CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210166Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: This 505 (b)(1) NDA is recommended for Approval from the OPQ perspective.

NDA 210166
Review #1

Drug Name/Dosage Form	Prucalopride tablets
Strength	1mg and 2 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Shire Development LLC, Lexington, MA
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	12/21/2017	OPQ
Amendment	1/19/2018	ONDP/DNDAPI
Amendment	2/13/2018	ONDP/DNDAPI
Amendment	3/5/2018	OPF/PAB
Amendment	3/23/2018	ONDP/API, ONDP/DNDAPI
Amendment	6/29/2018	ONDP
Amendment	7/18/2018	OPF

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Debasis Ghosh	CDER/OPQ/ONDP/ DNDAPI/NDBII
Drug Product and Environmental Analysis (EA)	Caroline Strasinger	CDER/OPQ/ONDP/ DNDPII/NDPBV
Process and Microbiology	Sydney Choi	CDER/OPQ/OPF/ DPAIII/PABVIII
Biopharmaceutics	Hansong Chen	CDER/OPQ/ONDP/ DB/BBII
Regulatory Business Process Manager	Oumou Barry	OMPT/CDER/OPQ/OPRO/DR BPMI/RBPMBI
Facilities	Sydney Choi	CDER/OPQ/OPF/ DPAIII/PABVIII
Application Technical Lead	Hitesh Shroff	CDER/OPQ/ONDP/ DNDPII/NDPBV
Laboratory (OTR)	N/A	N/A
ORA Lead	Paul Perdue Jr.	ORA/OO/OMPTO/ DMPTPO/MDTP

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	(b) (4)
	Type III			Active	N/A	
	Type III			Active	N/A	
	Type III			Active	N/A	
	Type III			Active	N/A	

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	55078	Shire Development LLC, Sept 7, 2012, for treatment of chronic idiopathic constipation

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 drug product.

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 information submitted in the label/labeling is deemed satisfactory from the CMC perspective.

Therefore, from the OPQ perspective, this NDA is recommended for approval with an expiration dating period of 18-month.

II. Summary of Quality Assessments

A. Product Overview

Prucalopride tablets are indicated for chronic idiopathic constipation (CIC) in adults. The immediate release tables are supplied in 1mg and 2mg strengths. Each 1mg tablet contains 1mg of prucalopride equivalent to 1.32mg of prucalopride succinate. Each 2mg tablet contains 2.64mg prucalopride succinate. Prucalopride is a serotonin type 4 (5-HT4) receptor agonist with enterokinetic activities.

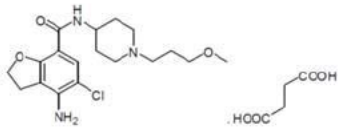
Prucalopride has never been approved and marketed in US, however, it is approved in EU in 2009 as Resolor tablets and in Canada in 2011 as Resotran tablets for the same indication.

Proposed Indication(s) including Intended Patient Population	For the treatment of chronic idiopathic constipation (CIC) in adults
Duration of Treatment	As long as needed
Maximum Daily Dose	Recommended dose is 2 mg once daily taken orally
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance:

The drug substance in Motegrity tablets is prucalopride succinate. It is an achiral, non-hygroscopic, water soluble and white to almost white powder (b) (4) [redacted] he applicant claimed that the drug substance is a Biopharmaceutical Classification System (BCS) Class I compound with high water solubility and high permeability. It has the following chemical structure:



Prucalopride succinate
Molecular Formula: $C_{18}H_{26}ClN_3O_3.C_4H_6O_4$
Molecular Weight: 485.96

Prucalopride succinate is manufactured (b) (4) [redacted] The detailed information regarding the drug substance manufacturing process, in-process controls, control of materials, control of critical steps and intermediates was provided. The chemical structure of prucalopride succinate was confirmed by elemental analysis, proton (^1H) and carbon (^{13}C) NMR spectroscopy; mass spectroscopy, IR spectroscopy, polymorph screening, and X-ray powder diffraction.

