CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211801Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

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

Date: **September 4, 2019**
From: **Hitesh Shroff, Ph.D.**
Application Technical Lead, Branch V
Division of New Drug Products II
Office of New Drug Products

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch V
Division of New Drug Products II
Office of New Drug Products

To: **CMC Review #1 of NDA 211801**

Subject: Final Recommendation for NDA 211801

At the time when the CMC Review #1 was completed on May 10, 2019 it had noted the following pending issues:

- The label/labeling issues have not been completely resolved.

Because of these deficiencies, the NDA was not recommended for approval from the OPQ perspective.

The applicant submitted the revised immediate container labels and Prescribing Information (PI) on June 2, 2019. The resubmitted CMC sections of the labeling/labels were reviewed and found acceptable. **(See the Attachment)**

Recommendation:
This NDA is now recommended for Approval from the OPQ perspective.

Application Technical Lead's Assessment and Signature

The NDA is recommended for Approval from quality perspective.

Hitesh Shroff, Ph.D.
Application Technical Lead,
Branch V Division of New Drug Products II
September 4, 2019

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

DATE: **July 16, 2019**

FROM: **Hamid R. Shafiei, Ph.D.**
Review Chemist (Branch V/DNDP II/ONDP)

Moo-Jhong Rhee, Ph.D.
Branch Chief (Branch V/DNDP II/ONDP)

TO: **Package Insert (PI) and Immediate Container Labeling/Label review # 1 for NDA 211801**

SUBJECT: **Final ONDP Recommendation from the Labeling/Label Review Perspective**

In the review # 1 of NDA 211801, this application was not recommended for approval in the form it was presented due to the CMC deficiencies noted in PI labeling and immediate container (bottle) label.

The CMC labeling-label deficiencies identified during the review # 1 have been satisfactorily addressed in the amendment submitted by the applicant on June 25, 2019 (**Attachment I**).

Recommendation: This application is now recommended for **approval** from the ONDP labeling-labels perspective.

Attachment I: Final PI and Labels

A. PI

a) Highlight Section

IBSRELA (tenapanor) tablets, for oral use
Initial U.S. Approval: 2019

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 50 mg tenapanor. (3)

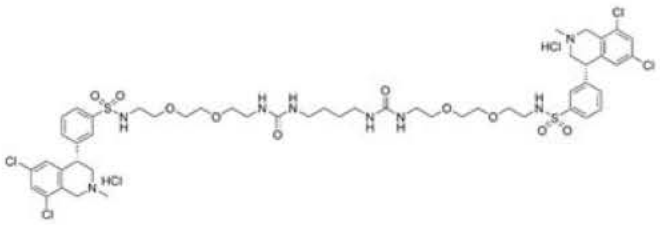
b) Full Prescribing Information

#3: Dosage Forms and Strengths

Tablets: 50 mg tenapanor supplied as an oval, white to off-white tablet debossed with " 50" on one side and "5791" on the other side.

#11: Description

IBSRELA (tenapanor) tablets contain tenapanor hydrochloride as an active ingredient. Tenapanor hydrochloride is a sodium/hydrogen exchanger 3 (NHE3) inhibitor for oral use. The chemical name for tenapanor hydrochloride is 12,15-Dioxa-2,7,9-triazaheptadecanamide, 17-[[[3-[(4S)-6,8-dichloro-1,2,3,4-tetrahydro-2-methyl-4-isoquinolinyl]phenyl]sulphonyl]amino]-N-[2-[2-[2-[[[3-[(4S)-6,8-dichloro-1,2,3,4-tetrahydro-2-methyl-4-isoquinolinyl]phenyl]sulphonyl]amino]ethoxy]ethoxy]ethyl]-8-oxo-, hydrochloride (1:2). Tenapanor hydrochloride has the molecular formula of $C_{50}H_{68}Cl_6N_8O_{10}S_2$, the molecular weight of 1218 Daltons, and the chemical structure below:



Tenapanor hydrochloride is a white to off-white to light brown hygroscopic amorphous solid. It is practically insoluble in water.

IBSRELA tablets contain 50 mg of tenapanor (equivalent to 53.2 mg of tenapanor hydrochloride). Inactive ingredients in the tablet are colloidal silicon dioxide, hypromellose, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, propyl gallate, stearic acid, tartaric acid powder, titanium dioxide and triacetin. (b) (4)

#16: HOW SUPPLIED/STORAGE AND HANDLING

IBSRELA tablets contain 50 mg tenapanor and are oval, white to off-white, debossed with " 50" on one side and "5791" on the other side.

IBSRELA is supplied in a white, opaque, high-density polyethylene bottle containing 60 tablets with a silica gel canister (as the desiccant) and screw-top polypropylene child-resistant cap lined and induction-activated aluminum foil liner (NDC 73154-050-60).

Store at [redacted] (b) (4) Keep in original container and protect from moisture.

Do not remove desiccant from the bottle. Do not subdivide or repackage.

B. <u>Container/Carton Labels:</u>

a. Immediate container labels: Bottle

[redacted] (b) (4)

b. Carton Label: Not applicable.

Hamid Shafiei

Digitally signed by Hamid Shafiei
Date: 7/16/2019 11:34:27AM
GUID: 507d824300005f344cf8b5e5989f0057

Moo Jhong Rhee

Digitally signed by Moo Jhong Rhee
Date: 7/16/2019 12:00:35PM
GUID: 502d0913000029f9798ca689a802fa55

Recommendation: As of this review, this 505 (b)(1) NDA is NOT ready for Approval in its present form per 21 CFR 314.125(b)(6).

NDA 211801
Review #1

Drug Name/Dosage Form	Tenapanor Tablets
Strength	50 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Ardelyx, Inc.; Fremont, CA
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	9/12/2018	OPQ
Amendment	2/1/2019	OPQ/OPF
Amendment	2/5/2019	ONDP/DNDAPI
Amendment	3/28/2019	OPQ/OPF, OPQ/ONDP
Amendment	5/2/2019	OPQ/OPF
Amendment	5/9/2019	OPQ/OPF

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sam Bain	CDER/OPQ/ONDP/ DNDAPI/NDBII
Drug Product and Environmental Analysis (EA)	Hamid Shafiei	CDER/OPQ/ONDP/ DNDPII/NDPBV
Process and Microbiology	Yuesheng Ye	CDER/OPQ/OPF/ DPAIII/PABVIII
Biopharmaceutics	Sarah Ibrahim	CDER/OPQ/ONDP/ DB/BBII
Regulatory Business Process Manager	Oumou Barry	OMPT/CDER/OPQ/OPRO/DR BPMI/RBPMBI
Facilities	Yuesheng Ye	CDER/OPQ/OPF/ DPAIII/PABVIII
Application Technical Lead	Hitesh Shroff	CDER/OPQ/ONDP/ DNDPII/NDPBV
Environmental Analysis	Raanan Bloom	CDER/OPQ/ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III	(b) (4)		Active	N/A	LOA April 24, 2017
	Type III			Active	N/A	LOA September 8, 2017
	Type III			Active	N/A	LOA April 24, 2017

N/A: There is enough data in the application, therefore, the DMF did not need to be reviewed.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	108732 (b) (4)	Constipation related diseases (b) (4) From: Ardelyx Inc., CA

2. CONSULTS: None

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed Tradename (tenapanor) tablets, 50mg.

The Office of Process and Facilities (OPF) has made a final overall "**Approval**" recommendation for the facilities involved in this application,

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The label/labeling issues have **not** been completely resolved as of this review.

