

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208745Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

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

Date: January 11, 2017
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 208745

Subject: Final Recommendation for NDA 208745

At the time when the CMC Review #1 was completed on October 6, 2016, it had noted the following pending issues:

- The label/labeling issues were not resolved.
- Final “Acceptable” recommendation from the Office of Process and Facilities was not issued.

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

On October 11, 2016, the applicant submitted revised labeling. The CMC sections of the labeling were reviewed and found acceptable (**Attachment -1**).

On December 5, 2016, the Office of Process and Facilities issued the overall “Approval” recommendation for the facilities involved in this NDA (**Attachment – 2**).

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
January 11, 2017

Hitesh N.
Shroff -S

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Shroff -S
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ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=20
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-S
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Attachment 1:

Labeling:

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

Date: October 18, 2016

From: Moo-Jhong Rhee, Ph.D.
Chief, Branch V
Division of New Drug Products II Rhee -S
Office of New drug Products

Moojhong

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ou=FDA, ou=Regulatory, cn=Moojhong Rhee -S,
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Date: 2016.10.18 10:13:00 -0400

To: Labeling Review #1 of NDA 208745

Subject: Final Recommendation

The Labeling review #1 has noted the following two pending issues:

1. Manufacturer information [e.g., name and location of business (street address, city, state and zip code)] is required in labeling and should be located after section 17, Patient counseling information
2. "Do not remove the desiccant packet from the bottle" should be added in section 16, How Supplied/Storage and Handling.

And because of these deficiencies, in the Labeling Review #1, this NDA was not recommended for approval from the labeling perspective.

On October 11, 2016, the applicant amended the labeling and the above issues are satisfactorily resolved (see the **Attachment**).

Recommendation:

This NDA is now recommended for approval from the labeling perspective.

Attachment:

16 HOW SUPPLIED/STORAGE AND HANDLING

TRULANCE tablets are packaged in an aluminum foil unit dose blister pack of 30 in a child-resistant pack or in a white, opaque, high-density polyethylene round bottle with a screw-top polypropylene child-resistant cap and heat-activated induction seal. Each bottle container-closure system also contains a desiccant and a polyester coil.

TRULANCE 3 mg tablets are white to off-white, plain and round, debossed with "SP" on one side and "3" for 3 mg on the other side and supplied as:

NDC Number	Size
70194-203-30	Bottle of 30
70194-003-30	Aluminum foil unit dose blister pack of 30 in a child-resistant pack

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

Keep TRULANCE in a dry place. Protect from moisture. For bottles, keep TRULANCE in the original bottle. Do not remove desiccant from the bottle. Do not subdivide or repackage.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Advise Patients:

Diarrhea

- To stop TRULANCE and contact their healthcare provider if they experience severe diarrhea [see *Warnings and Precautions* (5.2)].

Accidental Ingestion

- Accidental ingestion of TRULANCE in children, especially in children less than 6 years of age, may result in severe diarrhea and dehydration. Instruct patients to take steps to store TRULANCE securely and out of reach of children and to dispose of unused TRULANCE [see *Contraindications* (4), *Warnings and Precautions* (6)(9)(5.2)].

Administration and Handling Instructions

- To take TRULANCE once daily with or without food [see *Dosage and Administration* (2)].
- If a dose is missed, skip the missed dose and take the next dose at the regular time. Do not take two doses at the same time.
- To swallow TRULANCE tablets whole.
- If adult patients have swallowing difficulties, TRULANCE tablets can be crushed and administered orally in either applesauce or with (b) (4) water or administered with water via a nasogastric or gastric feeding tube, as described in the Medication Guide.
- To keep TRULANCE in a dry place. Protect from moisture. For bottles, keep TRULANCE in the original bottle. Do not remove desiccant from the bottle. Do not subdivide or repackage. Remove and discard polyester coil after opening. Keep bottles closed tightly [see *How Supplied/Storage and Handling* (16)].

TRULANCE™ is a trademark of Synergy Pharmaceuticals Inc.

Manufactured for:
Synergy Pharmaceuticals Inc.
420 Lexington Avenue, Suite 2012

Attachment 2:

Facilities:

NDA/BLA > NDA 208745

NDA-208745-ORIG-1

[Request More Access](#) | [Project Actions](#)



Project Owner

Status	Condition	Planned Completion	Percent Complete
Current	At Risk	Jan 27, 2017	88.1%

- [Project Summary](#)
- [Project Details](#)
- [Application Life Cycle](#)
- [Application History](#)
- [Inspection View](#)
- [Tasks](#)
- [Submission Facility Status View](#)**

As of Jan 11, 2017 9:49 am GMT

Submission Overall Manufacturing Facility Status

Overall Status	Completion Date	Submission Status	Project Name
Approve	12/5/2016	Pending	NDA-208745-ORIG-1

Submission Manufacturing Facilities

Facility Status	Completion Date	Project Name	FEE	DUNS	Facility ID	Facility Name	Profile Code	As of
Approve Facility	11/22/2016	NDA-208745-ORIG-1					(b) (4)	(b) (4) PEN
Approve Facility	10/2/2016	NDA-208745-ORIG-1						PEN
No Further Evaluation	10/2/2016	NDA-208745-ORIG-1					CTL CONTROL TESTING LABORATOR...	PEN
Approve Facility	10/2/2016	NDA-208745-ORIG-1					CTL CONTROL TESTING LABORATOR...	PEN
Approve Facility	10/2/2016	NDA-208745-ORIG-1					CTL CONTROL TESTING LABORATOR...	PEN
Approve Facility	10/2/2016	NDA-208745-ORIG-1					CTL CONTROL TESTING LABORATOR...	PEN
Approve Facility	10/2/2016	NDA-208745-ORIG-1						(b) (4) PEN
Approve Facility	10/2/2016	NDA-208745-ORIG-1					CTL CONTROL TESTING LABORATOR...	PEN
Cancelled	5/8/2016	NDA-208745-ORIG-1					CTX CONTROL TESTING LABORATOR...	PEN
Approve Facility	3/8/2016	NDA-208745-ORIG-1						(b) (4) PEN
Approve Facility	3/8/2016	NDA-208745-ORIG-1					TCM TABLETS, PROMPT RELEASE	PEN
Cancelled	3/8/2016	NDA-208745-ORIG-1					CTX CONTROL TESTING LABORATOR...	PEN
Cancelled	2/15/2016	NDA-208745-ORIG-1					CTX CONTROL TESTING LABORATOR...	PEN
Cancelled	2/15/2016	NDA-208745-ORIG-1						(b) (4) PEN
Cancelled	2/2/2016	NDA-208745-ORIG-1					CTL CONTROL TESTING LABORATOR...	PEN



Hitesh
Shroff

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FACILITIES

Product Background:

The application provides for plecanatide immediate release-tablets (3 mg (b) (4) drug product, indicated for the treatment of adults with chronic idiopathic constipation. There is currently no marketed drug product using plecanatide drug substance; as such, this proposed drug product contains an NME.

