CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216190Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	December 5, 2024
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 216190
Product Name, Dosage Form, and Strength:	Ontralfy (tizanidine oral solution), 2 mg/5 mL
Applicant Name:	Fidelity BioPharma Co. (Fidelity)
FDA Received Date:	December 4, 2024
TTT ID #:	2023-5037-4
DMEPA 2 Safety Evaluator:	Rina Patel, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

Fidelity BioPharma Co. submitted revised container label received on December 4, 2024 for Ontralfy. The Division of Neurology 1 (DN 1) requested that we review the revised container label for Ontralfy (Appendix A) to determine if it is 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

Fidelity BioPharma Co. implemented all of our recommendations and we have no additional recommendations at this time.

[a] Patel, R. Addendum to Previous Label and Labeling Review Memorandum for Ontralfy (NDA 216190). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 Nov 5. TTT ID: 2023-5037-3.

APPENDIX A. IMAGE OF CONTAINER LABEL RECEIVED ON DECEMBER 4, 2024

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/s/

RINA N PATEL
12/05/2024 11:25:55 AM

STEPHANIE L DEGRAW
12/05/2024 11:49:47 AM

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

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

Memorandum

Date: December 04, 2024

To: Michael Dimyan
Division of Neurology Products 1 (DN1)

Amy Bolger, Regulatory Project Manager, (DN1)

Tracy Peters, Associate Director for Labeling, (DN)

From: Samuel Fasanmi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Taylor Burnett Mmagu, Team Leader, OPDP

Subject: OPDP Labeling Comments for Ontralfy (tizanidine oral solution)

NDA: 216190

In response to DN1's consult request dated September 16, 2024, OPDP has reviewed the proposed product labeling (PI) and container labeling for the original NDA submission for Ontralfy (tizanidine oral solution).

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DN1 on November 21, 2024, and are provided below.

Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on July 15, 2024, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Samuel Fasanmi at (301) 796-5188 or samuel.fasanmi@fda.hhs.gov.

18 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SAMUEL A FASANMI
12/04/2024 01:36:13 PM

MEMORANDUM
ADDENDUM TO PREVIOUS LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	November 5, 2024
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 216190
Product Name, Dosage Form, and Strength:	Ontralfy (tizanidine oral solution), 2 mg/5 mL
Applicant Name:	Fidelity BioPharma Co. (Fidelity)
FDA Received Date:	June 12, 2024 and July 15, 2024
TTT ID #:	2023-5037-3
DMEPA 2 Safety Evaluator:	Rina Patel, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

Fidelity submitted a Class 2 Resubmission for NDA 216190 for Ontralfy (tizanidine oral solution). Subsequently, the Division of Neurology 1 (DN 1) requested that we review the proposed prescribing information and container label for areas of vulnerability that may lead to medication errors.

This memorandum is an addendum to our original label and labeling review.[a] At that time, bioequivalence information for tizanidine products was still under review by DN1. As such, we requested that our container label recommendations not be sent to Fidelity until a final decision regarding the substitution of Ontralfy with other tizanidine products was determined. Based on the currently agreed upon substitutability information in the Ontralfy Prescribing Information, this memorandum provides updated container label recommendations to be sent to Fidelity and implemented prior to approval of NDA 216190.

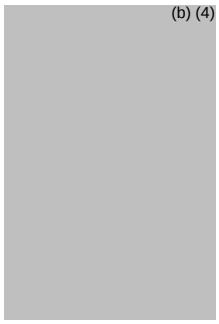
2 CONCLUSION

The proposed container label may be improved to promote the safe use of this product from a medication error perspective. We provide two container label recommendations for Fidelity in Section 3.

3 RECOMMENDATIONS FOR FIDELITY BIOPHARMA CO.

CONTAINER LABEL

A. We note the container label submitted on November 10, 2023 contained a placeholder for the product identifier and expiration date; however, this information is not present on the container label received on July 15, 2024. Please confirm that the inclusion and format for the product identifier information and expiration date for your proposed container label is the same as previously submitted. For example:



B. The container label contains a statement instructing pharmacists to dispense in a (b) (4) but this information in not present in Section 16. Conflicting storage and dispensing conditions across product labeling may cause confusion. We

[a] Patel, R. Label and Labeling Review for Ontralfy (NDA 216190). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 SEP 26. TTT ID: 2023-5037-2.

recommend removing instructions to dispense in a [redacted] (b) (4) as the drug product is not [redacted] (b) (4)

APPENDIX A. IMAGE OF CONTAINER LABEL RECEIVED ON JULY 15, 2024

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/s/

RINA N PATEL
11/05/2024 03:47:19 PM

STEPHANIE L DEGRAW
11/05/2024 04:08:01 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	September 26, 2024
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 216190
Product Name, Dosage Form, and Strength:	Ontralfy (tizanidine oral solution) 2 mg/5 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Fidelity BioPharma Co. (Fidelity)
FDA Received Date:	June 12, 2024 and July 15, 2024
TTT ID #:	2023-5037-2
DMEPA 2 Safety Evaluator:	Rina Patel, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

Fidelity submitted a Class 2 Resubmission for NDA 216190 for Ontralfy (tizanidine oral solution). Subsequently, the Division of Neurology 1 (DN 1) requested that we review the proposed prescribing information and container label for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND AND REGULATORY HISTORY

NDA 216190 is a 505(b)(2) NDA and the listed drug products are Zanaflex tablets and capsules (NDA 020397 and NDA 021447, respectively).