The overall quality of prucalopride succinate is controlled by its specification (b) (4) [redacted]. Satisfactory batch analyses of the drug substance batches used in nonclinical, clinical, commercial and stability studies were provided. The in-house, non-compendial analytical methods were validated. On the basis of satisfactory results of long-term and acclerated stability testing of multiple batches, a retest period o (b) (4) months was granted when stored (b) (4) in the proposed container closure system.

The CMC information regarding the drug substance, prucalopride succinate, was reviewed by the drug substance reviewer, Dr. Debasis Ghosh, and concluded that sufficient information is provided to ensure consistent manufacturing of prucalopride succinate with respect to identity; strength, purity and quality (see the **Drug Substance** review).

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

Prucalopride succinate is manufactured and controlled per the manufacturing process described in Sec. 3.2.S.2 (b) (4) [redacted] and conforms to the requirements (specification) for drug product formulation of Prucalopride tablets.

Drug Product:

Prucalopride is a serotonin 4 (5-HT4) receptor agonist indicated for the treatment of chronic idiopathic constipation (CIC) in adults. Prucalopride immediate release tablets are supplied in 1 mg and 2 mg strengths. Each 1mg tablet is a white to off-white, round, biconvex film-coated tablet debossed with "PRU 1" on one side. Each 2mg tablet is a pink, round, biconvex film-coated tablet debossed with "PRU 2" on one side. Prucalopride tables also contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, silicone dioxide colloidal, magnesium stearate and (b) (4) film-coating. Prucalopride tablets are packaged in a high-density polyethylene (HDPE) bottle with child-resistant (b) (4) closure (b) (4) Each bottle contains 30 tablets.

Prucalopride tablets are manufacture (b) (4) (b) (4) he drug substance particle size was controlled by the drug substance specification. During the tablet manufacturing process (b) (4)

(b) (4)

(b) (4) he exhibit batch size was (b) (4) tablets for both 1mg and 2mg tablets. The proposed commercial batch size for 1 mg tablets is (b) (4) kg (b) (4) tablets) 2 mg tablets i (b) (4) kg (b) (4) tablets). The drug product manufacturing process and microbiology assessment were reviewed by Dr. Sydney Choi and were found to be acceptable (see the **Process** review).

The overall control strategy for the drug product is deemed adequate based on raw material controls, drug product specification including appearance, identity, assay, impurities, uniformity of dosage units, dissolution, and microbial purity.

Based on satisfactory long-term and accelerated stability data of the drug product for assuring its identity, strength, purity, and quality, the proposed **18-month of expiration dating period** is granted when stored at room temperature in the proposed container closure system per drug product reviewer, Dr. Caroline Strasinger (see the **Drug Product** review).

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

The applicant submitted a claim for a categorical exclusion from the requirements of an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b) with a statement that no extraordinary circumstances existed, and the claim was

reviewed and found to be acceptable.

The drug product dissolution method development, dissolution data, dissolution specification and bridging the different manufacturing processes (b) (4) (b) (4)), manufacturing sites, and different shape tablets used in the clinical studies and to-be-marketed tablets were reviewed by Dr. Hansong Chen and deemed adequate from biopharmaceutical perspective. (see the **Biopharmaceutics** review)

The submitted information for the label/labeling is deemed adequate from the CMC perspective per Dr. Caroline Strasinger (see **Labeling** review).

C. Lifecycle Management Consideration

(b) (4)

D. Special Product Quality Labeling Recommendations

None

E. Final Risk Assessment (see Attachment)

F. List of Deficiencies: None

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
August 20, 2018

Hitesh N. Shroff -S

Digitally signed by Hitesh N. Shroff -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S
Date: 2018.08.20 20:03:16 -04'00'

LABELING

R. Regional Information

I. Package Insert

1. HIGHLIGHTS OF PRESCRIBING INFORMATION

1) Title

MOTEGRITY (prucalopride) tablets, for oral use
Initial U.S. Approval: XXXX

2) DOSAGE FORMS AND STRENGTHS

DOSAGE FORMS AND STRENGTHS
Tablets: 1 mg, 2 mg (3)

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: Motegrity Established Name: (prucalopride) tablets	Adequate
Dosage form, route of administration	Dosage: Tablets Route: for oral use	Adequate
Controlled drug substance symbol(if applicable)		NA
Dosage Forms and Strengths (201.57(a)(8))		
Summary of dosage form and strength	Tablet: 1 mg, 2 mg	Adequate

Reviewer Assessment: ADEQUATE

2. "FULL PRESCRIBING INFORMATION

#3: DOSAGE FORM AND STRENGTHS

3 DOSAGE FORMS AND STRENGTHS
MOTEGRITY Tablets:

- 1 mg prucalopride: White to off-white, round, biconvex film-coated debossed with "PRU 1" on one side and no debossing on the other side.