NDA/ANDA: *NDA 208745*

Drug Product Name / Strength: *Plecanatide Immediate-Release Tablets, 3 mg (b) (4)*

Route of Administration: *Oral*

Applicant Name: *Synergy Pharmaceuticals, Inc.*

Review Summary:

There appear to be no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facilities' inspectional history, relevant experience, and capabilities. The facilities are determined acceptable to support approval of NDA 208745.

List Submissions being reviewed (table):

0000 – Original
0003 through 0007 – Quality Response to Information Request
0011 – Quality Response to Information Request
0018 – Quality Response to Information Request
0030 through 31 – Quality Response to Information Request
0037 through 40 – Quality Response to Information Request
0044 – Quality Response to Information Request
0048 – Quality Response to Information Request
0051 – Quality Response to Information Request

Highlight Key Outstanding Issues from Last Cycle: N/A



Juandria
Williams

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Vidya
Pai

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APPEARS THIS WAY ON ORIGINAL

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) and 21 CFR 314.125(b)(13)**

**NDA 208745
Review 1**

Drug Name/Dosage Form	Plecanatide tablets
Strength	3 mg. (b)(4)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Synergy Pharmaceuticals Inc., New York, NY
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	1/29/2016	OPQ
Amendment	2/26/2016	OPF, ONDP
Amendment	3/25/2016	DB, OPF
Amendment	3/30/2016	DB, ONDP
Amendment	4/07/2016	DB
Amendment	5/4/2016	ONDP
Amendment	5/9/2016	ONDP
Amendment	5/13/2016	ONDP
Amendment	6/8/2016	ONDP
Amendment	7/5/2016	ONDP, OPF
Amendment	8/12/2016	ONDP
Amendment	8/19/2016	ONDP
Amendment	9/7/2016	ONDP
Amendment	9/15/2016	ONDP
Amendment	9/29/2016	ONDP, OPF
Amendment	8/8/2016	DNDAPI
Amendment	8/22/2016	DNDAPI
Amendment	9/26/2016	DNDAPI

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Matin Haber	CDER/OPQ/ONDP/ DNDAPI/NDBII
Drug Product	Zhengfang Ge	CDER/OPQ/ONDP/ DNDPII/NDPBV
Process	Bo Jiang	CDER/OPQ/OPF/ DPAI/PABI
Microbiology	Bo Jiang	CDER/OPQ/OPF/ DPAI/PABI
Facility	Juandria Williams	CDER/OPQ/OPF/DIA/IABIII
Biopharmaceutics	Kalpana Paudel	CDER/OPQ/ONDP/ DB/BBII
Regulatory Business Process Manager	Maureen Dewey	CDER/OND/ODEIII/ DGIEP
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
Environmental Analysis (EA)	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)	N/A	N/A	N/A
	Type III		N/A	N/A	N/A	
	Type III		N/A	N/A	N/A	
	Type III		N/A	N/A	N/A	
	Type III		N/A	N/A	N/A	
	Type III		N/A	N/A	N/A	

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

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	74883	Synergy Pharmaceuticals Inc. currently has an active IND for the investigational use of plecanatide for the 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 drug product.

The Office of Process and Facilities (OPF) has *not* made a final overall “Approval” recommendation for the facilities involved in this application as of this review.

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 per 21 CFR 314.125(b)(6) and 21 CFR 314.125(b)(13), until the above issues are satisfactorily resolved. (see Attachment II)

II. Summary of Quality Assessments

A. Product Overview

Plecanatide tablets are proposed in (b) (4) and (b) (4) only 3 mg strength tablets will be marketed. Plecanatide tablets are white to off-white, plain, round and debossed with “SP” on one side and “3” on the other side. Thirty tablets of Plecanatide are supplied in a bottle or in a child-resistant blister pack.

Proposed Indication(s) including Intended Patient Population	Plecanatide tablets are indicated in adults for treatment of chronic idiopathic constipation (CIC)
Duration of Treatment	As long as needed
Maximum Daily Dose	Recommended adult dosage is 3 mg taken orally once daily
Alternative Methods of Administration	N/A

Quality Assessment Overview

Drug Substance:

The active pharmaceutical ingredient (API), plecanatide, in the drug product is a cyclic peptide containing 16 amino acids and 2 disulfide bonds. (b) (4)

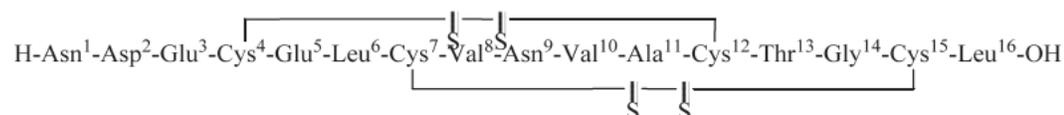
(b) (4)

(b) (4)

The detailed API manufacturing process is provided and it is well controlled. Plecanatide is fully characterized by mass spectroscopy, amino acid sequence analysis, proton and carbon NMR spectroscopy, X-ray powder diffraction and optical rotation analysis.

Plecanatide is an analogue of endogenous human peptide, uroguanylin, with replacement of Asp³ in human peptide with Glu³. The synthetic peptide is white to off-white powder and is soluble in water and slightly more soluble at acidic pH. It is a chiral compound with optical rotation of $-154.5^{\circ} \pm 20.5^{\circ}$.

The molecular formula of plecanatide is $C_{65}H_{104}N_{18}O_{26}S_4$ and the molecular weight is 1682 Daltons. The amino acid sequence of plecanatide is shown below:



The quality of the API is controlled by a specification including identification, assay, purity, 9 specified impurities (b) (4)

residual solvents, optical rotation and particle sizes, which are deemed adequate per Drug Substance reviewer, Dr. Martin Haber (see his drug substance review).

The bulk API is packaged into (b) (4)

(b) (4)

Drug Product:

Plecanatide tablets, 3 mg, are supplied in an aluminum foil blister pack of 30 tablets or in a white, opaque, high-density polyethylene bottle with a screw-top polyethylene child-resistant cap with an induction seal and a polyester coil. In

addition to the 3 mg of API, each tablet also contains USP grade inactive ingredients, microcrystalline cellulose and magnesium stearate.

The drug product manufacturing process involves (b) (4) and packaging in blister or bottles.

The drug product is controlled by a specification including identity, assay, impurities, (b) (4) content uniformity, dissolution, and microbes, and they are deemed adequate per drug product reviewer, Dr. Zhengfang Ge (see her drug product review).