Fidelity previously submitted NDA 216190 on May 31, 2023. During that review cycle, we reviewed the PI and container label and provided our recommendations to the Division and the Applicant.[a] Subsequently, we reviewed the revised container label submitted in response to our recommendation, which we found acceptable.[b] However, NDA 216190 received a Complete Response letter on March 29, 2024, due to product quality and nonclinical issues, and therefore, labeling negotiations for the Prescribing Information (PI) did not occur.[c]

Thus, Fidelity submitted a Class 2 Resubmission on June 12, 2024.[d] The proposed container label and PI were received on July 15, 2024.

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
Labels and Labeling	B

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI) and container label may be improved to promote the safe use of this product from a medication error perspective. We provide the identified

[a] Patel, R. Label and Labeling Review for Ontralfy (NDA 216190). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 OCT 20. TTT ID No.: 2023-5037.

[b] Patel, R. Label and Labeling Review MEMO for Ontralfy (NDA 216190). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 DEC 11. TTT ID No.: 2023-5037-1.

[c] Jawidzik, L. Complete Response for NDA 216190. Silver Spring (MD): FDA, CDER, OND, Division of Neurology 1 (DN 1) (US); 2024 MAR 29.

[d] Response to FDA Complete Response Letter of March 29,2024. New Haven (CT): Fidelity BioPharma Co.; 2024 JUN 12. Available from: \\CDSESUB1\EVSPROD\nda216190\0014\m1\us\111-information-amendment\resp-fda-crl-rec-20240329-cmc.pdf.

medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division.

The proposed container label is nearly identical to the container label we previously found acceptable on December 11, 2023, under the last review cycle. However, two changes were made to the storage statement and the contents statement in response to an Information Request submitted by OPQ on January 12, 2024.[e] We did not identify any medication error concerns associated with these proposed revisions. One additional difference since our last review is the product identifier and expiration date placeholders are missing from the container label in the current submission. We provide one container label recommendation and a container label comment confirming the inclusion of the product identifier and expiration date for Fidelity in Section 5.

4 RECOMMEDATIONS FOR DIVISION OF NEUROLOGY 1 (DN 1)

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	Recommended dosage is presented inconsistently in multiple units of measure (mg and/or mL).	Expressing the dosage in a manner that is inconsistent may lead to dosing errors.	We recommend ensuring the unit of measure for the recommended dosage throughout the Prescribing Information is consistent. We recommend presenting the doses as “mg (mL)” or “mL (mg)”. See Guidance for Industry: *Safety Considerations for Product Design to Minimize Medication Errors (April 2016)*.
Highlights of Prescribing Information			
1.	As currently presented, the route of administration is missing from the dosage statement. Additionally, the dosage information	Unclear dosage information and omitting important information such as the route of administration may lead to administration medication errors.	We recommend adding the route of administration to the dosing information and revising the dosage information for clarity. For example:

[e] Keafer, E. Information Request for changes to the container label. Message to Ms. DeLeon. Silver Spring (MD): FDA, CDER, OND, DN1 (US); 2024 JAN 12.

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	may be improved for readability.		• Recommended starting dose: 2 mg (5 mL). Administer orally every 6 hours to 8 hours as needed, up to a maximum of three doses in 24 hours (2.1). • The dose can be increased by 2 mg (5 mL) to 4 mg (10 mL) per dose, no more frequently than every 1 to 4 days. The total daily dose should not exceed 36 mg (90 mL) (2.1).
2.	The last bullet point under "Dosage and Administration" references Section 2.2 for further information on discontinuing Ontralfy. However, information on discontinuing the product is in Section (b) (4)	Incorrect citations may make dosing information in the full PI difficult to find.	We recommend modifying the reference section to read (b) (4)
Full Prescribing Information – Section 2 Dosage and Administration			
1.	We note that the RLD (Zanaflex) PI contains a bioequivalence (BE) statement for Zanaflex tablets and capsules. A similar statement is not present in the Ontralfy PI.	Based on discussion with the review team, it appears that Ontralfy may not be bioequivalent with the currently marketed tizanidine capsules. Inadvertent substitution can lead to medication errors such as wrong drug errors leading to no treatment effect or overdose/underdose leading to adverse events or lack of efficacy.	If appropriate, we recommend adding the statement "Ontralfy is NOT substitutable on a mg-to-mg basis with Zanaflex capsules and tizanidine capsules" to the Dosage and Administration section in the HPI and full PI. We defer to the Division to consider if this type of statement is needed. If the Division considers this statement necessary, a similar statement will need to be