- 2 mg prucalopride: Pink, round, biconvex film-coated tablet debossed with "PRU 2" on one side and no debossing on the other side.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Available dosage forms	tablets	Adequate
Strengths: in metric system	1 mg, 2 mg,	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	Not Present	INADEQUATE: Although no equivalency statement is made, since that statement is made in the Description section as well as container and carton labels, it is deemed **ACCEPTABLE.** (OND prefers to not include the equivalency statement in section 3)
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	White/Off-White, round, biconvex film-coated tablet with PRU 1; Pink, round, biconvex film-coated tablet with PRU 2	Adequate

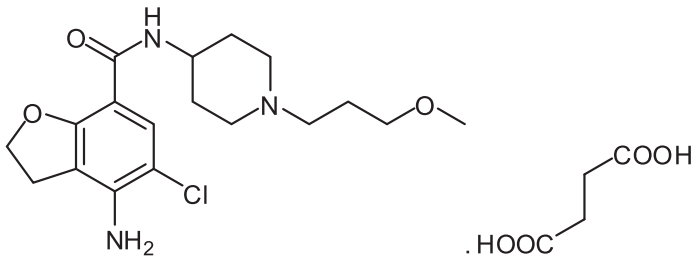
Reviewer Assessment: ADEQUATE

#11: DESCRIPTION

11 DESCRIPTION

MOTEGRITY (prucalopride) tablets, for oral use contain prucalopride succinate, a dihydrobenzofurancarboxamide that is a serotonin type 4 (5-HT$_4$) receptor agonist. The IUPAC name is: 4-amino-5-chloro-N-[1-(3-methoxypropyl)piperidin-4-yl]-2,3-dihydrobenzofuran-7-carboxamide succinate.

The molecular formula is $C_{18}H_{26}ClN_3O_3.C_4H_6O_4$ and the molecular weight is 485.96. The structural formula is:



Prucalopride succinate is a white to almost white powder. It is highly soluble in acidic aqueous media and alkaline aqueous media up to a pH of approximately 9.

Each 1 mg film-coated tablet of MOTEGRITY contains 1 mg of prucalopride (equivalent to 1.32 mg prucalopride succinate), and the following inactive ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The coating for the 1 mg tablet contains hypromellose, lactose monohydrate, polyethylene glycol 3000, titanium dioxide and triacetin.

Each 2 mg film-coated tablet of MOTEGRITY contains 2 mg of prucalopride (equivalent to 2.64 mg prucalopride succinate), and the following inactive ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The coating for the 2 mg tablet contains hypromellose, lactose monohydrate, polyethylene glycol 3000, titanium dioxide, triacetin, red iron oxide, yellow iron oxide and FD&C Blue #2.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Proprietary name and established name	Motegrity (prucalopride) tablets	Adequate
Dosage form and route of administration	tablets; for oral administration	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	1 mg of prucalopride (equivalent to 1.32 mg prucalopride succinate) 2 mg of prucalopride (equivalent to 2.64 mg prucalopride succinate)	Adequate
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	colloidal silicon dioxide, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The coating for the 1 mg tablet contains hypromellose, lactose monohydrate, polyethylene glycol 3000, titanium dioxide and triacetin The coating for the 2 mg tablet contains hypromellose, lactose monohydrate, polyethylene glycol 3000, titanium dioxide, triacetin, red iron oxide, yellow iron oxide and FD&C Blue #2.	Adequate (ingredients are correctly listed in alphabetical order and coating ingredients are included)
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	serotonin type 4 (5-HT_4) receptor agonist	Adequate
Chemical name, structural formula, molecular weight	Structure, molecular weight, formula presented	Adequate
If radioactive, statement of important nuclear characteristics.	NA	
Other important chemical or physical properties (such as pKa or pH)	highly soluble in acidic aqueous media and alkaline aqueous media up to a pH of approximately 9.	Adequate