The Division of Pharmaceutical Analysis, FDA performed validation of two drug product analytical procedures. The method validation report dated 05 July, 2016 stated that both methods were evaluated and deemed acceptable for quality control and regulatory purposes (see Attachment III).

Based on the submitted stability data, 24-month expiration dating period is granted when stored at room temperature in the proposed blister packs and bottles. The applicant agreed that the expiration dating period is to be calculated from the manufacturing date of the drug product including the bulk hold-time.

The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The required statement of no extraordinary circumstances was included. The claim was reviewed and found to be acceptable.

B. Special Product Quality Labeling Recommendations (NDA only)

None

Final Risk Assessment (see Attachment I)

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LABELING

NDA 208745

R Regional Information

1.14 Labeling

Labeling & Package Insert

1. Package Insert

(a) “Highlights” Section

TRADENAME (plecanatide) tablets, for oral use

DOSAGE FORMS AND STRENGTHS _____

Tablets: 3 mg (**Error! Reference source not found.**)

Item	Information Provided in NDA
Drug name (201.57(a)(2))	
Proprietary name and established name	TRADENAME (plecanatide) tablets Tradename has not been designated. Inadequate
Dosage form, route of administration	tablets, for oral use Adequate
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (201.57(a)(8))	Tablets: 3 mg Adequate
Whether the drug product is scored	N/A

(b) “Full Prescribing Information” Section

3: Dosage Forms and Strengths

TRADENAME Tablets:

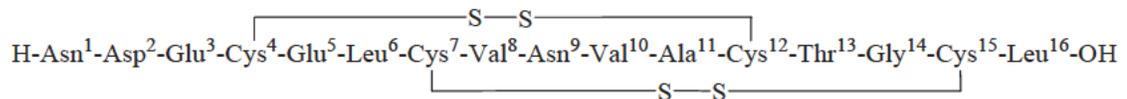
- 3 mg: white to off-white, plain, round tablet debossed with “SP” on one side and “3” for 3 mg on the other side.

Item	Information Provided in NDA
Available dosage forms	Tablets Adequate
Strengths: in metric system	3 mg Adequate
Active moiety expression of strength with equivalence statement (if applicable)	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	white to off-white, plain, round tablet debossed with "SP" on one side and "3" for 3 mg on the other side Adequate

#11: Description

TRADENAME (plecanatide) (b) (4) is a guanylate cyclase-C agonist. Plecanatide is a 16 amino acid peptide with the following chemical name: L-Leucine, L-asparaginyl-L- α -aspartyl-L- α -glutamyl-L-cysteinyl-L- α -glutamyl-L-leucyl-L-cysteinyl-L-valyl-L-asparaginyl-L-valyl-L-alanyl-L-cysteinyl-L-threonylglycyl-L-cysteinyl-, cyclic (4 \rightarrow 12),(7 \rightarrow 15)-bis(disulfide)

The molecular formula of plecanatide is C₆₅H₁₀₄N₁₈O₂₆S₄ and the molecular weight is 1682 Daltons. The amino acid sequence for plecanatide is shown below:



The solid lines linking cysteines illustrate disulfide bridges.

Plecanatide is an amorphous, white to off-white powder. It is soluble in water. TRADENAME tablets are (b) (4) as a 3 mg tablet for oral administration. The inactive ingredients are microcrystalline cellulose and magnesium stearate.

Item	Information Provided in NDA
Proprietary name and established name	TRADENAME (plecanatide) should be revised to Tradename (plecanatide) tablets Inadequate
Dosage form and route of administration	tablet for oral administration Adequate
Active moiety expression of strength with equivalence statement (if applicable)	N/A
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names (if any) in alphabetical order (USP <1091>)	The inactive ingredients are microcrystalline cellulose and magnesium stearate Adequate
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	guanylate cyclase-C agonist Adequate
Chemical name, structural formula, molecular weight	Provided. Adequate
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	Plecanatide is an amorphous, white to off-white powder. It is soluble in water Adequate

HOW SUPPLIED section

TRADENAME tablets are packaged in an aluminum foil unit dose blister pack of 30 in a child-resistant pack or in a white, opaque, high-density polyethylene round bottle with a screw-top polypropylene child-resistant cap and heat-activated induction seal. Each bottle container-closure system also contains a desiccant and a polyester coil.

TRADENAME

3 mg tablets are white to off-white, plain and round, debossed with “SP” on one side and “3” for 3 mg on the other side and supplied as:

NDC Number	Size
XXXXXX-XXX-XX	Bottle of 30
XXXXXX-XXX-XX	Aluminum foil unit dose blister pack of 30 in a child-resistant pack

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

Item	Information Provided in NDA
Strength of dosage form	3 mg Adequate
Available units (e.g., bottles of 100 tablets)	Bottle of 30 counts and blister pack of 30 Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided Adequate
Special handling (e.g., protect from light)	“Do not remove the desiccant packet from the bottle” should be added Not Adequate
Storage conditions	Provided Adequate
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Not provided Not Adequate

Information Request

- Manufacturer information [e.g., name and location of business (street address, city, state and zip code)] is required in labeling and should be located after section 17 patient counseling information
- “Do not remove the desiccant packet from the bottle” should be added in section 16 How Supplied

Immediate Container Label

3 mg/30 ct. Bottle Label



3 mg/7 ct. sample label



3MG 30CT CALENDAR BLISTER



Reviewer's Final Assessment: Adequate

The bottle label contains proprietary name (space for Trade Name), established name (plecanatide), strength, net quantity, administration route (tablets), lot number, expiration, Rx only, storage, NDC number, bar code and manufacturer. *The information on the bottle label is adequate*

The label on the blister contains trade name, expiration, lot number and bar code. The applicant needs to include Trade Name (established name) tablets X mg (b) (4) Rx only and manufacturer on the blister

Information Request:

- Include “Trade Name (established name) tablets 3 mg ^{(b) (4)}”, “Rx only” and name of manufacturer on the blister card

Amendment Submitted 7-Sep-2016

The applicant revised the blister label as shown below. The revised label is adequate

(b) (4)

Carton Labeling

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Reviewer's Assessment: Adequate

The bottle carton label contains Trade Name (plecanatide) tablets 3mg (b) (4), net quantity, lot number, expiration, Rx only, storage, NDC number, bar code and manufacturer, "Keep out of reach of children". The special instruction for the storage includes "protect from moisture. Do not remove the desiccant from inside the bottle. The carton also includes "each tablet contains 3 mg plecanatide". *The information on the bottle carton label is adequate*

The carton label on the blister *package* includes Trade Name (plecanatide) tablets 3 mg (b) (4), net quantity, lot number, expiration, Rx only, storage, NDC number, bar code and manufacturer. The applicant should be asked to include "Keep out of reach of children"

Information Request:

- Include "Keep out of reach of children" on the carton of the blister package

Amendment Submitted 7-Sep-2016

The applicant revised the blister label as shown below. The revised label is adequate

List of Deficiencies:

- Manufacturer information [e.g., name and location of business (street address, city, state and zip code)] is required in labeling and should be located after section 17 patient counseling information
- “Do not remove the desiccant packet from the bottle” should be added in section 16 How Supplied

Primary Labeling Reviewer Name and Date:

Zhengfang Ge, Ph.D.