Therefore, from the OPQ perspective, this NDA is not deemed ready for approval at this time in its present form 21 CFR 314.125(b)(6) until above mentioned issues are satisfactorily resolved. **(**see the **List of Deficiencies)**

II. Summary of Quality Assessments

A. Product Overview

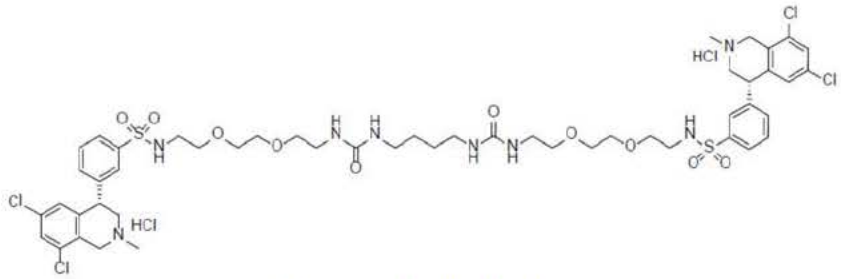
Tenapanor is a small molecule, minimally absorbed and locally acting sodium/hydrogen exchanger 3 (NHE3) inhibitor indicated for treatment of irritable bowel syndrome with constipation. Tenapanor tablets are white to off-white tablets containing 50 mg tenapanor equivalent to 53.2 mg of tenapanor hydrochloride.

Proposed Indication(s) including Intended Patient Population	For the treatment of irritable bowel syndrome with constipation (IBS-C) in adults
Duration of Treatment	As long as needed
Maximum Daily Dose	Recommended dose is 50 mg orally twice daily
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance:

Tenapanor hydrochloride is the active ingredient in IBSRELA (tenapanor) tablets. It is a white to off-white to light brown amorphous solid. It is a chiral molecule with S configuration in the two chiral centers. It is hygroscopic based on [redacted] profile. Its partition coefficient log P [redacted]. It is (BCS class IV compound due to its poor water solubility and permeability.



Tenapanor Hydrochloride
Molecular Formula: $C_{50}H_{68}Cl_6N_8O_{10}S_2$
Molecular Weight: 1217.97 (Free Base: 1145.04)

Tenapanor hydrochloride is manufactured by [redacted] is deemed adequate for the drug product.

The chemical structure of tenapanor hydrochloride was unequivocally [redacted] structure determination.

The quality of tenapanor hydrochloride is assured by its specification which includes identity by IR and HPLC; assay by HPLC, related substances by HPLC, elemental impurities, [redacted] and particle size. All potential impurities including [redacted] Satisfactory batch analyses of the drug substance batches used in nonclinical, clinical, commercial and stability studies have confirmed that the manufacturing process is robust.

All the analytical methods were validated by the applicant and also verified by the Division of Pharmaceutical Analysis, St. Louis, MO. to confirm that they are adequate for regulatory methods.

Based on long-term and acclerated stability testing of multiple batches, a retest period of [redacted] months was granted when stored at [redacted] C in the [redacted]

(b) (4)

The above CMC information was reviewed by the drug substance reviewer, Dr. Sukhamaya (Sam) Bain, and concluded that the submitted information is adequate to support the drug product (see the **Drug Substance** review).

Drug Product:
Tenapanor tablets, 50 mg are white to off-white, oval (b) (4) immediate release tablets. Each tablet contains 50 mg of tenapanor as 53.2 mg of tenapanor hydrochloride. The tablets are debossed with "A50" on one side and "5791" on the other side. Tenapanor tablets also contains the following inactive ingredients: microcrystalline cellulose, low-substituted hydroxypropyl cellulose, colloidal silicone dioxide, tartaric acid, stearic acid as well as propyl gallate as (b) (4). The tablets are supplied in a 75 mL white high-density polyethylene (HDPE) bottle with silica gel desiccant. The bottles are induction sealed and capped with polypropylene child-resistant closures. Each bottle contains 60 tablets.

The overall control strategy for the drug product is deemed adequate based on raw material controls and specification including the product quality attributes e.g. appearance, identity, drug substance and (b) (4) assays, impurities, content uniformity and dissolution.

Based on satisfactory 12-month long-term, 12-month intermediate and 6-month accelerated stability data from three primary registration batches of the drug product assuring its identity, strength, purity, and quality, the proposed **24-month of expiration dating period** is granted when stored at room temperature in the proposed container closure system per drug product reviewer, Dr. Hamid Shafiei (see the **Drug Product** review).

Manufacturing:
Tenapanor tablets are manufactured by (b) (4)
(b) (4)

There is no overage of the drug substance in the tablet formulation. There are no reprocessing or reworking procedures proposed. The proposed commercial batch size for Tenapanor tablets is (b) (4) kg (approximately (b) (4) tablets). The drug product manufacturing process was reviewed by Dr. Yuesheng Ye and was found to be acceptable (see the **Process** review).

The overall control strategy for the drug product is deemed adequate based on
(b) (4)

Facilities:
The drug substance, tenapanor hydrochloride, is manufactured and controlled per the manufacturing process described in Sec. 3.2.S.2 by (b) (4) and conforms to the requirements (specification) for drug product formulation of Tenapanor tablets.

The Office of Process and Facilities (OPF) reviewer, Dr. Yuesheng Ye has made an "Adequate" recommendation for the drug substance manufacturing and testing facility and also has made an "Adequate" recommendation for the drug product manufacturing and testing facilities (see the **Facilities** review).

Environmental Assessment: The applicant's claim of categorical exclusion under 21 CFR Part 25.31(b) and provided statement of no extraordinary circumstances exist were reviewed by Dr. Raanan Bloom and deemed acceptable. (see **Environmental Review**)

Biopharmaceutics: The drug product dissolution method development, dissolution method, dissolution data, dissolution specification, effect of change in formulation, effect of manufacturing sites, bridging of the registration batch product and Phase 3 product were reviewed by Dr. Sarah Ibrahim and deemed acceptable from Biopharmaceutics perspective. (see the **Biopharmaceutics** review)

Labeling: The proposed labels and labeling are under review and they are not deemed adequate from the CMC perspective according to Dr. Hamid Shafiei. (see **Labels/ Labeling** review).

C. Lifecycle Management Consideration: None
D. Special Product Quality Labeling Recommendations : None
E. Final Risk Assessment (see Attachment)

III. List of Deficiencies:

A. Regarding Labeling

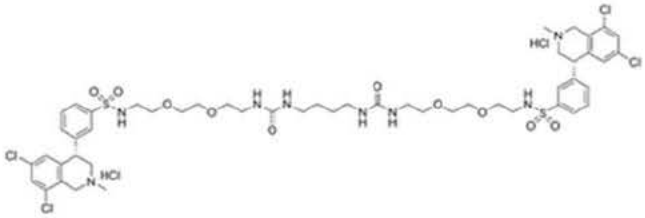
1. PI

#11: Description

Dosage form should be added to the starting section, (b) (4) should be removed, and a brief description of the API should be added to this section. For clarity, the following revision has been recommended:

IBSRELA (tenapanor) tablets contain tenapanor hydrochloride as an active ingredient. Tenapanor hydrochloride is a sodium/hydrogen exchanger 3 (NHE3) inhibitor for oral use. The chemical name for tenapanor hydrochloride is 12,15-Dioxa-2,7,9-triazaheptadecanamide, 17-[[[3-[(4S)-6,8-dichloro-1,2,3,4-tetrahydro-2-methyl-4-isoquinolinyl]phenyl]sulphonyl]amino]-N-[2-[2-[2-[[[3-[(4S)-6,8-dichloro-1,2,3,4-tetrahydro-2-methyl-4-

isoquinolinyl]phenyl]sulphonyl]amino]ethoxy]ethoxy]ethyl]-8-oxo-, hydrochloride (1:2). Tenapanor hydrochloride has the molecular formula of C50H68Cl6N8O10S2, the molecular weight of 1218 Daltons, and the chemical structure below:



Tenapanor hydrochloride is a white to off-white to light brown hygroscopic amorphous solid. It is practically insoluble in water.