Reviewer Assessment: ADEQUATE

#16: HOW SUPPLIED/STORAGE AND HANDLING

16 HOW SUPPLIED/STORAGE AND HANDLING

MOTEGRITY tablets containing 1 mg prucalopride are white to off-white, round, biconvex film-coated tablets debossed with "PRU 1" on one side and no debossing on the other side. They are supplied as:

- NDC 54092-546-01: HDPE bottle of 30 tablets, with child-resistant closure.

MOTEGRITY tablets containing 2 mg prucalopride are pink, round, biconvex film-coated tablets debossed with "PRU 2" on one side and no debossing on the other side. They are supplied as:

- NDC 54092-547-01: HDPE bottle of 30 tablets, with child-resistant closure.

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

Store MOTEGRITY in the original container to protect from moisture.

Item	Information Provided in NDA	Reviewer's Comment and Recommendations
Strength of dosage form	1 mg; 2 mg	Adequate
Available units (e.g., bottles of 100 tablets)	Bottles of 30 tablets	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	white, round, biconvex film-coated tablets debossed with "PRU 1" on one side and no debossing on the other side pink, round, biconvex film-coated tablets debossed with "PRU 2" on one side and no debossing on the other side	Adequate
Special handling (e.g., Dispense in tight and light resisteant container as defined in USP)	Protect from moisture;	Adequate
Storage conditions	Store at 20ºC – 25ºC (68ºF – 77ºF); excursions permitted to 15ºC-30ºC (59ºF-86ºF) [See USP Controlled Room Temperature]	Adequate
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Manufactured for: Shire US Inc. 300 Shire Way Lexington, MA 02421	Adequate

Reviewer Assessment: ADEQUATE

II. Labels (Provided October 20, 2017)

1. IMMEDIATE CONTAINER LABEL

Outer panel

The immediate container labels include a 30 count bottle label for each strength and a patient sample label (7 count and 30 count). The comments below are applicable to all presentations and strengths. The bottle for the 1 mg tablets and the 2 mg patient sample have been provided above as example container labels. All bottles are labeled with the 2 ply peel-away configuration label. For the trade configuration, the PI will be attached to the bottle cap.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Motegrity (prucalopride) tablets	Adequate
Dosage strength Active moiety expression of strength with equivalence statement (if applicable), if space is available	Equivallency presented correctly and in proper format	Adequate
Net contents	30 tablets	Adequate
"Rx only" displayed prominently on the main panel	Rx only	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Present	Adequate
Lot number and expiration date (21 CFR 201.17)	Place Reserved	Adequate
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store at 20ºC – 25ºC (68ºF – 77ºF); excursions permitted to 15ºC-30ºC (59ºF-86ºF) [See USP Controlled Room Temperature]	Adequate
Bar code (21CFR 201.25)	Place Reserved	Adequate
Name of manufacturer/distributor	Shire	Adequate
And others, if space is available		

Reviewer Assessment: ADEQUATE

2. CARTON LABELS:

The Applicant proposes a carton for only the sample configurations (7 count and 30 count). The trade packaging configuration will include only the 2-ply bottle label depicted above. This was confirmed in an IR clarification dated 13-JUL-2018 and attached below for reference.

IR Labeling Clarification.pdf

The carton review below is applicable to the sample carton 1 mg (30 count) and 2 mg (7 count and 30 count); a 2 mg carton has been provided as an example.