Branch V, DNDP II/ONDP

The labeling and labels are satisfactory from CMC perspective, except for the deficiencies noted above, and therefore, this application is not deemed ready for approval until the final labeling get resolved above deficiencies.

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

I concur with Dr. Ge’s assessment on the labeling and labels, and agree with that this application is not ready for approval till those two deficiencies are resolved.

Moo-Jhong Rhee, Ph.D.

Chief, Branch V

DNDP II/ONDP



Moo Jhong
Rhee

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Zhengfang
Ge

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BIOPHARMACEUTICS

Product Background:

NDA/ANDA: NDA 208745/N000 (A new molecular entity; NME)

Drug Product Name / Strength: Plecanatide tablets/ 3 mg (one strength only)

Route of Administration: Oral

Applicant Name: Synergy Pharmaceuticals Inc

Review Summary:

The proposed drug product, Plecanatide immediate-release 3 mg tablet, is indicated for the treatment of chronic idiopathic constipation (CIC) in adults. The Applicant seeks approval of this NDA/N000 for an NME via the 505(b)(1) regulatory pathway.

Composition of proposed drug product:

(b) (4) the to-be-marketed formulation of plecanatide tablets (3 mg (b) (4) were (b) (4) proposed as shown in Table 1 below. (b) (4) the proposed 3 (b) (4) to-be-marketed tablet formulation had been tested clinically in the Phase 3 trials.

Table 1: Composition of plecanatide Tablets, 3 mg (b) (4)

Component	Function	Tablet Dosage Strength	
		3mg	(b) (4)
Plecanatide ^a	Drug substance	3.0	(b) (4)
Microcrystalline cellulose ^b USP-NF			(b) (4)
Magnesium stearate USP-NF			(b) (4)
Total (mg)			(b) (4)

^a The drug substance is corrected for assay (wt/wt%).

(b) (4)

Note: Plecanatide formulation is designed for locally acting in the GI lumen. (b) (4)

(b) (4)
The Applicant (b) (4) developed 3 (b) (4) mg tablet strength (b) (4)

List Submissions being reviewed (table):

Dissolution method and acceptance criterion, biowaiver, bridging

Highlight Key Outstanding Issues from Last Cycle:

N/A

Concise Description Outstanding Issues Remaining:

N/A

BCS Designation**Reviewer's Assessment:**

No information is provided on BCS of the API.

Solubility:

Permeability:

N/A

Dissolution:

Please see below.

Dissolution Method and Acceptance Criteria

The Applicant has provided the dissolution method development report including the justification for the proposed dissolution parameters, discriminating ability of the dissolution method, dissolution method validation, and dissolution data of the plecanatide tablets in this submission which were presented and reviewed in the respective sections below.

A dissolution method (TR-00284) was developed, and proposed dissolution conditions are shown below.

Table 4: Proposed dissolution method for plecanatide tablets

Parameter	Conditions
Apparatus	USP Apparatus 2 (Paddles)
Media	35 mM Phosphate buffer pH 6.2
Media Temperature	37°C
Paddle Speed	50 RPM
Media Volume	
3 mg	500 mL
6 mg	900 mL
Sampling times ^a	Per current IND specification requirement (currently Q = (b)(4)% at 30 minutes; report dissolution results at 15, 30, 45, and 60 minutes). Dissolution profile comparison: 10, 15, 20, 30, 45, and 60 minutes

^a Sampling times may be revised.

The proposed dissolution acceptance criterion is as follows.

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

Dissolution Method Development

The Applicant has provided data for the justification of dissolution apparatus, paddle speed, dissolution medium and pH for the dissolution method TR-00284.

Dissolution media and rpm selection

(b) (4)



Dissolution

profiles of plecanatide:

The Applicant has conducted dissolution studies on plecanatide tablets, 3 mg and 6 mg in proposed dissolution medium. The summary of the results for 3 mg and 6 mg is provided below. The batches utilized in dissolution studies were the same batches that were tested in clinical studies and in stability testing. Individual dissolution data for all the clinical studies are provided in M.2.7.1. Table 6 shows the dissolution summary of plecanatide IR tablets, 3 and 6 mg.

Table 6: Dissolution summary of plecanatide tablets, 3 mg and 6 mg

Dissolution Conditions		Apparatus:	USP Apparatus 2 (Paddles)						
		Paddle Speed:	50 RPM						
		Medium:	35 mM pH 6.2 phosphate buffer						
		Volume:	500 mL (3 mg); 900 mL (6 mg)						
		Temperature:	37°C ±0.5°C						
Firm's Proposed Specifications		Q = ^{(b) (4)} in 30 minutes							
Dissolution Testing Site (Name, Address)		^{(b) (4)}							
Clinical Study Ref No.	Testing Date	Product ID \ Batch No. (Test - Manufacture Date)	Dosage Form & Strength	No. of Dosage Units	Collection Times (minutes)				
					15	30	45	60	
SP304203-01	17JUN2013	Site of Mfg: ^{(b) (4)} Batch: 13C049 Manufacture Date: 23MAR2013	Tablet 3 mg	12	Mean	^{(b) (4)}			
					Range				
					%CV				
SP304203-01	17JUN2013	Site of Mfg.: ^{(b) (4)} Batch: 13C050 Manufacture Date: 25MAR2013	Tablet 3 mg	12	Mean	^{(b) (4)}			
					Range				
					%CV				
SP304203-00, SP304203-03	18JUN2013	Site of Mfg: ^{(b) (4)} Batch: 13E090 Manufacture Date: 22MAY2013	Tablet 3 mg	12	Mean	^{(b) (4)}			
					Range				
					%CV				
SP304203-00, SP304203-01, SP304203-03	17JAN2014	Site of Mfg: ^{(b) (4)} Batch: 13M262 Manufacture Date: 16DEC2013	Tablet 3 mg	12	Mean	^{(b) (4)}			
					Range				
					%CV				

SP304203-01	17JUN2013	Site of Mfg: (b) (4) Batch: 13C051 Manufacture Date: 26MAR2013	Tablet 6 mg	12	Mean Range %CV	(b) (4)
SP304203-00, SP304203-01, SP304203-03	17JUL2013	Site of Mfg: (b) (4) Batch: 13F106 Manufacture Date: 25JUN2013	Tablet 6 mg	12	Mean Range %CV	(b) (4)
SP304203-01	23SEP2014	Site of Mfg: (b) (4) Batch: 14J256 Manufacture Date: 09/11/14	Tablet 6 mg	12		(b) (4)

CV = coefficient of variance; ID = identification; Mfg. = manufacturing; No. = number; Q = quantity; RPM = revolutions per minute; USP = United States Pharmacopeia

Analytical Method Validation:

In vitro dissolution analytical method validation report for Plecanatide IR tablets (Analytical Method Validation Report AC-MVR-00329) was submitted in M.3.2.P.5.3, which were validated in terms of specificity, linearity, precision, accuracy, solution stability, (b) (4) compatibility, and robustness, and is summarized below in Table 7.