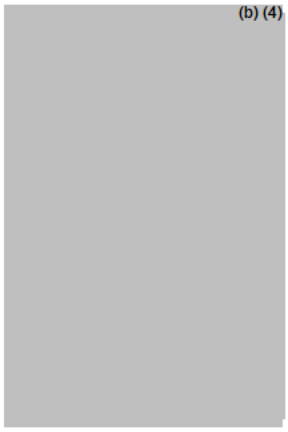
Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			added to the container label PDP.
2.	As currently presented, information on how to measure the appropriate dose is missing.	Selecting an unacceptable measuring device may increase the risk for wrong dose medication errors.	We propose specifying acceptable types of measuring devices. For example, "A calibrated measuring device, such as an oral syringe or oral dosing cup, is recommended to measure and deliver the prescribed dose accurately. A household measuring cup, teaspoon, or tablespoon is not an adequate measuring device."
3.	As currently presented, the route of administration is missing from the dosage statement. Additionally, the dosage information may be improved for readability.	Unclear dosage information and omitting important information such as the route of administration may lead to administration medication errors.	We recommend adding the route of administration to the dosing information and revising the dosage information for clarity. For example: "The recommended starting dose is 2 mg (5 mL). Administer orally every 6 hours to 8 hours as needed, up to a maximum of three doses in 24 hours. Doses can be increased by 2 mg (5 mL) to 4 mg (10 mL) per dose, no more frequently than every 1 to 4 days. The total daily dose should not exceed 36 mg (90 mL). Single doses greater than 16 mg (40 mL) have not been studied."
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The storage statement on the container label includes a temperature range rather than a	Not including the full storage information and the statement, (b) (4) (b) (4) may result in (b) (4)	Revise the storage statement in the PI to align with the container label (i.e., store at

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	singular temperature as presented in Section 16 (i.e., 25°C (77°F)). The container label also contains a statement instructing pharmacists to dispense in a (b) (4) but this information in not present in Section 16.	(b) (4) if stored incorrectly.	20°C to 25°C (68°F to 77°F); excursions…). Add missing storage conditions (i.e., (b) (4) in Section 16 in accordance with 21 CFR 201.57(c)(17) if this is in fact a storage requirement. We defer to OPQ regarding the appropriate storage conditions.
Full Prescribing Information – Section 17 Patient Counseling			
1.	As currently presented, no statement is present to instruct patients or their caregivers to use a calibrated oral dosing device to measure the appropriate dose.	Selecting an unacceptable measuring device may increase the risk for wrong dose medication errors.	We propose specifying acceptable types of measuring devices. For example, "Inform patients that a calibrated measuring device, such as an oral syringe or oral dosing cup, should be obtained from the pharmacy to measure and deliver the prescribed dose accurately. A household measuring cup, teaspoon, or tablespoon is not an adequate measuring device."

5 RECOMMENDATIONS FOR FIDELITY BIOPHARMA CO.

1. The RLD (Zanaflex) container labels contain the bioequivalence warning statements "Not interchangeable with tizanidine tablets or Zanaflex tablets" and "Zanaflex (tizanidine hydrochloride) tablets are not interchangeable with Zanaflex Capsules" on Zanaflex capsule and tablet container labels, respectively. We note that Ontralfy is not bioequivalent with the currently marketed tizanidine capsules. Inadvertent substitution can lead to medication errors such as wrong drug errors leading to no treatment effect or overdose/underdose leading to adverse events or lack of efficacy. Therefore, we recommend adding a similar bioequivalence statement to the container label for Ontralfy. For example, "Ontralfy is not substitutable on a mg-to-mg basis with Zanaflex (tizanidine) capsules or other tizanidine capsules".

2. We note the container label submitted on November 10, 2023 contained a placeholder for the product identifier and expiration date; however, this information is not present on the container label received on July 15, 2024. Please confirm that the inclusion and format for the product identifier information and expiration date for your proposed container label is the same as previously submitted. For example:



If any additional changes to the container label are made subsequent to the version submitted on July 15, 2024, please submit a revised container label for our review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED
APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION
Table presents relevant product information for Ontralfy that Fidelity BioPharma Co. submitted on July 15, 2024, and the listed drugs (LD).

Table 4. Relevant Product Information for the Listed Drugs and Ontralfy		
Product Name	Zanaflex	Ontralfy
Initial Approval Date	November 27, 1996	N/A
Active Ingredient	Tizanidine hydrochloride	Tizanidine
Indication	(b) (4) of spasticity	(b) (4) of spasticity
Route of Administration	Oral	Oral
Dosage Form	Tablet Capsule	Oral solution
Strength	Tablet: 4 mg Capsule: 2 mg, 4 mg, and 6 mg	2 mg/5 mL
Dose and Frequency	• The recommended starting dose is 2 mg every 6 to 8 hours, as needed, to a maximum of three doses in 24 hours. • Dosage can be gradually increased by 2 mg to 4 mg at each dose, with 1 to 4 days between dosage increases. • The total daily dose should not exceed 36 mg.	• The recommended starting dose is 2 mg (5 mL) every 6 to 8 hours, as needed, to a maximum of three doses in 24 hours. • Dosage can be increased by 2 mg (5 mL) to 4 mg (10 mL) per dose, with 1 to 4 days between increases. • The total daily dose should not exceed 36 mg (90 mL).
How Supplied	Bottle of 150 tablets or capsules	473 mL filled into a 16 oz (b) (4) bottle
Storage	Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].	Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
Container Closure	Child resistant closure	Child resistant closure

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following Ontralfy labels and labeling submitted by Fidelity BioPharma Co.