(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	motegrity (prucalopride) tablets	Adequate
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	1 mg, 2 mg	Adequate
Net quantity of dosage form	30 tablets; 7 tablets (sample)	Adequate
"Rx only" displayed prominently on the main panel	Displayed on back panel	Adequate
Lot number and expiration date	Bottom panel	Adequate
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	Store at 20°C – 25°C (68°F – 77°F); excursions permitted to 15°C-30°C (59°F-86°F) [See USP Controlled Room Temperature]. Protect from moisture	Adequate
Bar code (21CFR 201.25)	Side panel	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Multiple panels	Adequate
Manufacturer/distributor's name	Side panel	Adequate
Quantitative ingredient information (injectables) (21 CFR 201.100 (b))	Not Present (oral formulation)	Adequate ingredient list required for non-oral dosage forms
Statement of being sterile (if applicable)	NA	Adequate
(b) (4)	Back Panel.	Adequate
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Side Panel	Adequate

Based on the clarifying IR response received 10-JUL-2018 and dated 13-JUL-2018 in DARRTS regarding the packaging configuration (i.e. for the trade configuration there is no carton) there are no deficiencies to communicate as all information is now adequately presented for all packaging configurations and the eCTD has been updated.

Reviewer Assessment: ADEQUATE

III. LIST OF DEFICIENCIES: None

IV. OVERALL ASSESSMENT AND RECOMMENDATION:

The Label and Labeling of NDA 210166 is now adequate.

The NDA is recommending for approval from the Label and Labeling Perspective.

Primary Labeling Reviewer Name and Date:

Caroline Strasinger, PhD 30-JULY-2018
OPQ, ONDP, DNDP II, BV

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I agree with Dr. Strasinger's assessment on the labeling and labels and concur with her recommendation that this application is ready for approval as of this review.

Moo-Jhong Rhee, Ph.D. 30-JUL-2018
Chief, Branch V
DNDP II/ONDP

Caroline Strasinger

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Moo Jhong Rhee

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BIOPHARMACEUTICS

IQA Review Guide Reference

Product Background:

NDA/ANDA: NDA 210166

Drug Product Name / Strength: Motegrity™ - Prucalopride succinate tablets 1 mg and 2 mg

Route of Administration: Oral

Applicant Name: Shire Development LLC

Review Recommendation: **Adequate**

Review Summary:
Shire Development LLC developed Motegrity™ (Prucalopride succinate) tablets 1 mg and 2 mg and submitted the application under NDA 210166 to seek approval on 12/21/2017. The proposed indication is the treatment of chronic idiopathic constipation (CIC) in adults.

The Biopharmaceutics review focuses on the dissolution method development, dissolution data, and dissolution specification, and bridging for different manufacturing processes and sites.
The proposed dissolution method was reviewed and found acceptable. The proposed dissolution acceptance criterion (i.e. NLT (b) (4)% in 20 minutes) is also acceptable.
The Applicant provided sufficient data to bridge the formulations manufactured with different manufacturing processes (b) (4) and manufacturing sites, as well as different shapes tablets used in the clinical studies and intended for commercialization.

From the Biopharmaceutics perspective, this Reviewer concludes that NDA 210166 for Motegrity™ (Prucalopride succinate) tablets 1 mg and 2 mg is **adequate** for approval.

List Submissions being reviewed (table):

12/21/2017	NDA 210166/Original submission
3/5/2018	eCTD-0010/Response to Biopharmaceutics Information Requests
5/4/2018	eCTD-0026/Response to Biopharmaceutics Information Requests

Highlight Key Outstanding Issues from Last Cycle: None.

Concise Description Outstanding Issues Remaining: None.

BCS Designation

Reviewer's Assessment: The Applicant claimed that Prucalopride Succinate is a BCS Class I drug, which has high solubility and high permeability.

Solubility:

Table 1. Solubility of Prucalopride Succinate (R108512) in Solvent as a Function of pH after 24-hours Equilibration in Different Solvents at 20°C

Solvent	pH of solvent	Solubility in g/100mL solution	pH of solution
Water	5.68	16	4.61
0.1N HCl	1.20	20	4.33
0.01N HCl	2.01	16	4.58
Citrate-HCl Buffer	2.00	18	4.45
Citrate-NaOH Buffer	5.00	17	4.71

Table 2. Solubility of Prucalopride Succinate (R108512) after 24-hours Equilibration in Different Media at 37°C