Table 7: Summary of Method Validation for Dissolution of Plecanatide tablets (from M.3.2.P.5.3)

Parameter	Type of Sample	Details	Desired Results	Results																								
Specificity	Placebo Blend Mixture	A single injection of a solution containing the placebo blend mixture, equivalent to the final composition of the 3 mg strength	Any diluent or solvent peak at the retention time of Plecanatide is \leq (b) (4) of the peak area of the Plecanatide peak in the working standard solution	No peak was found at the retention time of Plecanatide																								
Linearity	Reference Standard or API	25%, 50%, 75%, 100%, 125% and 150% of the nominal working standard concentration of (b) (4) Plecanatide. Single injections were made.	Linear Regression: (b) (4) Report Slope and y-intercept	(b) (4)																								
Accuracy	Spiked Solutions Containing Placebo Blend	Recovery of API from placebo blend solutions spiked at 50%, 100%, and 150% of the nominal concentration of (b) (4) Plecanatide. Solutions were prepared in triplicate. Single injections were made.	%Recovery (b) (4) for all levels	<table border="1"> <thead> <tr> <th colspan="4">%Recovery</th> </tr> <tr> <th>Prep</th> <th>50%</th> <th>100%</th> <th>150%</th> </tr> </thead> <tbody> <tr> <td>1</td> <td></td> <td></td> <td>(b) (4)</td> </tr> <tr> <td>2</td> <td></td> <td></td> <td></td> </tr> <tr> <td>3</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Mean</td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	%Recovery				Prep	50%	100%	150%	1			(b) (4)	2				3				Mean			
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Parameter	Type of Sample	Details	Desired Results	Results																																																																												
Precision (Content Uniformity) Analyst 1	Drug product	Performed analysis of six aliquots at the nominal CU sample concentration, taken from a solution composite for each dosage strength.	RSD \leq 3.0% for the six replicates of CU from each solution composite	<table border="1"> <thead> <tr> <th colspan="3">%Label Claim</th> </tr> <tr> <th>Analyst 1</th> <th>3 mg Tablets</th> <th>6 mg Tablets</th> </tr> </thead> <tbody> <tr><td>1</td><td></td><td>(b) (4)</td></tr> <tr><td>2</td><td></td><td></td></tr> <tr><td>3</td><td></td><td></td></tr> <tr><td>4</td><td></td><td></td></tr> <tr><td>5</td><td></td><td></td></tr> <tr><td>6</td><td></td><td></td></tr> <tr><td>Mean</td><td></td><td></td></tr> <tr><td>%RSD</td><td></td><td></td></tr> </tbody> </table>	%Label Claim			Analyst 1	3 mg Tablets	6 mg Tablets	1		(b) (4)	2			3			4			5			6			Mean			%RSD																																																
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Intermediate Precision (Content Uniformity)	Drug Product	A second analyst repeated the experiments described under Precision above on different instruments and columns, and using separate standard and mobile phase preparations.	The results for the second analyst meet the criteria stated above (for analyst 1). For the composite samples: Results for the two analysts agree with each other within \pm 3% RSD for 12 replicates of CU samples \leq 3.0%	<table border="1"> <thead> <tr> <th colspan="3">%Label Claim</th> </tr> <tr> <th>Analyst 2</th> <th>3 mg Tablets</th> <th>6 mg Tablets</th> </tr> </thead> <tbody> <tr><td>1</td><td></td><td>(b) (4)</td></tr> <tr><td>2</td><td></td><td></td></tr> <tr><td>3</td><td></td><td></td></tr> <tr><td>4</td><td></td><td></td></tr> <tr><td>5</td><td></td><td></td></tr> <tr><td>6</td><td></td><td></td></tr> <tr><td>Mean</td><td></td><td></td></tr> <tr><td>%RSD</td><td></td><td></td></tr> </tbody> </table> <table border="1"> <thead> <tr> <th>Both Analysts</th> <th>3 mg Tablets</th> <th>6 mg Tablets</th> </tr> </thead> <tbody> <tr><td>%Diff</td><td></td><td>(b) (4)</td></tr> <tr><td>%RSD(n=12)</td><td></td><td></td></tr> </tbody> </table>	%Label Claim			Analyst 2	3 mg Tablets	6 mg Tablets	1		(b) (4)	2			3			4			5			6			Mean			%RSD			Both Analysts	3 mg Tablets	6 mg Tablets	%Diff		(b) (4)	%RSD(n=12)																																							
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Robustness	Drug Product	<p>Impact of deliberate variations of phosphate buffer concentrations (b) (4) 35, and (b) (4) mM) was evaluated by analysis of a solution at the nominal sample concentration for one dose.</p> <p>For CU, the effects of buffer concentration on sample preparation were evaluated on one sample of each dose. For dissolution, the effect of buffer concentration in dissolution media was evaluated on one sample of each dose.</p>	<p>Meet System Suitability criteria in AC-AM-00586-R1.0 (Draft) and results agree with baseline condition (35 mM phosphate buffer) within 2%</p>	<table border="1"> <thead> <tr> <th colspan="3">CU</th> </tr> <tr> <th>%Baseline condition</th> <th>3 mg</th> <th>6 mg</th> </tr> </thead> <tbody> <tr><td colspan="3">(b) (4)</td></tr> </tbody> </table>	CU			%Baseline condition	3 mg	6 mg	(b) (4)																											
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Parameter	Type of Sample	Details	Desired Results	Results																																																																											
Solution Stability	Reference Standard and Drug product	Stability of the standard and sample solutions, of each dose strength, was evaluated by measuring the concentration of Plecanatide in aged solutions versus freshly prepared standards for each stability interval. Studies were performed at refrigerated conditions (2-8°C) over at least three days and at room temperature (25°C) at the 6, 12 and 24 hour time points.	% Recovery: [redacted] (b) (4) of the initial concentration	<p>% of Initial Concentration 25C</p> <table border="1"> <thead> <tr> <th></th> <th colspan="2">3 mg</th> <th colspan="2">6 mg</th> </tr> <tr> <th></th> <th>CU</th> <th>Disso</th> <th>CU</th> <th>Disso</th> </tr> </thead> <tbody> <tr> <td>6hrs</td> <td>[redacted]</td> <td>[redacted]</td> <td>[redacted]</td> <td>[redacted] (b) (4)</td> </tr> <tr> <td>24hrs</td> <td>[redacted]</td> <td>[redacted]</td> <td>[redacted]</td> <td>[redacted]</td> </tr> <tr> <td>4days</td> <td>[redacted]</td> <td>[redacted]</td> <td>[redacted]</td> <td>[redacted]</td> </tr> <tr> <td colspan="5" style="text-align:center">Standard</td> </tr> <tr> <td></td> <td>6hrs</td> <td>24hrs</td> <td>5days</td> <td>8days</td> </tr> <tr> <td></td> <td>[redacted]</td> <td>[redacted]</td> <td>[redacted]</td> <td>[redacted] (b) (4)</td> </tr> </tbody> </table> <p>% of Initial Concentration 2-8C</p> <table border="1"> <thead> <tr> <th></th> <th colspan="2">3 mg</th> <th colspan="2">6 mg</th> </tr> <tr> <th></th> <th>CU</th> <th>Disso</th> <th>CU</th> <th>Disso</th> </tr> </thead> <tbody> <tr> <td>4days</td> <td>[redacted]</td> <td>[redacted]</td> <td>[redacted]</td> <td>[redacted] (b) (4)</td> </tr> <tr> <td>7days</td> <td>[redacted]</td> <td>[redacted]</td> <td>[redacted]</td> <td>[redacted]</td> </tr> <tr> <td colspan="5" style="text-align:center">Standard</td> </tr> <tr> <td></td> <td>5days</td> <td>8days</td> <td></td> <td></td> </tr> <tr> <td></td> <td>[redacted]</td> <td>[redacted]</td> <td>[redacted]</td> <td>[redacted] (b) (4)</td> </tr> </tbody> </table>		3 mg		6 mg			CU	Disso	CU	Disso	6hrs	[redacted]	[redacted]	[redacted]	[redacted] (b) (4)	24hrs	[redacted]	[redacted]	[redacted]	[redacted]	4days	[redacted]	[redacted]	[redacted]	[redacted]	Standard						6hrs	24hrs	5days	8days		[redacted]	[redacted]	[redacted]	[redacted] (b) (4)		3 mg		6 mg			CU	Disso	CU	Disso	4days	[redacted]	[redacted]	[redacted]	[redacted] (b) (4)	7days	[redacted]	[redacted]	[redacted]	[redacted]	Standard						5days	8days				[redacted]	[redacted]	[redacted]	[redacted] (b) (4)
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System Suitability	Reference Standard	Performed system suitability tests as outlined in AC-AM-00586-R1.0 (Draft)	<p>Any peak present at the Any diluent or solvent peak present at the retention time of the peak of interest must have an area \leq [redacted] (b) (4) the area of the peak of interest in the quantitation standard.</p> <p>The %RSD of the peak areas for five injections of WS A must be [redacted] (b) (4)</p> <p>The average response factor for WS B must compare to the average response factor of WS A within [redacted] (b) (4)</p> <p>Report the number of theoretical plates of the HPLC column for the Plecanatide peak in the fifth Standard A injection.</p>	<p>All runs during the validation met the system suitability criteria.</p> <p>There was no peak present at the retention time of the Plecanatide peak throughout the runs.</p> <p>The %RSDs of the peak areas for five injections of WS A ranged from [redacted] (b) (4)</p> <p>The average response factors for WS B compared to the average response factor of WS A ranged from [redacted] (b) (4)</p> <p>Theoretical plates of the HPLC column for the Plecanatide peak in the fifth Standard A injection ranged from [redacted] (b) (4)</p>																																																																											

