CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216190Orig1s000

NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	216-190
Supporting document:	14
Applicant's letter date:	June 12, 2024
CDER stamp date:	June 12, 2024
Product:	ONTRALFY (tizanidine oral solution)
Indication:	(b) (4) of Spasticity
Applicant:	Fidelity BioPharma Co.; New Haven, CT
Review Division:	Division of Pharmacology/Toxicology for Neuroscience
Reviewer:	Christopher D. Toscano, Ph.D., DABT
Team Leader:	David L. Carbone, Ph.D.
Supervisor:	Lois M. Freed, Ph.D.
Division Director:	Emily Freilich, MD
Project Manager:	Susan B. Daugherty

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1 Executive Summary

1.1 Introduction:

The applicant is seeking marketing approval for ONTRALFY, an oral solution of tizanidine (2 mg/5 mL), for the management of spasticity. The applicant intends to rely on the Agency's previous determination of safety and effectiveness of tizanidine, with Zanaflex tablets (NDA 20-397) and capsules (NDA 21-447) as the Listed Drugs. Given that the applicant is seeking approval of ONTRALFY under 505 (b)(2), no new nonclinical data were provided to support the initial NDA submission. A Complete Response (CR) letter was issued on March 29, 2024, that included two deficiencies (unqualified levels of (b) (4) and inadequate specifications for (b) (4) impurities) that prevented approval.

1.2 Brief Discussion of Nonclinical Findings

There were no new nonclinical data provided in the initial NDA or resubmission.

1.3 Recommendations

1.3.1 Approvability

The applicant's justification for the level of (b) (4) in ONTRALFY is acceptable. Furthermore, the applicant has agreed to the recommended limits for the (b) (4) drug substance-related impurities. Therefore, the application is approvable from a nonclinical perspective.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

The proposed nonclinical labeling for ONTRALFY is identical to that of the listed drugs and is, therefore, acceptable.

2 Drug Information

Detailed information on the drug substance and drug product can be found in the nonclinical review of the initial submission (Toscano C, Carbone D, Freed L, Nonclinical Review, March 29, 2024).

2.5 Comments on Impurities/Degradants of Concern

(b) (4)

The applicant's justification for the proposed daily intake of (b) (4) is based on the established allowable levels of (b) (4) in (b) (4) (b) (4)%) (b) (4) (b) (4)%), as per USP monograph specifications. Reliance on the USP monograph for the qualification of (b) (4) was determined by the CMC review team to be an acceptable approach (Heimann M, Integrated Quality Review, November 7, 2024). Therefore, based on the USP monograph acceptance criteria and the (b) (4) (b) (4) for (b) (4) (b) (4) mg) (b) (4) mg) via the oral route, the maximum daily exposure to (b) (4) is calculated to be mg from both excipients. The

applicant's specification for (b) (4) in ONTRALFY would result in a maximum daily intake of (b) (4) mg (b) (4) As such, the proposed specification for (b) (4) n ONTRALFY is acceptable from a nonclinical perspective.

(b) (4)

Information provided in a July 16, 2024, communication from OTS/OCP/DARS stated that (b) (4) is an appropriate surrogate for determining the daily acceptable intake (AI) for (b) (4) Therefore, based on read-across analysis, a daily AI of (b) (4) ng/day is, acceptable for (b) (4) Additionally, an adequate surrogate for (b) (4) could not be determined. Therefore, the recommended AI for (b) (4) is (b) (4) ng/day based on the class-specific limit for (b) (4) impurities.

3 Studies Submitted

There were no new nonclinical studies submitted to support the NDA.

11 Integrated Summary and Safety Evaluation

Given that the applicant provided adequate support for the proposed daily intake of (b) (4) and has accepted the recommended daily intake for the two drug substance-related impurities, the nonclinical deficiencies stated in the Complete Response letter issued in response to the initial NDA submission have been adequately addressed in the resubmission. From a nonclinical perspective, the NDA for ONTRALFY is considered approvable.

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/s/

CHRISTOPHER D TOSCANO
11/18/2024 10:08:33 AM

DAVID L CARBONE
11/18/2024 10:16:52 AM

LOIS M FREED
11/18/2024 11:04:09 AM
I concur.

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	216-190
Supporting document:	1
Applicant's letter date:	May 31, 2023
CDER stamp date:	June 6, 2023
Product:	ONTRALFY (tizanidine oral solution)
Indication:	(b) (4) of Spasticity
Applicant:	Fidelity BioPharma Co.; New Haven, CT
Review Division:	Division of Pharmacology/Toxicology for Neuroscience
Reviewer:	Christopher D. Toscano, Ph.D., DABT
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1.2 Brief Discussion of Nonclinical Findings

There were no new nonclinical data provided in the NDA. During the review cycle, it was determined that ONTRALFY contains an unqualified degradant, (b) (4)

1.3 Recommendations

1.3.1 Approvability

Not approvable based on the presence of a degradant, (b) (4) for which adequate safety data to support the proposed specification have not been provided.

1.3.2 Additional Non Clinical Recommendations

The applicant should either reduce the specification for the degradant (b) (4) (b) (4) to a level that is at or below the qualification threshold or provide additional nonclinical data to demonstrate that the maximum proposed daily intake of (b) (4) mg/day is safe.

1.3.3 Labeling

The proposed nonclinical labeling for ONTRALFY is identical to that of the listed drugs and is, therefore, acceptable.