- Container label received on July 15,2024
- Prescribing Information (Image not shown) received on July 15, 2024, available from \\CDSESUB1\EVSPROD\nda216190\0001\m1\us\114-labeling\draft\labeling\drft-label-txt.pdf

B.2 Label and Labeling Images

Container label

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

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/s/

RINA N PATEL
09/26/2024 08:36:27 AM

STEPHANIE L DEGRAW
09/26/2024 11:45:07 AM

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

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

Memorandum

Date: April 08, 2024

To: Susan Daugherty, Regulatory Project Manager,
Division of Neurology 1(DN1)

Michael Dimyan, (DN)

Tracy Peters, Associate Director for Labeling, (DN)

From: Samuel Fasanmi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for Ontralfy (tizanidine) oral solution, for oral use

NDA: 216190

This memo is in response to DN1's labeling consult request dated July 17, 2023. Reference is made to a Complete Response letter that was issued on March 29, 2024. Therefore, OPDP defers comment on the proposed labeling at this time, and requests that DN1 submit a new consult request during the subsequent review cycle. If you have any questions, please contact Sam Fasanmi at (301) 796-5188 or samuel.fasanmi@fda.hhs.gov.

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/s/

SAMUEL A FASANMI
04/08/2024 01:03:25 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 1/26/2024

TO: Division of Neurology I (DN I)
Office of Neuroscience (ON)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 216190

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) conducted an inspection for the clinical site in August 2023. The inspection was conducted under the following submission: ANDA NON-RESPONSIVE

The following objectionable condition was observed:

- The general requirements for informed consent were not met in that the site did not seek consent under circumstances that minimized the possibility of coercion or undue influence.

After review of the objectionable condition and the written response from the site, OSIS recommended that the review division consider the totality of information in the informed consent firm to determine the impact on data reliability. (Final OSIS Review - August 2023).

Site

Facility Type	Facility Name	Facility Address
Clinical	Scitus Pharma Services Pvt., Ltd.	2/294, DRR Avenue, 2nd Cross Street, AUDCO Nagar, Kattupakkam, Poonamallee, Chennai, Tamil Nadu, India

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/s/

WENDY NG
01/26/2024 06:51:06 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: December 13, 2023

From: Interdisciplinary Review Team for Cardiac Safety Studies

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

To: Shannon Snyder, RPM
DN1

Subject: QT Consult to NDA 216190 (SDN 001)

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 10/19/2023 regarding the Review Division's QT related question. We reviewed the following materials:

- Previous IRT review(s) for NDA 21447 and NDA 20397 dated 01/28/2015; in DARRTS;
- Highlights of clinical pharmacology and cardiac safety (Previous IRT review(s) for NDA 21447 and NDA 20397 dated 01/28/2015, Appendix 5; link).
- Clinical Study Reports for Study TIZA-21-086 (link) and TIZA-22-046 (link)

1 Responses for the Review Division

Consult request: In TIZA-21-086, Review Division have identified 5 subjects that experienced 6 events of QT Prolongation >440 ms, 4 episodes occurring after treatment with Test and 2 after treatment with Reference Drug. Please advise whether the episodes of QT prolongation with the Test drug are concerning and require further assessment of the arrhythmogenic potential of this product.

IRT's response: We do not consider the 6 episodes of QTc prolongation with the Test drug to be of clinical concerns and therefore do not warrant further QT risk assessment for the following reasons:

1) The study's baseline QTc inclusion criteria of ≤ 440 msec and the cutoff used to identify subjects with QTc prolongation as those with QTcF > 440 msec are considered to be within normal QT limits of < 450 msec for males and < 470 msec for female.

2) Only one of the identified cases of mild QTc prolongation exceeded 470 msec and was < 480 msec.

3) The largest change from baseline in QTc were > 30 msec but < 60 msec.

4) Other treatment periods did not indicate higher frequency of mild QT prolongation for Test compared to the Reference drug.

5) Test drug met the bioequivalence (BE) criteria after 4 mg/day dose and no significant QTc prolongation effect of tizanidine was observed at higher dose of 8 mg and 24 mg in the previous TQT study (IRT TQT Study Review).

2 BACKGROUND

2.1 Product Information

Fidelity BioPharma Co. (Fidelity) has developed an oral solution dosage form (2 mg/5 mL (Tizanidine Oral Solution)) for patient compliance. Fidelity proposes to have a dosage regimen and indication identical to Zanaflex® (Tizanidine Hydrochloride) Tablets and Zanaflex (Tizanidine Hydrochloride) Capsules [the approved listed drugs (ALDs)] which were previously approved by the FDA. Tizanidine is a centrally acting α2 adrenergic agonist indicated for the (b) (4) of spasticity in the US, EU, and Japan.

The key clinical prescribing information for Tizanidine Oral Solution is similar to that for Zanaflex Tablets and Zanaflex Capsules. There are no differences in the indications, contraindications, precautions, and warnings.