¹ Does not meet acceptance criteria
Refer to CN-02842

Reviewer’s Assessment:

- The Applicant’s proposed dissolution method and its development report are acceptable. The Applicant has provided adequate data for the justification of dissolution method parameters.
- The Applicant’s proposed dissolution specification is too liberal based on the data and hence is not acceptable. In an email dated June 22, 2016, the following Information Request (IR) was sent:

Your proposed dissolution specification of $Q = \text{(b)}_{(4)}\%$ at 30 minutes is too liberal based on the dissolution data provided. We recommend that you implement a specification of $Q = \text{(b)}_{(4)}\%$ at 20 minutes in your drug product release and stability specification.

The Applicant accepted the specification and responded as follows:

As recommended by FDA, Synergy has revised the dissolution acceptance criterion to $Q = \text{(b)}_{(4)}\%$ at 20 minutes (Module 3.2.P.5.1).

(b) (4)

Applicant question

In reference to Module 2.7.1, Summary of Biopharmaceutics Studies, data tables submitted in the CIC NDA will be updated $\text{(b)}_{(4)}$. Batches used in CIC $\text{(b)}_{(4)}$ clinical studies are manufactured and tested using the same procedures. At the time of release testing, dissolution was performed using conditions of 15, 30, 45, and 60 minutes. Based upon a request from the Biopharmaceutics group during review of the CIC NDA, the agreed upon dissolution specification is $Q = \text{(b)}_{(4)}\%$ in 20 minutes. As this specification was agreed upon post release testing of the clinical batches, dissolution data contained in Module 2.7.1 summary tables will reflect the original testing of 15, 30, 45, and 60 minutes. It is noted that 20 minute dissolution testing will be added to the stability protocols and testing criteria for current and all new and future batches, $\text{(b)}_{(4)}$. Synergy does not believe that submission of the Module 2.7.1 summary tables without 20 minute dissolution testing presents an issue as the 20 minute acceptance criteria was agreed upon based on the original 15 and 30 minute data. $\text{(b)}_{(4)}$

Does the Agency agree with this approach?

Meeting Discussion Points:

FDA and Synergy agree to retain the originally proposed dissolution acceptance criteria of $Q = \text{(b)}_{(4)}\%$ in 30 minutes thru presumed approval of the current NDA 208745. Synergy will update the drug product specification in Module 3.2.P.5.1. Additional dissolution data will be collected at 20 min for the commercial batches up to one year post approval. Synergy will generate, analyze, and submit the complete dissolution data for review in the first CMC annual report, assuming approval of NDA 208745 for plecanatide in CIC. This will include the dissolution profile data at 15, 20, 30, and 45 minutes on the first three commercial batches.

- The dissolution testing included the 3 mg, 6 mg, and other strengths that were used in the clinical studies.

- The analytical method and its validation report are reviewed and considered acceptable. Linearity was demonstrated over the range 25%-150% of 0.006 mg/mL.