2 Drug Information

2.1 Drug

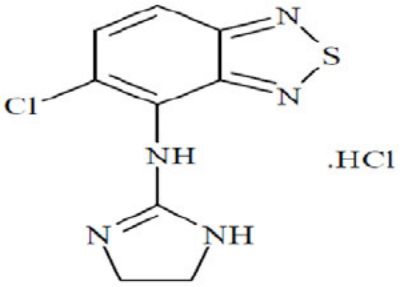
CAS Registry Number: 64461-82-1

Generic Name: Tizanidine hydrochloride

Chemical Name: 2,1,3-Benzothiadiazol-4-amine,5-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-, monohydrochloride

Molecular Formula/Molecular Weight: $C_9H_8ClN_5S \bullet HCl$; 290.17 g/mol

Structure: Applicant's figure, below



Established Pharmacologic Class: Central alpha-2 adrenergic agonist

2.2 Relevant INDs and NDAs:

The applicant developed ONTRALFY under IND 156316 and refers to NDAs 20-397 and 21-447 as the listed drugs. The applicant was informed during the review cycle that it is not necessary to rely on NDA 21-447 (Advice Letter, March 7, 2024).

2.3 Drug Formulation:

ONTRALFY is formulated as described in the applicant's table, below. There are no nonclinical concerns regarding the excipients present in ONTRALFY.

Table 1: Qualitative and Quantitative Composition of Tizanidine Oral Solution

Name of Ingredients	Grade	Standard Quantity		Function
		mg/mL	% w/v	
Tizanidine Hydrochloride	USP	0.46 mg	0.046 %	Active 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)	(b) (4)			
Purified Water	USP			

[1]Quantitative Composition of Strawberry Flavor (b) (4)

Ingredient	Percent (w/v)	Percent (w/v) (Worst case consideration)	mg/mL (Based on 0.5 mg)
(b) (4)			

Note: Refer to Drug Master File (DMF) (b) (4) This flavor ingredient has been used in other FDA approved drugs products. As reported by the manufacturer, all (b) (4) flavoring ingredients are listed as GRAS (Generally Recognized As Safe) by the Flavor and Extract Manufacturers Association (FEMA) and / or are approved in accordance with the US Code of Federal Regulations, Title 21 (FDA).

2.4 Comments on Novel Excipients

There are no novel excipients.

2.5 Comments on Impurities/Degradants of Concern

In a December 4, 2023, response to an FDA request for CMC information (issued October 20, 2023), the applicant has proposed a specification of NMT (b) (4)% for (b) (4) a degradant of the (b) (4) contained in the formulation of ONTRALFY (see CMC review for additional details). At the proposed specification, the (b) (4) f 90 mL of the oral solution would result in a daily intake of (b) (4) mg (b) (4) For a drug with a maximum daily dose of 10 to 100 mg (MRHD of tizanidine is 36 mg), the qualification threshold is (b) (4)% or (b) (4) µg total daily intake, whichever is lower. The proposed specification of NMT (b) (4)%, would result in a daily intake of (b) (4) that exceeds the qualification threshold.

To support the proposed specification, the sponsor referenced the OECD SIDS Initial Assessment Report on (b) (4) which indicated that the NOAEL in rats administered daily oral doses of (b) (4) for 45 days was (b) (4) mg/kg. Based on the information provided in the OECD report, the applicant calculated a permissible daily exposure of (b) (4) mg/day for (b) (4) Although the applicant asserts that the proposed daily exposure to (b) (4) is qualified by the information in the OECD report, individual line listings for the data used to support the conclusion were not provided for review. Therefore, the applicant has not provided adequate safety data to support the proposed specification. It is recommended that the applicant either reduce the specification for (b) (4) to below the qualification threshold or provide additional nonclinical data to justify that the proposed daily intake of (b) (4) mg (b) (4) is qualified.

2.6 Proposed Clinical Population and Dosing Regimen

The applicant is proposing to market ONTRALFY for use in adults with spasticity. The recommended starting dose is 2 mg, repeated every 6 to 8 hours, up to a maximum of 3 doses in 24 hours. The maximum recommended daily dose is the same as the maximum daily dose of Zanaflex, 36 mg.

2.7 Regulatory Background

ONTRALFY was developed under IND 156316. In the Written Responses to the questions in the preIND meeting package submitted on July 22, 2021, the applicant was informed that no additional nonclinical studies would be necessary to support an NDA provided a scientific bridge is established to the listed drug and that there are no formulation issues, such as impurities or excipients, that would require nonclinical safety assessment. Initially, there was a concern regarding the daily dose of EDTA due to the applicant relying on an inaccurate entry in the Inactive Ingredient Database (IID). This error was fixed in the IID in October 2021, and the applicant was informed that the corrected IID would not support the daily dose of EDTA. The applicant's submitted an amended strategy (email dated September 13, 2021), which was determined to be acceptable (email dated September 21, 2021). The initial clinical protocol under the IND was submitted on January 28, 2022, and was allowed to proceed on February 24, 2022.

3 Studies Submitted

There were no new nonclinical studies submitted to support the NDA.

11 Integrated Summary and Safety Evaluation

No new nonclinical studies were conducted to support the NDA, consistent with advice given to the applicant under IND 156316, i.e., no new nonclinical studies would be needed to support an NDA, provided a scientific bridge was established to the proposed listed drug(s) and there no safety concerns that would require nonclinical assessment. Provided a scientific bridge has been determined, upon review, to have been established, there remains one nonclinical concern regarding the degradant (b) (4) (b) (4) The applicant has not provided adequate data to support the proposed specification of (b) (4)% for (b) (4) a paraben degradant. Therefore, from a nonclinical perspective, a Complete Response is recommended. To address this deficiency, the applicant should either reduce the specification for (b) (4) (b) (4) to a level that provides for a daily intake of the degradant that falls below the appropriate qualification threshold or provide adequate nonclinical data to support the proposed specification.

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/s/

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03/28/2024 01:29:55 PM

DAVID L CARBONE
03/28/2024 07:07:30 PM

LOIS M FREED
03/29/2024 09:33:46 AM
I concur.