Solvent	Concentration	Number	Visual Observation	pH
Water	6 mg / 250 ml	1	clear solution	5.44
Water	6 mg / 250 ml	2	clear solution	5.45
Water	6 mg / 250 ml	3	clear solution	5.53
Water	20 mg / 250 ml	1	clear solution	5.16
Water	20 mg / 250 ml	2	clear solution	5.10
Water	20 mg / 250 ml	3	clear solution	5.19
USP buffer pH 1	6 mg / 250 ml	1	clear solution	0.96
USP buffer pH 1	6 mg / 250 ml	2	clear solution	0.95
USP buffer pH 1	6 mg / 250 ml	3	clear solution	0.96
USP buffer pH 1	20 mg / 250 ml	1	clear solution	0.94
USP buffer pH 1	20 mg / 250 ml	2	clear solution	0.94
USP buffer pH1	20 mg / 250 ml	3	clear solution	0.95
USP buffer pH 4.5	6 mg / 250 ml	1	clear solution	4.45
USP buffer pH 4.5	6 mg / 250 ml	2	clear solution	4.46
USP buffer pH 4.5	6 mg / 250 ml	3	clear solution	4.46
USP buffer pH 4.5	20 mg / 250 ml	1	clear solution	4.49
USP buffer pH 4.5	20 mg / 250 ml	2	clear solution	4.48
USP buffer pH 4.5	20 mg / 250 ml	3	clear solution	4.49
USP buffer pH 6.8	6 mg / 250 ml	1	clear solution	6.78
USP buffer pH 6.8	6 mg / 250 ml	2	clear solution	6.78
USP buffer pH 6.8	6 mg / 250 ml	3	clear solution	6.78
USP buffer pH 6.8	20 mg / 250 ml	1	clear solution	6.77
USP buffer pH 6.8	20 mg / 250 ml	2	clear solution	6.77
USP buffer pH 6.8	20 mg / 250 ml	3	clear solution	6.78
USP buffer pH 7.5	6 mg / 250 ml	1	clear solution	7.53
USP buffer pH 7.5	6 mg / 250 ml	2	clear solution	7.53
USP buffer pH 7.5	6 mg / 250 ml	3	clear solution	7.53
USP buffer pH 7.5	20 mg / 250 ml	1	clear solution	7.52
USP buffer pH 7.5	20 mg / 250 ml	2	clear solution	7.52
USP buffer pH 7.5	20 mg / 250 ml	3	clear solution	7.52

Permeability: The Applicant did not report the permeability of prucalopride succinate. However, in Study PRU-BEL-32, the Applicant reported that the absolute bioavailability of the 2 mg market tablet exceeds 90%.

Dissolution: See Section "Dissolution Method and Acceptance Criteria".

Dissolution Method and Acceptance Criteria

Reviewer's Assessment: ***{Adequate}***

1. Dissolution method

The Applicant developed the following dissolution method for Motegrity™ (Prucalopride succinate) 1 mg and 2 mg Tablets:

Table 3. The proposed dissolution method

Apparatus	USP Apparatus 2 (Paddle)
Speed	50 rpm
Dissolution media	0.1 N Hydrochloric Acid
Volume	900 mL
Time	10, 20, 30, and 45 min
Temperature	37 ± 0.5 °C
Specifications	NL (b) (4)% (Q) in 20 minutes

2. Dissolution method development

(b) (4)

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Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: ***{Adequate/Inadequate}***

N/A

Application of dissolution/IVIVC in QbD

Reviewer's Assessment: ***{Adequate/Inadequate}***

N/A

Bridging of Formulations

Reviewer's Assessment: ***{Adequate}***

1. Bridging between different manufacturing processe (b) (4) (b) (4)

In the response to Clinical Pharmacology Information Request (IR), the Applicant clarified the formulations used in the two pivotal clinical studies (PRU-CRC-3001 and SPD555-302), four supportive clinical studies (PRU-INT-6, PRU-USA-11, PRU-USA-13, and SPD555-401) as well as pharmacoepidemiology study SPD555-802, which are listed in the following tables:

Table 6. Summary of Clinical Formulations and Relevant Comparative Bioavailability Study to Proposed Commercial