Bridging of Formulations

Reviewer’s Assessment:

- The Applicant has bridged the capsule and the tablet formulation. The Applicant conducted in vitro dissolution studies to compare between plecanatide Phase 3/commercial tablets and Phase 2 capsule formulations. The dissolution of tablets and capsules were rapid and similar (Table 8).

Table 8: Comparison of tablet and capsule dissolution using proposed dissolution conditions

Time	3 mg Tablet (Batch 12G080)	3 mg Capsule (Batch 11H140)
15 minutes	(b) (4)	
Mean (n = 12)		
% RSD		
20 minutes		
Mean (n = 12)		
% RSD		
30 minutes		
Mean (n = 12)		
% RSD		
45 minutes		
Mean (n = 12)		
% RSD		
60 minutes		
Mean (n = 12)		
% RSD		

RSD = relative standard deviation

No difference was observed in dissolution rates between plecanatide tablets with (b) (4) versus plecanatide tablets with (b) (4) thereby demonstrating equivalence between these 2 formulations (Table 5, Table 7, and Table 8).

- The Applicant also compared dissolution between plecanatide tablets with (b) (4) (phase 3/commercial formulation) versus plecanatide tablets with (b) (4) (phase 1 food effect study), which were similar between these 2 formulations (Table 9).

Table 9: Comparison of tablet formulation with (b) (4)

Time	(b) (4) (Batch 12G080)	(b) (4) (Batch 13M262) Proposed Formulation
15 minutes	(b) (4)	
Mean (n = 12)		
% RSD		
20 minutes		
Mean (n = 12)		
% RSD		
30 minutes		
Mean (n = 12)		
% RSD		

Biowaiver Request

Reviewer’s Assessment:

The Applicant requested a biowaiver from the requirement of a bioequivalence/bioavailability studies for its 3 mg dosage strengths of plecanatide tablets. In a Phase 3 clinical trial (No. SP304203-03), a subset of patients (n=95) were enrolled in a pharmacokinetic (PK) substudy; approximately 32 patients per dose arm of placebo, 3 mg and 6 mg QD regimen. Blood samples were obtained predose and intensive samples were obtained on Day 28, 24-hr sample on Day 29, and 72-hr sample on Day 31. PK data, however, show that neither drug nor its active metabolite levels are measurable in the human systemic circulation. Since 3 mg plecanatide tablet was part of a PK substudy in Phase 3 clinical trial, the biowaiver request is considered not needed.

Dissolution studies showed similar release profiles for the 3 mg tablet strength in comparison with the 6 mg tablet strength (Tables 10 and 11). The in vitro drug release was > (b) (4)% in 15 minutes for both strengths. Batches 14E116 and 14E117 were used for comparative dissolution study and were manufactured as clinical supplies for phase 3 studies SP304203-00 and SP304203-03 using the proposed commercial formulation and process.

Figure 5. Dissolution profile comparison for 3 mg and 6 mg Plecanatide tablets



(b) (4)

Table 10: Dissolution of 3 mg plecanatide tablets (Batch: 14E116)

Product ID / Batch No.	No.	Timepoint (minutes)					
		5	10	15	20	30	45
14E116 (3 mg) Mfg Date: 07May2014 Site: (b) (4)	1	(b) (4)					
	2						
	3						
	4						
	5						
	6						
	7						
	8						
	9						
	10						
	11						
	12						
	Mean						
	RSD						
Min							
Max							

Table 11: Dissolution of 6 mg plecanatide tablets (Batch: 14E117)

Product ID / Batch No.	No.	Timepoint (minutes)					
		5	10	15	20	30	45
14E117 (6 mg) Mfg Date: 08May2014 Site: (b) (4)	1	(b) (4)					
	2						
	3						
	4						
	5						
	6						
	7						
	8						
	9						
	10						
	11						
	12						
	Mean						
	RSD						
Min							
Max							

Alternate dosing Study

The Applicant has provided verification of dosing procedures and in-use stability study for plecanatide tablets which are mentioned below.

1. Verification of Alternative Dosing Procedures for Plecanatide Tablets

The Applicant submitted protocol entitled "*Verification of Alternative Dosing Procedures for Plecanatide Tablets*" and data for the addition of four dosing alternatives for (b) (4) (b) (4) plecanatide tablets for inclusion in the Medication Guide. The protocol and the supporting data were not submitted in the original NDA application. Since the Applicant (b) (4) decided to pursue approval of the 3 mg tablet strength in this NDA review cycle, only the 3 mg plecanatide tablet will be discussed in the sections below.

The four alternative administration methods were to disperse a tablet in applesauce, dissolve a tablet in water for oral ingestion and to dissolve a tablet in water with administration through nasogastric and gastric feeding tubes. The final Experimental Design protocol (Protocol: EDP2016-006.01) and the Analytical Results Report ARF2016-029.01 (including raw data files) are provided in Module 1.11.1.

A validated (b) (4) HPLC method AC-AM-00586 was used to demonstrate recovery of Plecanatide after dissolving and processing as described in the Protocol: EDP2016-006.01. Results of qualification of (b) (4) method AC-AM-00586 is provided in table 12. For each tablet strength, the acceptance criteria for the mean recovery of Plecanatide from the sample matrices was (b) (4) % and RSD less than 5.0% (n=5). All dosing alternatives met these criteria for 3 mg tablet strength.

Note: The Applicant responded to chemist IR on the in vitro stability testing. Please see In Vitro stability testing on page 22 of this review for details.

Table 12: Results of qualification of (b) (4) method AC-AM-00586 on plecanatide placebo tablets

Plecanatide Placebo Tablets, Lot: 14E115, ATN: SS01-01 051916A001
 Plecanatide Reference Standard, Lot: 1222RS02, ATN: RS01-01-071813A001 (spiking)

Sample Identification	mg Plecanatide Added	mg Plecanatide Recovered	% Plecanatide Recovered	% Plecanatide Recovered (Reported)	% RSD (n=3)
Placebo Tablet	(b) (4)				
50% Spike					
100% Spike					
150% Spike					
Reference					

(b) (4) pp. 2-8, 15

1-1. Dosing in Applesauce

To study the effect of tablet content in the applesauce, 3 mg tablet was crushed using a glass mortar and pestle. To this, one teaspoon (ca. 5 g) of applesauce was added at ambient temperature. The crushed tablet was briefly dispersed with a glass stirring rod. This corresponds with the direction in medication guide “Crush the TRULANCE tablet and mix into 1 teaspoon of room temperature applesauce.” The results are provided below in tables 13-15.

