

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)

Item	Item 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)
Include information about child-resistant packaging[22] (if chosen by manufacturer).	Adequate	

Assessment: *Adequate*

When the PI opens for edit, it will be edited to address the deficiencies cited above.

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.

Not applicable

1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	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.	Adequate	

Assessment: *Adequate*

2.0 PATIENT LABELING

[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)
[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information): Not Applicable

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[24]	Choose an item.	Not applicable
Special preparation instructions (if applicable).	Choose an item.	
Storage and handling information (if applicable).	Choose an item.	
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 differ from the dosage form.	Choose an item.	
Active ingredient(s) (if applicable).	Choose an item.	
Alphabetical listing of inactive ingredients (if applicable).	Choose an item.	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Choose an item.	

Assessment: Not Applicable

3.0 CONTAINER AND CARTON LABELING[25]

3.1 Container Labels[26]

Copy of the container label from SDN8:

[24] Established name = [Drug] [Route of Administration] [Dosage Form]
[25] Carton and Container Labeling Resources
[26] Per § 201.10(h)(2)(i)(1), if the drug container is too small to bear all labeling information required by section 502(e)(1)(A)(ii) and (B) of the FD&C Act, the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.

3.2 Carton Labeling

Not applicable

Item	Item in Proposed ~~Carton~~ Container Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[27], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Choose an item.	
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[28]	Adequate	Choose an item.	

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

[28] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

Item	Item in Proposed ~~Carton~~ Container Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Choose an item.	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	Adequate	Choose an item.	
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[29]	Adequate	Choose an item.	
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Choose an item.	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Choose an item.	
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Choose an item.	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Inadequate	Choose an item.	Single temperature is stated for storage. This will be edited per USP controlled temperature range.
For injectable drug products for parenteral 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. (See USP <659>).	N/A	Choose an item.	

[29] § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed ~~Carton~~ Container Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	Adequate	Choose an item.	
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	Choose an item.	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Choose an item.	
Linear Bar code [§ 201.25(c)(2)].[30]	Adequate	Choose an item.	
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	Choose an item.	
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Choose an item.	
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	N/A	Choose an item.	
If there is a Medication Guide, must include a statement about dispensing a	N/A	Choose an item.	

[30] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed ~~Carton~~ Container Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Medication Guide to each patient.			
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Choose an item.	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Choose an item.	
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.[31]	N/A	Choose an item.	
And others if space is available.	N/A	Choose an item.	

Assessment of Carton Labels and Container Labeling: *Adequate*

The container label will be edited to ensure the storage temperature is stated as a range. In addition, "USP" will be deleted from the container label. Towards this end, we have sent the following labeling comments:

Please refer to the container label submitted in SDN8 and address the following comments:

1. The storage condition is stated as a single temperature. This is not appropriate. Per USP <659>, the controlled room temperature should be stated as a range. Therefore, we recommend editing the storage statement as follows:

[31] USP General Notices 3.20 Indicating Conformance

"Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]."

2. In accordance with our current labeling practice, delete "USP" from "Tizanidine Hydrochloride, USP" in the salt equivalency statement, as reference to compliance with the USP monograph is not required in the labeling.

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

None

Primary Labeling Assessor: Mariappan V Chelliah

Secondary Assessor Name: Martha Heimann

Mariappan Chelliah

Digitally signed by Mariappan Chelliah
Date: 2/06/2024 03:00:50PM
GUID: 5399cb2c00032b7c21877aa0d4d5f794

Martha Heimann

Digitally signed by Martha Heimann
Date: 2/06/2024 03:11:22PM
GUID: 504f845f00000ed260627d268a8cdc9d

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U.S. FOOD & DRUG ADMINISTRATION

MICROBIOLOGY

Product Information	
NDA Number	216190
Assessment Cycle Number	1
Drug Product Name / Strength	Tizanidine Oral Solution, 0.4 mg/mL, 5 mL fill (2 mg/5 mL)
Route of Administration	Oral solution
Applicant Name	Fidelity BioPharma Co.
Manufacturing Site	Novitium Pharma LLC. 70 Lake Drive East Windsor, NJ 08520 FEI #: 3012541241 DUNS #: 080301870
Method of Sterilization	N/A. Drug product is non-sterile

Assessment Recommendation: **Adequate**

Theme: N/A

☐ 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: N/A

Assessment Summary: The submission **is recommended** for approval on the basis of sterility assurance.

List Submissions Being Assessed:

Submit	Received	Review Request	Assigned to Reviewer
May 31, 2023 (eCTD Sequence #0001)	May 31, 2023	N/A	June 2, 2023
August 7, 2023 (eCTD Sequence #0005)	August 7, 2023	N/A	August 7, 2023

August 7, 2023 submission provides response to Agency July 6, 2023 Information Request.

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

Concise Description of Outstanding Issues: N/A

Select Number of Approved Comparability Protocols: 0

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –**
  The drug product is a clear, colorless to pale yellow non-sterile solution for oral administration filled as 0.4 mg/mL, 5 mL fill (2 mg/5 mL) in 16 oz plastics bottles.

- **Drug product composition** –

Ingredient	Quantity per mL (mg/mL)	Function
Tizanidine Hydrochloride, USP	0.46	Active Pharmaceutical Ingredient
Edetate Disodium Dihydrate, USP	(b) (4)	
Sucralose, NF		
Methylparaben Sodium, NF		
Propylparaben Sodium, NF		
Citric acid Anhydrous (b) (4) USP		
Sodium Citrate, Anhydrous, NF		
Strawberry Flavor (b) (4)		
Purified Water, USP		

- **Description of container closure system –**

Component	Description	Manufacturer and Distributor
Container	(b) (4)	

	(b) (4) Plastics Bottle
Closure	(b) (4)

Additional Information and Analysis, container/closure:
The 16 oz (b) (4) (b) (4). Microbial specifications for the were not provided. Since the drug product is non-sterile and microbial limits set for the drug solution, no further comment will be made.

Reviewer's Assessment: Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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/s/

MARTHA R HEIMANN
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