2.2 Division's position related to the question.

DN1 division is currently evaluating NDA 216190, a 505(b)(2) for an oral solution formulation of tizanidine hydrochloride (Test), a central acting muscle relaxant. The reference listed drug, Zanaflex (Reference) was approved in 1996 in tablet form (NDA 020397) and 2002 in capsule form (NDA 021447). The original nonclinical studies demonstrated some cases of prolonged QT interval at high doses and a PMR was issued under NDA 021447 for a Thorough QT study which was completed in 2014. In the current NDA, 2 crossover bioequivalence studies in healthy volunteers were submitted: The first one is study TIZA-21-086 which tested the new oral solution (Test) against the tablet formulation (Reference) under fasted and fed conditions and the second one is study TIZA-22-046 which tested the new oral solution against the capsule formulation in the fasted condition.

In study TIZA-21-086, the division has identified 5 subjects that experienced 6 events of QT Prolongation >440 ms, 4 episodes occurring after treatment with Test and 2 after treatment with Reference drug.

The review division have summarized the cases of QT prolongation in TIZA-21-086 as follows:

TIZA-21-(b) (6) During Period 3, having received a dose of Test drug (tizanidine hydrochloride oral solution) at 09:00 a.m on (b) (6) the subject experience AE#1 at at 09:55 a. m.,

where the 1.5hr post-dose ECG had a QTc of **443** ms. Subsequent ECG at 11:50 a.m. (3.5h post-dose) QTc was 420 ms.

TIZA-21-(b) (6) in Period 2 on (b) (6) had received a dose of Test drug at 09:18 a.m. At 8:55 p.m. during what was considered their 12 hr post-dose ECG QTc =**442** ms with heart rate of 85 bpm. A subsequent ECG performed at 9:46 a.m. on (b) (6) had a QTc of 428 ms with a heart rate of 91 bpm.

TIZA-21-(b) (6) in Period 3 had received Test product on (b) (6) 09:18 a.m. and on (b) (6) (b) (6) at 08:48 p.m. during the 12 hr post-dose ECG had a QTc of **442** ms and heart rate of 88 bpm. Subsequent ECG on (b) (6) 09:48 a.m. QTc had resolved to 414 ms with heart rate of 70 bpm.

TIZA-21-(b) (6) in Period 2 received Reference drug at 09:28 a.m. on (b) (6) and then on (b) (6) at 10:46 a.m. at the 1.5 hr post-dose ECG had a QTc of 443 ms with a heart rate of 48 bpm. At the 3.5 hr post-dose ECG (12:20 p.m.) QTc was still prolonged at **442** ms with heart rate of 51 bpm and a repeat ECG added at 3:55 p.m. the QTc had resolved to 427 ms with a heart rate of 70 bpm.

TIZA-21-(b) (6) in Period 1 on (b) (6) at 10:15 a.m. after receiving Test drug had QTc of 449 ms and heart rate of 78 bpm on the 1.5 hr post-dose ECG. ECG at the 3.5 hr and 12 hr post-dose evaluations at 12:07 p.m. and 4:02 p.m. had QTc of **474** ms and **442** ms with heart rates of 83 and 85 bpm. A repeat ECG at 8:52 p.m. had resolved with QTc of 423 ms and heart rate of 73 bpm.