IBSRELA tablets contain 50 mg of tenapanor (equivalent to 53.2 mg of tenapanor hydrochloride). Inactive ingredients in the tablet are colloidal silicon dioxide, hypromellose, low substituted hydroxypropyl cellulose, microcrystalline cellulose, propyl gallate, stearic acid, tartaric acid powder, titanium dioxide and triacetin.

#16: How Supplied/Storage and Handling

Provide the actual NDA number. For clarity, the following revision has been recommended:

IBSRELA tablets contain 50 mg tenapanor and are oval, white to off-white, debossed with "50" on one side and "5791" on the other side.

IBSRELA is supplied in a white, opaque, high-density polyethylene bottle containing 60 tablets with a silica gel canister (as the desiccant) and screw-top polypropylene child-resistant cap lined and induction-activated aluminum foil liner (the actual NDC Number is needed).

(b) (4)

Keep in original container and protect from moisture.

Do not remove desiccant from the bottle. Do not subdivide or repackage.

2. Container/Carton Labels:

a) Immediate Container Label:

Display the actual NDC number.

QUALITY ASSESSMENT

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
May 10, 2018

LABELING

R. Regional Information

1.14 Labeling

I. Package Insert

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

1) Title

IBSRELA (tenapanor) tablets, for oral use

Initial U.S. Approval: 20xx

2) DOSAGE FORMS AND STRENGTHS

Tablets: 50 mg tenapanor. (3)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	IBSRELA (tenapanor) tablets	Provided. **Satisfactory**
Dosage form, route of administration	tablets, for oral use	Provided. **Satisfactory**
Controlled drug substance symbol (if applicable)	Not applicable	Not applicable
Dosage Forms and Strengths (201.57(a)(8))	Tablets: 50 mg tenapanor	Provided. **Satisfactory**
Whether the drug product is scored	Not applicable	Not applicable

2. "FULL PRESCRIBING INFORMATION

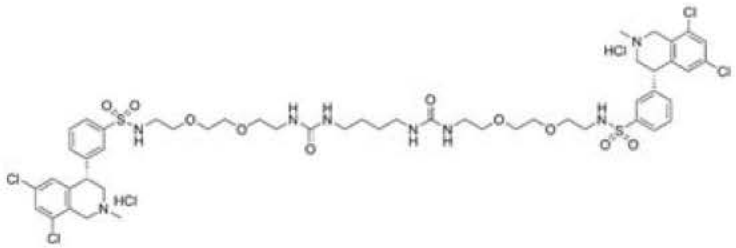
1) #3: DOSAGE FORM AND STRENGTHS

Tablets: 50 mg tenapanor supplied as an oval, white to off-white tablet debossed with "50" on one side and "5791" on the other side.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Available dosage forms	Tablets	Provided. **Satisfactory**
Strengths: in metric system	50 mg tenapanor	Provided. **Satisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	Not Required for this section	Not required for this section.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	supplied as an oval, white to off-white tablet debossed with "50" on one side and "5791" on the other side	Provided **Satisfactory**

2) #11: DESCRIPTION

IBSRELA (tenapanor) (b) (4) The chemical name for tenapanor (tenapanor hydrochloride) is 12,15-Dioxa-2,7,9-triazaheptadecanamide, 17-[[[3-[(4S)-6,8-dichloro-1,2,3,4-tetrahydro-2-methyl-4-isoquinolinyl]phenyl]sulphonyl]amino]-N-[2-[2-[2-[[[3-[(4S)-6,8-dichloro-1,2,3,4-tetrahydro-2-methyl-4-isoquinolinyl]phenyl]sulphonyl]amino]ethoxy]ethoxy]ethyl]-8-oxo-, hydrochloride (1:2). The molecular formula for tenapanor hydrochloride is $C_{50}H_{68}Cl_6N_8O_{10}S_2$ and the molecular weight is 1218 Daltons with a chemical structure as follows:



IBSRELA tablets contain 50 mg of tenapanor (equivalent to 53.2 mg of tenapanor hydrochloride). Inactive ingredients in the tablet are colloidal silicon dioxide, hypromellose, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, propyl gallate, stearic acid, tartaric acid powder, titanium dioxide and triacetin.

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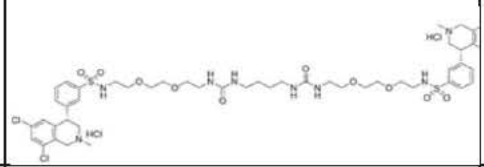
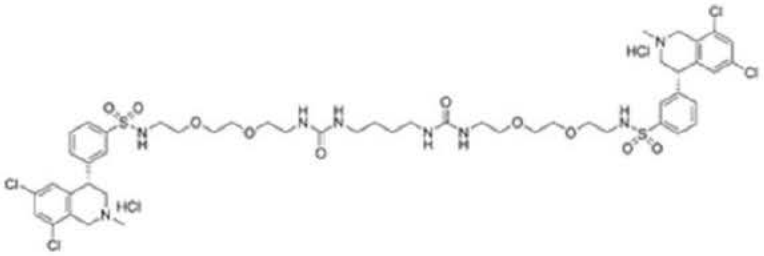
Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	IBSRELA (tenapanor)	Established name is not properly expressed. It should be, (tenapanor) tablets **Unsatisfactory**
Dosage form and route of administration	IBSRELA (tenapanor) is a (b) (4) sodium/hydrogen exchanger 3 (NHE3) inhibitor for oral use	See above. **Unsatisfactory**
Active moiety expression of strength with equivalence statement (if applicable)	tablets contain 50 mg of tenapanor (equivalent to 53.2 mg of tenapanor hydrochloride)	Provided. **Satisfactory**
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Inactive ingredients in the tablet are colloidal silicon dioxide, hypromellose, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, propyl gallate, stearic acid, tartaric acid powder, titanium dioxide and triacetin	Provided. **Satisfactory**
Statement of being sterile (if applicable)	Not applicable	Not applicable
Pharmacological/ therapeutic class	sodium/hydrogen exchanger 3 (NHE3) inhibitor	Provided. **Satisfactory**
Chemical name, structural formula, molecular weight	The chemical name for tenapanor (tenapanor hydrochloride) is 12,15-Dioxa-2,7,9-triazaheptadecanamide, 17-[[[3-[(4S)-6,8-dichloro-1,2,3,4-tetrahydro-2-methyl-4-isoquinolinyl]phenyl]sulphonyl]amino]-N-[2-[2-[2-[[[3-[(4S)-6,8-dichloro-1,2,3,4-tetrahydro-2-methyl-4-isoquinolinyl]phenyl]sulphonyl]amino]ethoxy]ethoxy]ethyl]-8-oxo-, hydrochloride (1:2). The molecular formula for tenapanor hydrochloride is C50H68Cl6N8O10S2 and the molecular weight is 1218 Daltons with a chemical structure as follows:  **Satisfactory**
If radioactive, statement of important nuclear characteristics.	Not applicable	Not applicable

Other important chemical or physical properties (such as pKa or pH)	Not provided	Not Provided. (See the revised one below.) **Unsatisfactory**