Study number	Strength	Formulation use	Relevant Comparability Study
PRU-CRC-3001	2 mg	Proposed commercial formulation (b) (4)	N/A
SPD555-302	1 mg	Proposed commercial formulation (b) (4)	N/A
	2 mg	Proposed commercial formulation (b) (4)	N/A
PRU-INT-6	2 mg	(b) (4)	PRU-USA-29
	4 mg[a]		PRU-BEL-31[a]
PRU-USA-11	2 mg		PRU-USA-29
	4 mg[a]		PRU BEL-31[a]
PRU-USA-13	2 mg		PRU-USA-29
	4 mg[a]		PRU BEL-31[a]

SPD555-401	1 mg	Proposed commercial formulation (b) (4)	N/A
	2 mg	Proposed commercial formulation (b) (4)	N/A
SPD555-802	commercial	Proposed commercial formulation (b) (4)	N/A

[a] The 4 mg dose strength is not intended for commercialization in the United States

The bioequivalence between the (b) (4) tablets (clinical formulations) and the (b) (4) (b) (4) tablets (commercial formulations) was demonstrated in the following clinical studies:

Study PRU-BEL-30: Illustrate BE between 1mg and 2 mg market tablets and 1 mg Phase 3 tablets

Study title: A trial in healthy volunteers to assess the bioequivalence of oral prucalopride market tablets with the phase-III clinical tablet

Study treatment:

Batch number	Drug product description	Formulation code
98H14/241	The market 1-mg (b) (4) tablet	F24
99A13/626	The market 2-mg (b) (4) tablet	F25
98D03/F6	The phase-III 1-mg (b) (4) table	F6

Study results:

PK-parameter	Least squares mean*)			Ratio, % (90% CI)		
n = 24	2 x 1mg F24	2 mg F25	2 x 1mg F6	F24/F6	F25/F6	F24/F25
C_{max}, ng/ml	4.01	4.10	4.18	96 (b) (4)	98 (b) (4)	98 (b) (4)
AUC_{last}, ng.h/ml	99.5	99.5	103	97	97	100
AUC_{∞}, ng.h/ml	105	106	110	95	96	99

Study PRU-BEL-29: Illustrate BE between 1mg and 2 mg market tablets and 2 mg clinical tablets

Study title: Evaluation of the Bioequivalence Between 1 x 2.0 mg Prucalopride (b) (4) vs. 2 x 1.0 mg Prucalopride (b) (4) vs. 1 x 2.0 mg clinical (b) (4) Tablets in Healthy Volunteers

Study treatment:

Batch number	Drug product description	Formulation code
TS02099	Prucalopride 2.0 mg tablets manufactured with (b) (4)	F25
99A13/626	Prucalopride 1.0 mg tablets manufactured with (b) (4)	F24

98D03/F6	Prucalopride 2.0 mg tablets manufactured with [redacted]	F8

Study results:

PK-parameter (N=30)	Least squares means*			Ratio, % (90% CI)		
	1 x 2-mg F25	2 x 1-mg F24	1 x 2-mg F8	F25/F8	F24/F8	F24/F25
C_{max}, ng/ml	4.16	4.08	4.33	96 [redacted]	94 [redacted]	98 [redacted]
AUC_{last}, ng.h/ml	86.9	83.6	88.6	98	94	96
AUC_{∞}, ng.h/ml	91.9	88.4	93.4	98	95	96

2. Bridging between different manufacturing site [redacted]

The tablets manufactured [redacted] were produced in different sites. Batch 99A13/626 (2 mg tablet) was manufactured [redacted] Batch TS16800 (2 mg tablet) was manufactured [redacted]. Primary Stability Batch 3144582R was manufactured [redacted] Per SUPAC-IR, this is a [redacted] manufacturing site change, and dissolution profile comparison is needed to bridge this change. All batches have a mean dissolution o [redacted]% a [redacted]minutes, therefore, they are considered similar on dissolution profiles without calculating the similarity factor (f2).