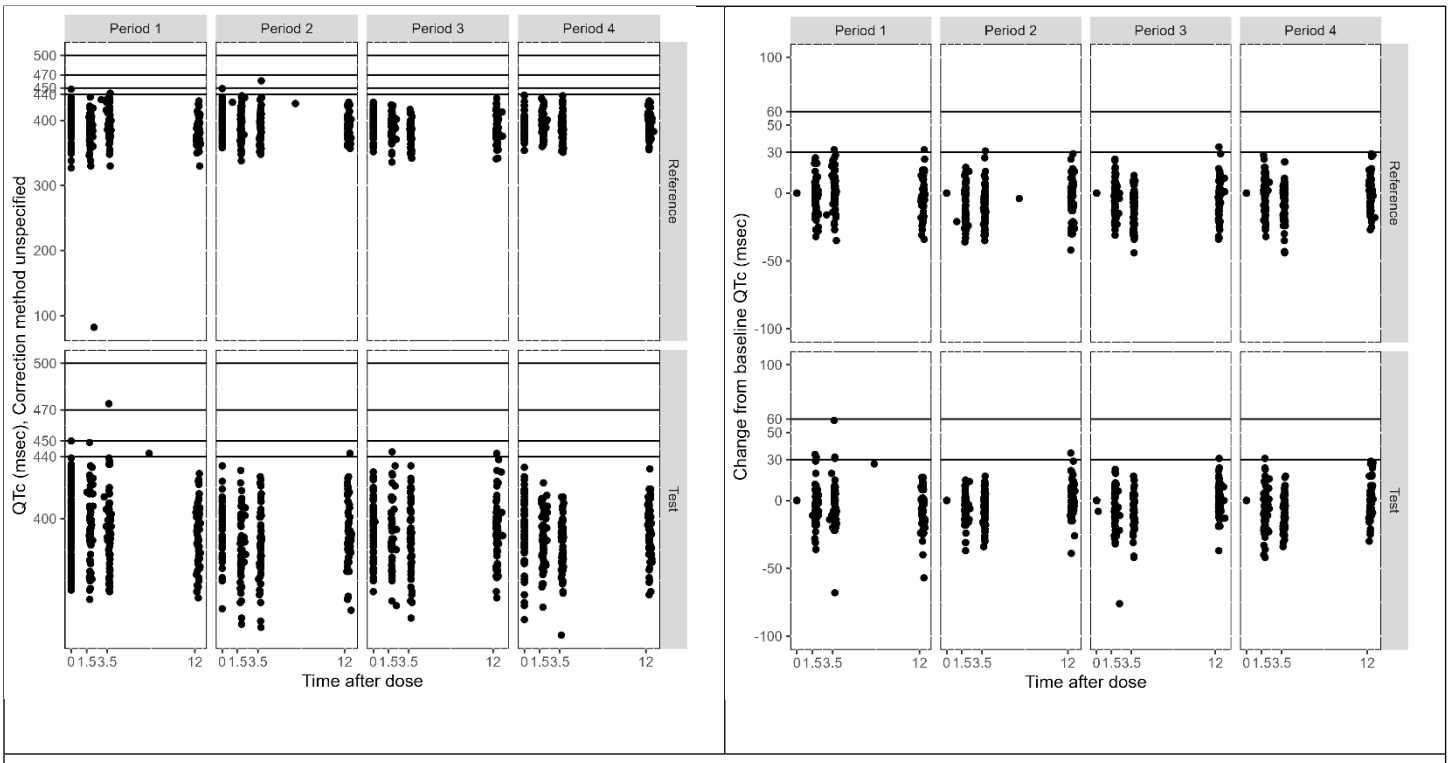
The same subject in Period 2 received Reference drug on (b) (6) at 09:20 a.m. and at the 1.5 hr post-dose ECG at at 10:15 a.m. had QTc of **449** ms and heart rate of 78 bpm. Subsequent ECG at 3.5 hr post-dose 12:07 p.m. QTc was **474** ms with heart rate of 83 bpm. A repeat ECG was donse at 04:02 p.m. to follow this QTc prolongation and was still mildly prolonged at **442** ms with heart rate of 85 bpm. The 12 hr post-dose ECG performed at 08:52 p.m. was normalized with QTc of 423 ms and heart rate of 73 bpm and the AE was considered resolved.

The review division seeks some advice whether the episodes of QT prolongation with the Test drug are concerning and require further assessment of the arrhythmogenic potential of this product.

Reviewer's Comment:

- *Independent analysis by the QT-IRT reviewer indicate that of the 6 cases identified as mild QT prolongation (at cutoff of 440 msec) in period 1, only one had QTc > 470 msec (i.e., subject (b) (6) QTc 474 msec in period 1). The QT-IRT reviewer's analysis also indicates that, in period 1, 2 and 5 subjects had QTc change from baseline of > 30 msec and < 60 msec when they received reference and test treatments respectively. None had > 60 msec change from baseline QTc in any of the treatment periods. Figure 1 indicate that most of the cases of mild QT prolongation occurred with the test drug in period 1.*

Figure 1. QTc and change from baseline in QTc after treatment with Test and Reference drugs in different periods.



Source: QT-IRT reviewer's independent analysis

- *A previous completed TQT analysis shows no significant QTc prolongation effect of tizanidine (8 mg and 24 mg), where the largest upper bounds of the 2-sided 90% CI for the mean difference between tizanidine (8 mg and 24 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcI for moxifloxacin was greater than 5 ms, indicating that assay sensitivity was established.*
- *The proposed dose in the BE study was 4 mg, which was lower than the supratherapeutic dose used in the TQT study analysis (24 mg),*
- *The QT prolongation cutoff used for the study was 440 ms which is within normal QTc limits and none of the prolongation episodes exceeded 500 msec.*

2.3 Clinical Pharmacology

Highlights of clinical pharmacology and cardiac safety are previously reviewed and can be located at Appendix 5 of Previous IRT review(s) for NDA 21447 and NDA 20397 dated 01/28/2015; link).

Table 1: Summary of dose and exposure assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	4 mg oral solution	5.32 ng/mL

Sponsor's High clinical exposure scenario	30%increase with food	6.92 ng/mL
Highest dose in QT assessment	24 mg QD, oral tablets	27.4 ng/mL ($C_{max,ss}$)
C_{max} Ratio	27.4/6.92	3.96

It is expected that co-administration of tizanidine with fluvoxamine can elevate tizanidine's mean Cmax as much as 12-fold, but fluvoxamine and other CYP1A2 inhibitors are contraindicated concominant tizanidine and thus not included here.

2.4 Nonclinical Cardiac Safety

From Zanaflex's tablets ® PI Precautions-Cardiovascular (label)
"Prolongation of the QT interval and bradycardia were noted in chronic toxicity studies in dogs at doses equal to the maximum human dose on a mg/m2 basis. ECG evaluation was not performed in the controlled clinical studies. Reduction in pulse rate has been noted in association with decreases in blood pressure in the single dose-controlled study (see WARNINGS)."