Dosage form should be added to the starting section. (b) (4) should be removed, and a brief description of the API should be added to this section. For clarity, the following revision has been recommended:

IBSRELA (tenapanor) tablets contain tenapanor hydrochloride as an active ingredient. Tenapanor hydrochloride is a sodium/hydrogen exchanger 3 (NHE3) inhibitor for oral use. The chemical name for tenapanor hydrochloride is 12,15-Dioxa-2,7,9-triazaheptadecanamide, 17-[[[3-[(4S)-6,8-dichloro-1,2,3,4-tetrahydro-2-methyl-4-isoquinolinyl]phenyl]sulphonyl]amino]-N-[2-[2-[2-[[[3-[(4S)-6,8-dichloro-1,2,3,4-tetrahydro-2-methyl-4-isoquinolinyl]phenyl]sulphonyl]amino]ethoxy]ethoxy]ethyl]-8-oxo-, hydrochloride (1:2). Tenapanor hydrochloride has the molecular formula of C50H68Cl6N8O10S2, the molecular weight of 1218 Daltons, and the chemical structure below:



Tenapanor hydrochloride is a white to off-white to light brown hygroscopic amorphous solid. It is practically insoluble in water.

IBSRELA tablets contain 50 mg of tenapanor (equivalent to 53.2 mg of tenapanor hydrochloride). Inactive ingredients in the tablet are colloidal silicon dioxide, hypromellose, low substituted hydroxypropyl cellulose, microcrystalline cellulose, propyl gallate, stearic acid, tartaric acid powder, titanium dioxide and triacetin.

3) #16: HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

(b) (4). Keep in original container and protect from moisture.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Strength of dosage form	tablet containing 50 mg tenapanor	Provided. **Satisfactory**
Available units (e.g., bottles of 100 tablets)	Bottles of 60 tablets	Provided. **Satisfactory**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4)	The actual NDC number has not been provided. **Unsatisfactory**
Special handling (e.g., protect from light)	Keep in original container and protect from moisture	Provided **Satisfactory**
Storage conditions	(b) (4)	Provided. **Satisfactory**
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Marketed by Ardelyx, Inc. 34175 Ardenwood Blvd., Suite 100 Fremont, CA 94555	Provided at the end of the PI. **Satisfactory**

Provide the actual NDA number. For clarity, the following revision has been recommended:

IBSRELA tablets contain 50 mg tenapanor and are oval, white to off-white, debossed with "Δ50" on one side and "5791" on the other side.

IBSRELA is supplied in a white, opaque, high-density polyethylene bottle containing 60 tablets with a silica gel canister (as the desiccant) and screw-top polypropylene child-resistant cap lined and induction-activated aluminum foil liner (the actual NDC Number is needed).

Store at (b) (4)
Keep in original container and protect from moisture.

Do not remove desiccant from the bottle. Do not subdivide or repackage.

II. Labels

1. IMMEDIATE CONTAINER

(b) (4)

60-count bottle label (commercial drug product)

(b) (4)

QUALITY ASSESSMENT

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	IBSRELA (tenapanor) tablets	Established name is properly provided. The font size is greater than 50% of the tradename. **Satisfactory**
Dosage strength	50mg	Provided. **Satisfactory**
Net contents	6 tablets (physician sample) 60 tablets (commercial drug product)	Provided. **Satisfactory**
"Rx only" displayed prominently on the main panel	Displayed.	Provided. **Satisfactory**
NDC number (21 CFR 207.35(b)(3)(i))	Mock NDC number provided.	The actual NDC number should be provided. **Unsatisfactory**
Lot number and expiration date (21 CFR 201.17)	The location for lot number and expiration is displayed.	Provided. **Satisfactory**
Storage conditions	Displayed.	Provided. **Satisfactory**
Bar code (21CFR 201.25)	Displayed.	Provided. **Satisfactory**
Name of manufacturer/distributor	Displayed.	Provided. **Satisfactory**
And others, if space is available	ATTENTION PHARMACIST: (b) (4)	Provided. **Satisfactory**

Actual NDA number is needed on the container label.

2. CARTON LABELS: Not applicable

No carton label is provided in this application:

III. LIST OF DEFICIENCIES:

A. Regarding PI

a) Highlights Section

None

b) Full Prescribing Information

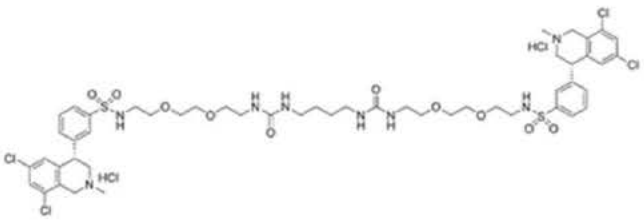
#3: Dosage Forms and Strengths

None

#11: Description

Dosage form should be added to the starting section, [redacted] (b) (4) should be removed, and a brief description of the API should be added to this section. For clarity, the following revision has been recommended:

IBSRELA (tenapanor) tablets contain tenapanor hydrochloride as an active ingredient. Tenapanor hydrochloride is a sodium/hydrogen exchanger 3 (NHE3) inhibitor for oral use. The chemical name for tenapanor hydrochloride is 12,15-Dioxa-2,7,9-triazaheptadecanamide, 17-[[[3-[(4S)-6,8-dichloro-1,2,3,4-tetrahydro-2-methyl-4-isoquinolinyl]phenyl]sulphonyl]amino]-N-[2-[2-[2-[[[3-[(4S)-6,8-dichloro-1,2,3,4-tetrahydro-2-methyl-4-isoquinolinyl]phenyl]sulphonyl]amino]ethoxy]ethoxy]ethyl]-8-oxo-, hydrochloride (1:2). Tenapanor hydrochloride has the molecular formula of C50H68Cl6N8O10S2, the molecular weight of 1218 Daltons, and the chemical structure below:



Tenapanor hydrochloride is a white to off-white to light brown hygroscopic amorphous solid. It is practically insoluble in water.

IBSRELA tablets contain 50 mg of tenapanor (equivalent to 53.2 mg of tenapanor hydrochloride). Inactive ingredients in the tablet are colloidal silicon dioxide, hypromellose, low substituted hydroxypropyl cellulose, microcrystalline cellulose, propyl gallate, stearic acid, tartaric acid powder, titanium dioxide and triacetin.

#16: How Supplied/Storage and Handling

Provide the actual NDA number. For clarity, the following revision has been recommended:

IBSRELA tablets contain 50 mg tenapanor and are oval, white to off-white, debossed with "50" on one side and "5791" on the other side.

IBSRELA is supplied in a white, opaque, high-density polyethylene bottle containing 60 tablets with a silica gel canister (as the desiccant) and screw-top polypropylene child-resistant cap lined and induction-activated aluminum foil liner (the actual NDC Number is needed).

Store at (b) (4) *excursions permitted to* (b) (4)
Keep in original container and protect from moisture.

Do not remove desiccant from the bottle. Do not subdivide or repackage.

B. Regarding of the Container/Carton Labels:

a) Immediate Container Label:

Display the actual NDC number.

b) Carton Label:

Not applicable

IV. OVERALL ASSESSMENT AND RECOMMENDATION:

- PI labeling needs to be revised.
- The container label needs to have an NDC number.

Recommendation:

From the ONDP perspective, this application is ***not*** recommended for approval in its present form per 21 CFR 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Reviewer Name:

Hamid Shafiei, Ph.D.
Reviewer, Branch V
DNDP II/ONDP/OPQ

Secondary Reviewer Name:

I concur with Dr. Shafiei's assessment and his recommendation that the labels and labeling are ***not*** ready for approval in its present form per 21 CFR 314.125 (b)(6) from the ONDP perspective.