Figure 7. Dissolution profile comparison between Batch 99A13/626 (2 mg tablet) and Batch TS16800 (2 mg tablet)

[redacted]

3. Bridging between th [redacted] **tablets used in the clinical studies and intended for commercialization**

The differences between the (b) (4) tablets used in the clinical studies and the (b) (4) tablets intended for commercialization include the (b) (4) tablet shape for the 1 mg tablets. The following table shows the details in difference between the commercial tablets and clinical tablets (b) (4)

Table 7. Tablet Appearance

Strength	Site	Acceptance Criteria
1 mg		(b) (4)
2 mg		
1 mg		
2 mg		
1 mg		
2 mg		

Figure 8. Dissolution Profile Comparison of (b) (4) (b) (4) batches, 1 mg

(b) (4)

Figure 9. Dissolution Profile Comparison of (b) (4) (b) (4) batches, 2 mg

(b) (4)

The (b) (4) tablets were manufactured (b) (4) (to-be-marketed), (b) (4) (clinical) and (b) (4) (clinical). For the (b) (4) site, dissolution profiles for batches 98H14/241 and 99A13/626 are provided. For the (b) (4) (b) (4) site, dissolution profiles for batches TS04200 and TS04300 are provided. For the (b) (4) site, dissolution profiles for batches 3144580R and 3144582R are provided.

Figures 8 and 9 show that the (b) (4) tablets manufactured at different sites have similar dissolution profiles because all of them have a mean dissolution o (b) (4) % a (b) (4) minutes. Therefore, the differences in the (b) (4) tablets between the clinical batches and commercial batches are sufficiently bridged.

Biowaiver Request

Reviewer's Assessment: ***{Adequate}***

The proposed products have two strengths: 2 mg and 1 mg. The Applicant conducted several BA/BE studies to compare the bioavailability of 2 mg and 1 mg strengths. Therefore, no biowaiver was requested.

Study PRU-BEL-30: Illustrate BE between 1mg and 2 mg market tablets and 1 mg Phase 3 tablets

Study PRU-BEL-29: Illustrate BE between 1mg and 2 mg market tablets and 2 mg clinical tablets

R Regional Information

Comparability Protocols

Reviewer's Assessment:

N/A

Post-Approval Commitments (For NDA only)

Reviewer's Assessment:

N/A

Lifecycle Management Considerations

List of Deficiencies:

None.

Primary Biopharmaceutics Reviewer Name and Date:

Hansong Chen, PharmD, Ph.D., 7/10/2018

Biopharmaceutics reviewer

OPQ/ONDP/DB

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Tien-Mien Chen, Ph.D. I Concur. 07/17/18
Acting Biopharm Lead.
DB/ONDP/OPQ

Hansong Chen

Digitally signed by Hansong Chen
Date: 7/18/2018 11:16:11AM
GUID: 525d7d660003845a197a2e1682433d0d

Tien Mien Chen

Digitally signed by Tien Mien Chen
Date: 7/18/2018 11:36:38AM
GUID: 508da7240002a26723d38018ce005126
Comments: I concur. 07/18/18!

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Attachment I: Final Risk Assessment

Initial Risk Assessment for NDA 210166 Prucalopride tablets, 1mg and 2mg

Product Attribute / CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation Approach	Risk Evaluation	LifeCycle consideration/Comments
Assay and content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment	L	Assay of the the drug substance, prucalopride succinate, is determined by the in-house validated HPLC method. During manufacturing process development critical steps were identified and in process controls (IPC) including tablet weight , hardness and friability were instituted for a robust manufacturing process and to constistantly produce quality DP. The content uniformity was assessed per USP <905> by HPLC method. The long-term and accelerated stability studies of the registration batches demonstrated that there is no significant change in the quality of the DP during the time tested	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	The related substances/ impurities are fully characterized and controlled by DS specification. The impurities are also controlled by DP specification at release and on stability. The impurities are assessed by the in-house validated HPLC method.	Low to None	None
Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment	L	The particle size of the drug substance is controlled by its specification and by multiple screen steps during the drug product manufacturing process. Dissolution is controlled by DP specification.	Low to None	None
Water Content	Raw materials and manufacturing process	L	The drug product is manufactured by dry blending ingredients and direct compression processes.	Low to None	The water content is not in drug product specification. In case of change in the manufacturing process e.g. wet granulation or supplier of lactose monohydrate the water content and/or microbial control shold be added to the drug product specification. Low to None