2.5 Summary results of prior QTc assessments

No significant QTc prolongation effect of tizanidine (8 mg and 24 mg) was detected in previous TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between tizanidine (8 mg and 24 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcI for moxifloxacin was greater than 5 ms, and the moxifloxacin assay sensitivity was established. In this randomized, partial-blind, parallel study with a nested crossover design, 136 healthy subjects received tizanidine (8 mg and 24 mg), placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1. The supratherapeutic dose (24 mg) produces mean Cmax values of 2.3-fold the mean Cmax for the therapeutic dose (8 mg) and ~4 fold for current proposed dose of 4 mg oral solution.

Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Tizanidine (8 mg and 24 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis).

Treatment	Time (hour)	ΔΔQTCI (ms)	90% CI (ms)
Tizanidine 8 mg	4	1.6	(-0.4, 3.6)
Tizanidine 24 mg	4	-1.8	(-4.6, 1.0)
Moxifloxacin 400 mg*	4	9.7	(7.5, 12.0)

* Multiple endpoint adjustment of 3 time points was applied.

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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12/13/2023 02:11:49 PM

CHRISTINE E GARNETT
12/13/2023 02:20:09 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 11, 2023
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 216190
Product Name, Dosage Form, and Strength:	Ontralfy (tizanidine oral solution), 2 mg/5 mL
Applicant/Sponsor Name:	Fidelity BioPharma Co.
TTT ID #:	2023-5037-1
DMEPA 2 Safety Evaluator:	Rina Patel, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted a revised container label received on November 10, 2023 for Ontralfy. The Division of Neurology 1 (DN 1) requested that we review the revised container label for Ontralfy (Appendix A) to determine if it is 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

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Patel, R. Label and Labeling Review for Ontralfy (NDA 216190). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 OCT 20. TTT ID No.: 2023-5037.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON NOVEMBER 10, 2023

Container label

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/s/

RINA N PATEL
12/11/2023 12:10:34 PM

STEPHANIE L DEGRAW
12/12/2023 07:41:38 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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 20, 2023
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 216190
Product Name, Dosage Form, and Strength:	Ontralfy (tizanidine oral solution) 2 mg/5 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Fidelity BioPharma Co.
FDA Received Date:	May 31, 2023
TTT ID #:	2023-5037
DMEPA 2 Safety Evaluator:	Rina Patel, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

As part of the approval process for Ontralfy (tizanidine oral solution), the Division of Neurology 1 (DN 1) requested that we review the proposed prescribing information and container label for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

NDA 216190 is a 505(b)(2) NDA and the listed drug products are Zanaflex tablets and capsules (NDA 020397 and NDA 021447, respectively).

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) and container label 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 Fidelity BioPharma Co.

4 RECOMMEDATIONS FOR DIVISION OF NEUROLOGY 1 (DN 1)

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	Recommended dosage is presented inconsistently in multiple units of measure (mg and/or mL).	Expressing the dosage in a manner that is inconsistent may lead to dosing errors.	We recommend ensuring the unit of measure for the recommended dosage throughout the Prescribing Information is consistent. We recommend presenting the doses as "mg (mL)". See Guidance for Industry: *Safety Considerations for Product Design to Minimize Medication Errors (April 2016)*.
Highlights of Prescribing Information			
1.	As currently presented, the route of administration is missing from the dosage statement. Additionally, the dosage information may be improved for readability.	Unclear dosage information and omitting important information such as the route of administration may lead to administration medication errors.	We recommend adding the route of administration to the dosing information and revising the dosage information for clarity. For example: • Recommended starting dose: 2 mg (5 mL). Administer orally every 6 hours to 8 hours as needed, up to a maximum of three doses in 24 hours (2.1). • The dose can be increased by 2 mg (5 mL) to 4 mg (10 mL) per dose, no more frequently than every 1 to 4 days. The total daily dose should not exceed 36 mg (90 mL) (2.1).
2.	The last bullet point under "Dosage and Administration" references Section 2.2 for further information	Incorrect citations may make dosing information in the full PI difficult to find.	We recommend modifying the reference section to read (b) (4).

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	on discontinuing Ontralfy. However, information on discontinuing the product is in Section (b) (4)		
Full Prescribing Information – Section 2 Dosage and Administration			
1.	As currently presented, information on how to measure the appropriate dose is missing.	Selecting an unacceptable measuring device may increase the risk for wrong dose medication errors.	We propose specifying acceptable types of measuring devices. For example, "A calibrated measuring device, such as an oral syringe or oral dosing cup, is recommended to measure and deliver the prescribed dose accurately. A household measuring cup, teaspoon, or tablespoon is not an adequate measuring device."
2.	As currently presented, the route of administration is missing from the dosage statement. Additionally, the dosage information may be improved for readability.	Unclear dosage information and omitting important information such as the route of administration may lead to administration medication errors.	We recommend adding the route of administration to the dosing information and revising the dosage information for clarity. For example: "The recommended starting dose is 2 mg (5 mL). Administer orally every 6 hours to 8 hours as needed, up to a maximum of three doses in 24 hours. Doses can be increased by 2 mg (5 mL) to 4 mg (10 mL) per dose, no more frequently than every 1 to 4 days. The total daily dose should not exceed 36 mg (90 mL). Single doses greater than 16 mg (40 mL) have not been studied."