Moo-Jhong Rhee, Ph.D.
Chief, Branch V
DNDP II/ONDP/OPQ

Hamid Shafiei

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Date: 4/19/2019 12:06:41PM
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Moo Jhong Rhee

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Date: 4/19/2019 01:20:57PM
GUID: 502d0913000029f9798ca689a802fa55

BIOPHARMACEUTICS

Product Background: The Applicant is seeking approval of IBSRELA (Tenapanor Immediate release Tablet). Tenapanor is a locally acting, highly selective, small molecule sodium (Na+)/hydrogen (H+) exchanger 3 (NHE3) inhibitor with minimal systemic availability by design. It is also a new molecular entity (NME) which belongs to BCS Class IV due to its low solubility and low permeability. The proposed dosage regimen is one 50 mg (equivalent to 53.2 mg of tenapanor hydrochloride) tablet taken orally twice daily to manage Irritable Bowel Syndrome (IBS)/ irritable bowel syndrome with constipation (IBS-C).

NDA: 211801

Drug Product Name / Strength: IBSRELA (Tenapanor Immediate Release Tablet)/50 mg (equivalent to 53.2 mg of tenapanor hydrochloride)

Route of Administration: Oral

Applicant Name: Ardelyx, Inc.

Review Summary:

Ardelyx, Inc.has developed Tenapanor tablets, 50 mg as an immediate release tablet containing 53.2 mg of tenapanor hydrochloride (equivalent to 50 mg tenapanor free base). The formulation of the to-be-marketed (TBM) formulation is given below:

Component	Quality Standard	Function	Amount per unit (mg/tablet)
Tenapanor Hydrochloride	In-house	Drug Substance	53.2[a]
Microcrystalline Cellulose[b]	USP-NF	(b) (4)	
Low-substituted Hydroxypropyl Cellulose	USP-NF		
Colloidal Silicon Dioxide	USP-NF		
Tartaric Acid[c]	USP-NF		
Propyl Gallate	USP-NF		
Stearic Acid[d]	USP-NF		
(b) (4)			

This Biopharmaceutics review evaluated:

- Choice of dissolution method and dissolution acceptance criterion
- Appropriateness of bridging of different phases of formulations

From the Biopharmaceutics perspective, NDA 211801 for Tenapanor Tablet is recommended for **approval.**

List Submissions being reviewed (table):

Date of Submission	Purpose of Submission
September 12, 2018	Original

Highlight Key Outstanding Issues from Last Cycle: N/A
Concise Description Outstanding Issues Remaining: N/A

Dissolution Method

Development of a Discriminatory Dissolution Method
Dissolution method development evaluated the following attributes. These studies support the discriminatory ability of the proposed dissolution method.

• Dissolution method development
o Effect of Dissolution Medium
o Effect of Hydrodynamic Conditions (paddle speed)
• Discriminatory Ability of Dissolution Method
o Formulation Composition Changes
o Drug Substance Particle Size Distribution and Drug Load
o Drug Substance Physical Form (Presence of Free Base)
o Manufacturing Process Parameters- (b) (4) ***and Tablet Hardness***

pH – Solubility
The pH solubility data for tenapanor hydrochloride base and its salt are shown in the following Table 1-1.

	HCl Salt Lot 17LV04SD.HQ00004	Free Base Lot 26653.0201/15600T0003

Buffer /Medium	Final pH	Equilibrium Solubility (mg/mL)*	Final pH	Equilibrium Solubility (mg/mL)*
Water	2.7	9.804	6.8	0.0000595
0.1 N HCl, pH 1.0	1.0	8.267	2.5	4.953
0.013 N HCl, pH 2.0	1.6	40.852	3.2	3.278
Citrate Buffer, pH 3.0	2.7	0.567	3.1	0.237
Citrate Buffer, pH 4.0	3.5	0.896	3.9	0.0375
Citrate Buffer, pH 5.0	4.6	0.000847	4.9	0.000636
Citrate Buffer, pH 6.0	5.6	0.0000713	6.0	0.00202
Phosphate Buffer, pH 7.0	6.6	0.0000317	7.0	0.000444
Simulated Gastric Fluid (SGF)	1.0	5.122	2.5	29.509
Simulated Intestinal Fluid	5.2	0.00198	6.3	Not Detected
Fed State SIF (FeSSIF) pH 5.0	4.7	0.226	5.0	0.0178
Fasted State SIF (FaSSIF), pH	4.5	0.285	6.4	0.00206

* Measured as tenapanor free base

Based on the solubility data, the highest dose of tenapanor tablets, 50 mg will not be dissolved in 250 mL of intestinal fluid with pH ≥5.0. Therefore, the drug substance is classified as a low solubility compound based on the BCS classification system.

As reported by the applicant, tenapanor is largely restricted to the lumen of the gastrointestinal tract. It was designed to be minimally absorbed. In rats, >90% of an oral dose of tenapanor was recovered in feces as unchanged tenapanor with minimal biliary excretion (2.5% of a radioactive dose), indicating tenapanor has low absorption and the hepatic contribution to the overall elimination of tenapanor is minimal. In a human ADME study, approximately 80% of a ^{14}C-tenapanor dose was excreted in feces mostly as the unchanged parent molecule (89.2% total recovery of radioactivity from urine and feces), indicating fecal excretion is the major elimination route of tenapanor. This information is consistent with nonclinical PK data (D5611C00007). The experimentally measured log P(o/w) was 4.07.

Based on the low solubility and low permeability/non-systemic absorption, as discussed above, tenapanor was classified as a BCS Class IV compound by the applicant.

Reviewer's Assessment:
Without going further in the experimental details of the solubility and permeability studies, based on the solubility and permeability information submitted by the applicant, the reviewer agrees that tenapanor can be classified as a BCS Class IV compound.

Dissolution Method

Dissolution Method: The Applicant proposed the following dissolution method:

Dissolution apparatus	Rotational speed	Dissolution media	Volume	Acceptance criterion
II	75 rpm	9.4 mM citrate buffer (pH 4)	900 mL	Q= (b) (4)% in 30 minutes

Dissolution method development included the evaluation of the followings:

- Effect of Dissolution Medium:

(b) (4)

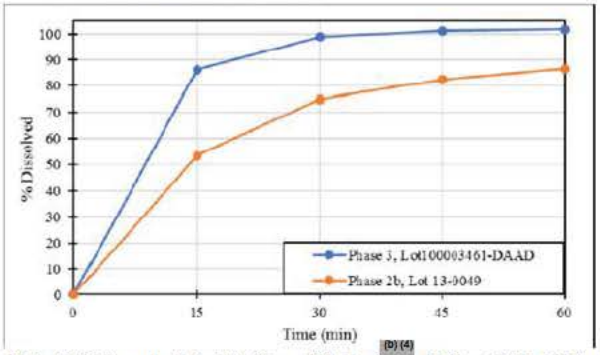
- Discriminatory Ability

➢ Effect of Formulation Composition Changes: The dissolution profiles for formulations used in phase 2b and phase 3 are different demonstrating that the method can differentiate between the different formulations as shown below:

Component	Composition (mg/tablet)	
	Phase 2b Clinical Trial	Phase 3 Clinical Trial/ TBM
Tenapanor HCl	53.2[a]	53.2[a]
Microcrystalline Cellulose		(b) (4)
Colloidal Silicon Dioxide		
(b) (4)		
Low-substituted Hydroxypropyl Cellulose		
Propyl Gallate		
Tartaric Acid		
Stearic Acid		
(b) (4)		
		(b) (4)

TBM = To be marketed

Figure 2-43 Dissolution of Tenapanor Tablets, 50 mg Used in Phase 2b and Phase 3 Clinical Trials for IBS-C (n =12)

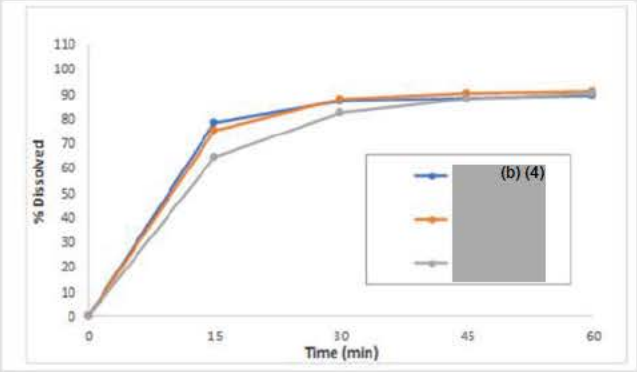


Dissolution Method: USP Apparatus II (paddle), 75 rpm, 900 mL of (b) (4) mM Citrate Buffer (pH 4), at (b) (4)°C

➢ Effect of Drug Substance (DS) Particle Size Distribution

Tablets manufactured with two DS particle sizes, d(v,50) (b) (4) µm and d(v,90) (b) (4) µm were used in the Phase 3 clinical trials for IBS-C.

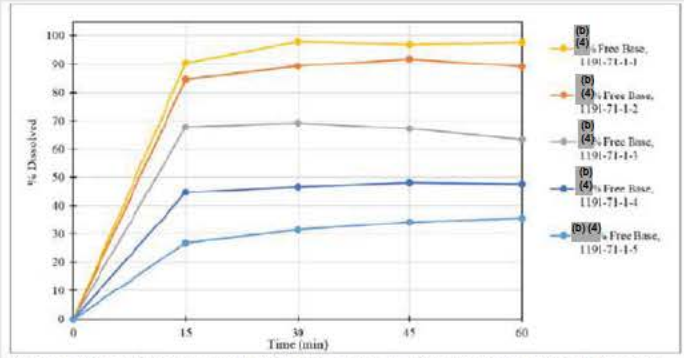
As demonstrated below, the dissolution profiles for three size ranges of drug substance showed that the effect of DS particle size on dissolution rate is minimal Therefore, provided that the applicant maintains a narrow DS particle size acceptance range, the impact of drug substance particle on dissolution will remain controlled.



Dissolution in Citrate Buffer pH 4.0 using USP Apparatus II at (b) (4)°C at 75 rpm of Tenapanor HCl Tablets 30 mg (Drug Load (b) (4)%) with Different Particle Size Distribution

➢ Effect of Drug Load: Effect of drug load on dissolution was studied at (b) (4)% drug load level on storage under accelerated stability condition. Tablets with (b) (4)% drug load showed significantly slower dissolution rate at release and after stability storage compared to tablets with (b) (4)% drug load. This was expected for a BCS class 4 DS which is expected to have a slower dissolution rate as the drug load increases.

- Drug Substance Physical Form (Presence of Free Base)
- A study was undertaken to evaluate the dissolution characteristics of tenapanor free base versus tenapanor HCl salt in the proposed dissolution medium at pH 4.0. Different combinations of free base and salt were mixed and dissolution study was conducted. The results are summarized in the following figure. As expected, tenapanor free base has lower equilibrium solubility than the hydrochloride salt in the proposed dissolution medium at pH 4.0, and therefore exhibited a slower dissolution rate. Higher dissolution rate was observed as the percentage of HCl salt was increased in the total (base+salt) combination.



Dissolution Method: USP Apparatus II (paddle), 75 rpm, 900 mL of 69.4 mM Citrate Buffer (pH 4), at 37°C

Effect of Manufacturing Process Parameters- (b) (4)

(b) (4)

(b) (4)

[redacted]

Dissolution Acceptance Criterion

- Dissolution profiles for all three commercial registration stability batches using the final dissolution method are shown below.

Batch No.	Tablet 1	2	3	4	5	6	Mean	%RSD
3148504R								
15 minutes	(b) (4)						77	3.2
30 minutes							91	3.7
45 minutes							96	3.8
60 minutes							98	3.6
3156463R								
15 minutes							80	1.1
30 minutes							94	1.2
45 minutes							97	1.2
60 minutes							98	1.2
3156464R								
15 minutes							82	1.2
30 minutes							96	1.5
45 minutes							99	1.6
60 minutes							100	1.6
3156465R								
15 minutes							79	2.3
30 minutes							93	1.9
45 minutes							96	1.6
60 minutes							97	1.6

Based on the above data, the Applicant proposed the following dissolution acceptance criterion:

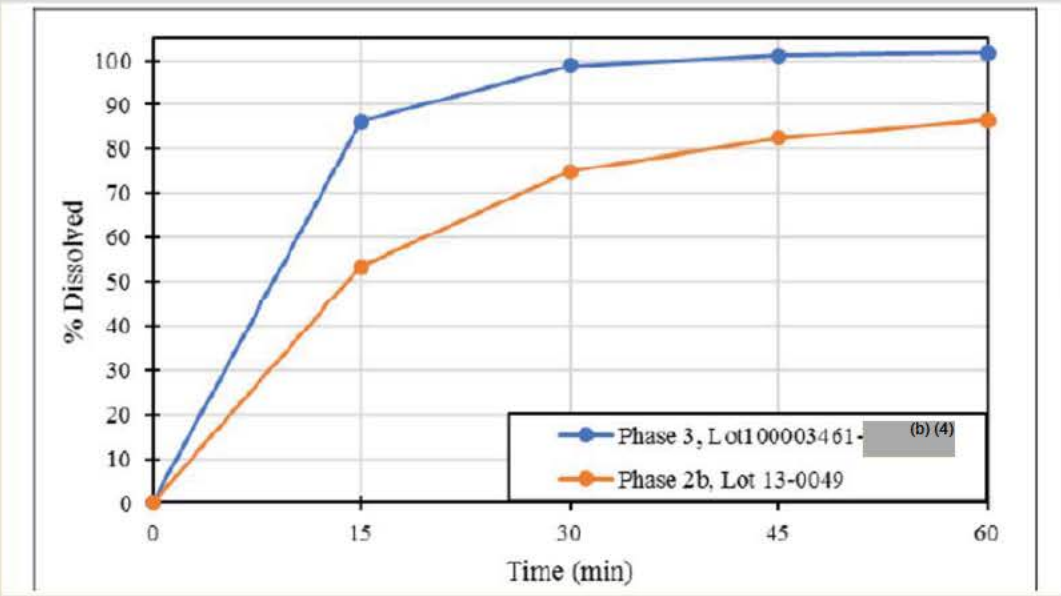
Q= (b) (4)% in 30 minutes

Reviewer's Assessment: *Overall, the dissolution method and the dissolution acceptance criterion are acceptable.*

Bridging of Formulations

Effect of Change of Formulations: In the product development program of Tenapanor tablet, several formulations were used starting from [redacted] to to-be-marketed (TMM) [redacted], 50 mg in different phases (Phase 1, 2, 2b and 3) of the program. A list of these studies with study title and formulation descriptions have been summarized in the "Pharmaceutical Development" section (Table 2.2 in section 2.3.P.2.2.1.1) of the original submission. While information from each Phase of development contributed to the ultimate development of the TBM formulation, bridging of all the formulations *in-vitro* was not found informative. Depending on the nature and extent of the differences among formulations, similarities or differences of *in-vitro* dissolution profiles were not considered very important. Due to minimal systemic exposure of tenapanor, whenever needed, the formulations were evaluated based on clinical endpoints rather than dissolution or PK endpoints.