Table 2. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The container label contains a statement instructing pharmacists to dispense in a (b) (4) (b) (4) but this information in not present in Section 16.	Not including the statement, (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)	Add missing storage conditions (i.e., (b) (4) in Section 16 in accordance with 21 CFR 201.57(c)(17) if this is in fact a storage requirement. We defer to OPQ regarding the appropriate storage conditions.
Full Prescribing Information – Section 17 Patient Counseling			
1.	As currently presented, no statement is present to instruct patients or their caregivers to use a calibrated oral dosing device to measure the appropriate dose.	Selecting an unacceptable measuring device may increase the risk for wrong dose medication errors.	We propose specifying acceptable types of measuring devices. For example, "Inform patients that a calibrated measuring device, such as an oral syringe or oral dosing cup, should be obtained from the pharmacy to measure and deliver the prescribed dose accurately. A household measuring cup, teaspoon, or tablespoon is not an adequate measuring device."

5 RECOMMENDATIONS FOR FIDELITY BIOPHARMA CO.

Table 3. Identified Issues and Recommendations for Fidelity BioPharma Co. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Container Label			
1.	The manufacturer logo competes in prominence with critical product information (e.g., proprietary name, established name,	Critical product information such as the proprietary name, established name, and product strength should appear as the most prominent information on	Decrease the size of the manufacturer logo so it does not compete with the prominence of important product information on the PDP.

Table 3. Identified Issues and Recommendations for Fidelity BioPharma Co. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	strength) on the principal display panel (PDP).	the principal display panel in accordance with 21 CFR 201.15.	See Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)*.
2.	The strength presentation could be made more prominent. Additionally, the strength appears near the net quantity statement [16 fl. oz. (473 mL)] on the PDP.	Critical product information, such as the strength, should be prominent to decrease the risk of dosing errors. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.	Consider increasing the font size, boxing, or other means to increase the prominence of the strength. We also recommend moving the net quantity statement and "Rx only" statement to the bottom on the PDP away from the strength. See Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)*.
3.	As currently presented, there is no placeholder for the product identifier.	In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: *Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers | FDA (June 2021).* If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the container label.

Table 3. Identified Issues and Recommendations for Fidelity BioPharma Co. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		machine-readable (2D data matrix barcode) format.	
4.	The format for expiration date is not defined.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash be used to separate the portions of the expiration date.
5.	The terminology within the Dosage statement (i.e., (b) (4)) is inconsistent with the terminology in the Prescribing Information.	To ensure consistency with the terminology in the Prescribing Information.	We recommend revising the recommended dosage statement to read, "Dosage: see Prescribing Information." See Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).*

Table 3. Identified Issues and Recommendations for Fidelity BioPharma Co. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
6.	The strength is presented with a trailing zero (e.g., 2.0 mg) in the solution contents statement on the side panel.	Trailing zeros can lead to tenfold dosing errors when the decimal point goes unnoticed (e.g., 2.0 mg is seen as 20 mg).	We recommend revising the contents statement to remove the trailing zero. See Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).*

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED
APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION
Table presents relevant product information for Ontralfy that Fidelity BioPharma Co. submitted on May 31, 2023, and the listed drugs (LD).

Table 4. Relevant Product Information for Listed Drugs and Ontralfy

Product Name	Zanaflex	Ontralfy
Initial Approval Date	November 27, 1996	N/A
Active Ingredient	Tizanidine hydrochloride	Tizanidine
Indication	(b) (4) of spasticity	(b) (4) of spasticity
Route of Administration	Oral	Oral
Dosage Form	Tablet Capsule	Oral solution
Strength	Tablet: 4 mg Capsule: 2 mg, 4 mg, and 6 mg	2 mg/5 mL
Dose and Frequency	• The recommended starting dose is 2 mg every 6 to 8 hours, as needed, to a maximum of three doses in 24 hours. • Dosage can be gradually increased by 2 mg to 4 mg at each dose, with 1 to 4 days between dosage increases • The total daily dose should not exceed 36 mg.	• The recommended starting dose is 2 mg (5 mL) every 6 to 8 hours, as needed, to a maximum of three doses in 24 hours. • Dosage can be increased by 2 mg (5 mL) to 4 mg (10 mL) per dose, with 1 to 4 days between increases • The total daily dose should not exceed 36 mg (90 mL).
How Supplied	Bottle of 150 tablets or capsules	473 mL filled into a 16 oz (b) (4) bottle
Storage	Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].	Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
Container Closure	Child resistant closure	Child resistant closure

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 data, we reviewed the following Ontralfy labels and labeling submitted by Fidelity BioPharma Co.

- Container label received on May 31, 2023
- Prescribing Information (Image not shown) received on May 31, 2023, available from \\CDSESUB1\EVSPROD\nda216190\0001\m1\us\114-labeling\draft\labeling\drft-label-txt.pdf

F.2 Label and Labeling Images

Container label

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

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 8/18/2023

TO: Division of Neurology I (DN I)
Office of Neuroscience (ON)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 216190

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS conducted a Remote Regulatory Assessment (RRA) for the site in (b) (4) The RRA was conducted under the following submissions: ANDAs NON-RESPONSIVE and NON-RESPONSIVE

OSIS concluded that data from the reviewed studies were reliable.

Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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