For example, the tablet formulation used for phase 2b and phase 3 mentioned earlier in the review are different [redacted] was eliminated from Phase 3 formulation screening since the firm concluded that [redacted] resulted in slower dissolution rates of the Phase 2b tablets. Additionally, a [redacted]% drug load was used for the Phase 2b formulation and [redacted]% drug load was used for the Phase 3 formulation. A comparative dissolution profile is provided below:



As evident above, the formulations have different *in vitro* dissolution profiles, which requires appropriate bridging. However, the formulations could not be bridged by pharmacokinetic (PK)/bioequivalence(BE) studies due to minimal systemic exposure. Nevertheless, the clinical end points of the phase 2 b and phase 3 were comparable. Therefore, the bridging of Phase 2b and Phase 3 formulations is found adequate.

Effect of Change of Manufacturing Sites:
The Phase 3 clinical study tablets were manufactured at [redacted] whereas, the

proposed commercial manufacturing site is (b) (4) Due to site change, bridging studies are necessary.

Dissolution profile comparisons (n = 12) between Phase 3 and the Registration stability tenapanor tablet, 50 mg batches in the proposed quality control (QC) Dissolution Method

(b) (4)

Comparison of Dissolution Profiles of Phase 3 and Tenapanor Tablets, 50 mg at different pHs (n = 12)

The dissolution profiles and the respective f2 analysis are shown in the following Table. The (b) (4) profiles were similar at each timepoint investigated and the f2 values were all >50 which ensures sameness or equivalence of the curves in each media. Therefore, the Registration stability test product is appropriately bridged with the Phase 3 reference product.

Comparative Dissolution Profile Results – (b) (4) mM Citrate Buffer pH 4.0 (Batch (b) (4) Pre-change] and Batch 3156465R (b) (4) Post-change])

Tablet No.	Percent Tenapanor Dissolved (b) (4) Batch (b) (4) Time (minutes)								Percent Tenapanor Dissolved (b) (4) Batch 3156465R Time (minutes)							
	5	10	15	20	30	45	60	75	5	10	15	20	30	45	60	75
1	(b) (4)															
2																
3																
4																
5																
6																
7																
8																
9																
10																
11																
12																
Mean	47	71	82	88	93	95	96	99	33	63	76	84	92	96	98	100
% RSD	6.5	2.7	1.6	1.1	1.0	1.2	1.3	1.2	11.7	5.1	3.5	2.7	1.9	1.6	1.6	1.6
Range	(b) (4)															
f2 (0–20 minutes)	Pre-Change Reference Batch								53							
f2 (0–30 minutes)									55							

RSD = relative standard deviation

Overall Reviewer's Assessment:

- Based on information submitted, the applicant's dissolution method and acceptance criterion are acceptable.

- Based on the very limited systemic exposure of tenapanor from the drug products used in various stages of the development of tenapanor tablet formulations, bridging by PK was not feasible and comparison of *in vitro* dissolution profiles are not always meaningful except for bridging the manufacturing site change between the (b) (4) pre-change and (b) (4) post-change. With the consensus from other disciplines, bridging had to be relied on clinical end points whenever possible. Also, bridging information had to be weighed in in light of the contribution of information from each formulation in the overall approvability and labeling language. Taking the whole picture into consideration, the bridging information/rationale provided by the applicant is considered acceptable.

- Overall, NDA 211801 for Tanapanor immediate release tablet (50 mg) submitted by Ardelyx, Inc. is recommended for approval from Biopharmaceutics perspective.

Primary Biopharmaceutics Reviewer Name and Date:
Sarah Ibrahim, Ph.D., November 11, 2018

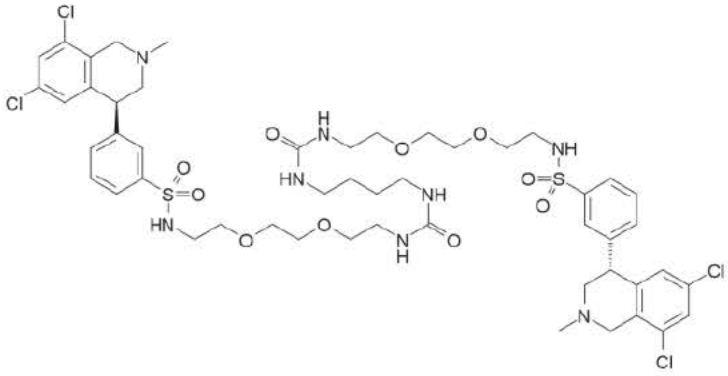
Secondary Reviewer Name and Date:
Tapash Ghosh, Ph.D.

ENVIRONMENTAL REVIEW

R 1. Regional Information

1.12.14: Environmental Analysis

Application: NDA 211801
API: tenapanor
Drug Product: IBSRELA oral tablet
Structure:



Indication: IBSRELA is a [redacted] (b) (4) NHE3 inhibitor indicated for treatment of irritable bowel syndrome with constipation (IBS-C) in adults.

MOA: IBSRELA is a gastrointestinally-restricted, [redacted] (b) (4) inhibitor of the Sodium/Hydrogen Exchanger 3 (NHE3), an antiporter expressed on the apical surface of the small intestine and colon primarily responsible for the absorption of dietary sodium. By actively reducing the dietary uptake of sodium from the small intestine and colon, IBSRELA increases water secretion into the intestinal lumen, which accelerates intestinal transit time and results in a softer stool consistency. Increased small intestinal and colonic permeability has been observed in studies using biopsies from IBS patients.

Claim of Categorical Exclusion: The applicant has provided a claim of categorical exclusion (21 CFR 25.31(b)) and a statement of no extraordinary circumstances (21 CFR 25.21). Minimal supporting information is provided. An estimated environmental concentration is calculated (see below). No environmental effects data are provided. According to the applicant, based on the available nonclinical data and known mechanism of action, tenapanor is not considered endocrine-active (no estrogenic, androgenic or thyroid activity).

> **Environmental Exposure**: The maximum projected production of tenapanor in 2024 is estimated to be [redacted] (b) (4) kg api/year. The total amount of the api introduced into the aquatic environment (EIC) as a result of the use of this product is estimated at no more than [redacted] (b) (4) part per billion (µg/L).

Application Review: In evaluation of the claim for categorical exclusion, in addition to the provided information, the following models were used:

Fish Plasma Model (FPM)

Production volume = [redacted] kg/year
Expected Introduction Concentration (EIC) = [redacted] ppb = [redacted] µg/L = [redacted] pM
MW = [redacted] g/mol; LogP = [redacted] LogD [redacted]
BCF (regression-based method; EpiSuite) = [redacted] L/kg wet wt (with Log P)
BCF (regression-based method; EpiSuite) = [redacted] L/Kg wet wt (with Log D)

- The recommended dose of dacomitinib is 50 mg taken orally twice daily.
- The drug is designed to act locally in the intestine. Clinical and non-clinical studies show that tenapanor exhibits minimal oral systemic bioavailability. (Cmax for tenapanor < 0.5 ng/mL; Cmax for major metabolite AZ13792925 < 20 ng/mL). Major metabolite, AZ13792925, is not an NHE3 inhibitor.
- In zebrafish, NHE3 is expressed in the kidney and gills. In the gills, it is highly expressed in ionocytes, which regulate salt concentrations of cells in relation to the external environment.
- Considering the low systemic availability of tenapanor, the fish model was calculated using inhibitory concentration (IC50) of tenapanor on NHE3 obtained from in vitro pharmacology studies rather than using a plasma Cmax value.
- BCF was not included in the calculation as tenapanor is a large molecule that acts locally and does not have significant systemic bioavailability.

IC50 for inhibition of rat NHE3 in vitro: [redacted] nM
IC50 for inhibition of human NHE3 in vitro: [redacted] nM
EIC/IC50 = [redacted] nM/[redacted] nM = [redacted]

➢ **IC50 for inhibition of NHE3 *in vitro* is approx [redacted] times higher than the EIC.**

Aquatic Toxicity Predictions

Aquatic tox predictions for tenapanor are not reported in the Danish QSAR toolbox database. Data for the top 4 analogues were retrieved. The analogues have similarity index of [redacted].

Fathead minnow: 96h LC50 estimated to range from [redacted] mg/L = [redacted] µg/L
Daphnia magnia: 48h EC50 estimated to range from [redacted] mg/L = [redacted] µg/L
Pseudokirchneriella s. 72h EC50 estimated to range from [redacted] mg/L = [redacted] µg/L.

➢ **Predicted acute toxicity concentration for top 4 analogues are more than [redacted] fold higher than the EIC.**

Potential for Interaction with Estrogen and Androgen receptors:

- Predictions for Estrogen receptor activity are reported in Mansouri et al., 2016 (2) (CERAPP paper). Predictions for estrogen receptor activity were performed using CERAPP models available at OCHEM web platforms:
  OCHEM categorical binding: inactive
  OCHEM categorical agonist: inactive
  OCHEM categorical antagonist: active (VERY WEAK)

- Predictions for Androgen receptor activity (COMPARA models):
  OCHEM categorical binding: active (VERY WEAK)
  OCHEM categorical agonist: inactive
  OCHEM categorical antagonist: active (VERY WEAK)

➢ **Models indicate 'very weak' to 'inactive' potential tenapanor activity with estrogen and androgen receptors.**

References:

1. Huggett, D. B., J. C. Cook, J. F. Ericson and R. T. Williams (2003). A theoretical model for utilizing mammalian pharmacology and safety data to prioritize potential impacts of human pharmaceuticals to fish. Human and Ecological Risk Assessment: An International Journal, 9(7):1789-1799.

2. Mansouri K, Abdelaziz A, Rybacka A, Roncaglioni A, Tropsha A, Varnek A, et al. CERAPP: Collaborative Estrogen Receptor Activity Prediction Project. Environ Health Perspect. 2016;124(7):1023-33. doi: 10.1289/ehp.1510267.

Reviewer's Assessment: Adequate

Modeled and available information indicates a low potential for tenapanor interaction with estrogen and androgen receptors. Modeled aquatic toxicity results show a large margin between exposure and effects. Results indicate a low environmental risk is expected due to approval of this application. The Fish Plasma Model output supports this conclusion.

The applicant's claim of categorical exclusion under 21 CFR 25.31(b) and provided statement of no extraordinary circumstance are acceptable.

Primary Environmental Reviewer Name and Date: Raanan A. Bloom, Ph.D.

Secondary Reviewer Name and Date: Scott Furness, Ph.D.

Raanan Bloom

Digitally signed by Raanan Bloom
Date: 4/26/2019 11:46:21AM
GUID: 508da72a0002a6d1071f3297897e4f1f

Michael Furness

Digitally signed by Michael Furness
Date: 4/26/2019 02:16:25PM
GUID: 502e8c7600003dd8331cf6eebf43697a

FDA/CDER/OPQ/OTR
Division of Pharmaceutical Analysis
645 S. Newstead Ave.
St. Louis MO 63110
P: 314.539.2135

METHOD VERIFICATION REPORT SUMMARY

Date: April 17, 2019

To: Sam Bain, Drug Substance Reviewer
Hamid Shafiei, Drug Product Reviewer
Hitesh Shroff, CMC Lead
Oumou Barry, RBPM

Through: Connie Ruzicka, Ph.D., Lab Chief, Branch II, CDER/OPQ/OTR/DPA

From: Jamie Mans, Chemist, CDER/OPQ/OTR/DPA
Wei Ye, Chemist, CDER/OPQ/OTR/DPA
Cynthia Sommers, Method Verification Coordinator, CDER/OPQ/OTR/DPA

Subject: Method Verification for NDA 211801: Ibsrela 50 mg Tablets (Tenapanor HCl)

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

1. 3.2.S.4.3, (b) (4): Identification, assay and related substances (by UPLC)
2. 3.2.P.5.2, 930726, Assay, Degradation Products, Identification, and Absence of Active
3. 3.2.P.5.2, Tenapanor HCl Tablets, 50 mg, Dissolution, method# 930724, pages 1-10, (b) (4)

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to the methods:

1. In both the DS and DP methods, the system suitability requirement for the blank injection failed due to an interfering peak at (b) (4) observed in the chromatograms of the drug substance sample preparations. DPA recommends that the firm modify the method, if possible, to eliminate any interfering peaks in the blank injection.

2. For the DS method, specifications were not provided in the specification sheet 3.2.S.4.1 for [redacted](b) (4)
3. For the DS method, specifications provided in the in the specification sheet 3.2.S.4.1 for [redacted](b) (4) did not match those shown in the certification of analysis for the drug substance, Tenapanor hydrochloride. This is shown in the DS related substances summary table below.

Original analyst worksheets and Additional Analysis worksheets can be viewed using this ECMS link: http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f8825fbe2e

Summary of Analysis

Drug Substance - Assay
Assay - % Tenapanor HCl [redacted](b) (4)
Sample 1 = 98.2%
Sample 2 = 98.9%
Average = 98.5%
Specification = [redacted](b) (4) % PASS

Drug Substance - Related Substances

Compound	AVG RT (min)	AVG RRT	AVG % Impurity (w/w)	Specification	PASS/FAIL
[redacted](b) (4)					PASS
					PASS
					PASS
					PASS
					PASS
					PASS
					NA
					PASS
					PASS
					PASS
					PASS

[a] *Value not provided in the specification sheet for the DS. Value was obtained from CoA.*

[b] *Value provided in the specification sheet for the DS does not match that of the value provided in the CoA.*

Drug Product - Assay

Assay - % Label Claim
Sample 1 = 92.2%
Sample 2 = 92.5%
Average = 92.3%
Specification = (b) (4) %

Drug Product - Related Substances

Compound	AVG RT (min)	AVG RRT	AVG % Impurity (w/w)	Specification	PASS/FAIL
(b) (4)					PASS
					PASS
					NA
					PASS

Drug Product - Dissolution

Time (min)	Sample #	Released (mg)	% Released/Tablet	Specification	PASS/FAIL
30	1	(b) (4)		Each unit at 30 min is NLT (b) (4) %	PASS
	2				PASS
	3				PASS
	4				PASS
	5				PASS
	6				PASS

Attachment I: Final Risk Assessment

Initial Risk Assessment for NDA 211801 Tenapanor tablets, 50 mg

Product Attribute / CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	LifeCycle consideration/Comments
Assay and content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment	L	(b) (4)	The drug product is expected to be safe for oral administration during the entire shelf life from product quality perspective. Low to None	None
Related Substances Impurities / Degradants	•Raw materials •Process parameters	L		Low to None	None
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment	L		Low to None	None
(b) (4)		L		Low to None	None

Hitesh Shroff

Digitally signed by Hitesh Shroff
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