Table 13: Results of feasibility of recovery of plecanatide placebo tablets from applesauce

Musselman's Unsweetened Applesauce, Lot: CASN3030 6032G11

Plecanatide Placebo Tablets, Lot: 14E115, ATN: SS01-01 051916A001

Plecanatide Reference Standard, Lot: 1222RS02, ATN: RS01-01-071813A001 (spiking)

Sample Identification	mg Plecanatide Added	mg Plecanatide Recovered	% Plecanatide Recovered	% Plecanatide Recovered (Reported)	% RSD (n=3)
Applesauce Blank	(b) (4)				
Applesauce/Placebo Tablet Blank					
2 mg Spike					
4 mg Spike					
8 mg Spike					

Reference

(b) (4) pp. 2-6, 15

Table 14: Recovery of plecanatide tablets from Mott's applesauce

Mott's Natural Applesauce, Lot: 033016WC

Sample Identification	mg Plecanatide Recovered	% Plecanatide Recovered	% Plecanatide Recovered (Reported)	% RSD (n=5)
3 mg Plecanatide Tablet	(b) (4)			
Average (n=5)				
6 mg Plecanatide Tablet				
Average (n=5)				

Reference (b) (4) pp. 7-14

Table 15: Recovery of plecanatide tablets from Musselman’s Unsweetened applesauce

Musselman’s Unsweetened Applesauce, Lot: CASN3030 6032G11

Sample Identification	mg Plecanatide Recovered	% Plecanatide Recovered	% Plecanatide Recovered (Reported)	% RSD (n=5)
3 mg Plecanatide Tablet	(b) (4)			
Average (n=5)				
6 mg Plecanatide Tablet				
Average (n=5)				

Reference (b) (4) pp. 7-14

1-2. Dosing in water solution for oral ingestion

To study the effect of tablet content in the water, 3 mg tablet was placed in a 50-ml glass beaker containing ca. 30 ml of HPIC-grade water at ambient temperature. The tablet rapidly disintegrates and the insoluble tablet excipients remain visible. This corresponds with the direction in medication guide “Place the TRULANCE tablet in a cup with 1-ounce (30 mL) of room temperature (b) (4) water. Gently swirl the TRULANCE tablet and water for at least 10 seconds. The TRULANCE tablet will fall apart in the water.” The results are provided below in table 16 below.

Table 16: Recovery of plecanatide tablets from water solution for oral ingestion

HPLC-Grade Water, Labconco WaterPro PS, Acceleration Asset Number AAN-00259

Sample Identification	mg Plecanatide Recovered	% Plecanatide Recovered	% Plecanatide Recovered (Reported)	% RSD (n=5)
3 mg Plecanatide Tablet	(b) (4)			
Average (n=5)				
6 mg Plecanatide Tablet				
Average (n=5)				

Reference (b) (4) pp. 7-14

1-3. Dosing in water solution for oral ingestion via Nasogastric (NG) tube

To study the effect of tablet content in the water, 3 mg tablet was placed in a 50-ml glass beaker containing ca. 30 ml of HPLC-grade water at ambient temperature. The tablet rapidly disintegrates and the insoluble tablet excipients remain visible. The preparation was transferred into a 60 cc catheter-tipped syringe (with plunger removed) attached to a NG tube, replacing the plunger and the preparation was infused through the NG tube and the effluent was collected in a 50-ml volumetric flask. This is in accordance with the direction in medication guide for “Taking TRULANCE via a nasogastric or gastric feeding tube” The results are provided below in table 17.

Table 17: Recovery of plecanatide tablets from water solution for oral ingestion via Nasogastric (NG) tube

Nasogastric Tube: Bard, Nasogastric Sump Tube, Part Number 0042160, Lot: NG2K0840
 16 Fr, 48 inches in length, material of construction not given

Sample Identification	mg Plecanatide Recovered	% Plecanatide Recovered	% Plecanatide Recovered (Reported)	% RSD (n=5)
3 mg Plecanatide Tablet	(b) (4)			
Average (n=5)				
6 mg Plecanatide Tablet				
Average (n=5)				
Reference	(b) (4) pp. 7-14			

1-4. Dosing in water solution for oral ingestion via Gastric Feeding tube To study the effect of tablet content in the water, 3 mg tablet was placed in a 50-ml glass beaker containing ca. 30 ml of HPIC-grade water at ambient temperature. The tablet rapidly disintegrates and the insoluble tablet excipients remain visible. The preparation was transferred into a 60 cc catheter-tipped syringe (with plunger removed) attached to a feeding tube, replacing the plunger and the preparation was infused through the gastric feeding tube and the effluent was collected in a 50-ml volumetric flask. This is in accordance with the direction in medication guide for “Taking TRULANCE via a nasogastric or gastric feeding tube”. The results are provided below in table 18.

Table 18: Recovery of plecanatide tablets from water solution for oral ingestion via Gastric Feeding tube

Gastric Feeding Tube: Bardia, Foley Catheter, Part Number not available, Lot: MYZLR075, 16 Fr, length not available, Material: latex

Sample Identification	mg Plecanatide Recovered	% Plecanatide Recovered	% Plecanatide Recovered (Reported)	% RSD (n=5)
3 mg Plecanatide Tablet	(b) (4)			
Average (n=5)				
6 mg Plecanatide Tablet	(b) (4)			
Average (n=5)				
Reference	(b) (4) pp. 7-14			

2. In-use stability study of plecanatide 3 mg in applesauce and water

On September 15, 2016, Synergy provided stability data for the assay of plecanatide as prepared in two brands of applesauce and in water per chemist’s request.

Q. from the chemist:

Please clarify how long the crushed tablets have been kept in the proposed dosing materials (applesauce and water) before testing.

A. Response from Applicant:

The crushed tablets were in the proposed dosing material less than 5 minutes before sample preparation for the analysis began. Once disintegration of the crushed tablets in water or applesauce was seen to be complete, the sample solutions for assay were prepared.

Disintegration was rapid and less than 5 minutes; however, disintegration times were not recorded for these preparations.

The above stability results are reviewed by the chemist which were found acceptable. .

Table 19 shows the stability protocol. The assay was measured using the HPLC procedure described in 3.2.P.5.2 for content uniformity and dissolution detection, and compared against the proposed specification of 3.2.P.5.1.

Table 19: Stability protocol of plecanatide 3 mg tablet in alternate dosing vehicle

Dosing preparation, at USP room temperature	T ₀	10 min	15 min	30 min
Mott's Natural Applesauce	X	X	X	X
Musselman's Unsweetened Applesauce	X	X	X	X
Water solution (same concentration used for drinking and NG tube)	X	X	X	X

min = minutes; NG = nasogastric; X = assay and degradation products.

The mean assay stability results are presented in Table 20 below.

Table 20: Stability of plecanatide 3 mg tablet

Dosing preparation, at USP room temperature	T ₀	10 min.	15 min.	30 min. (b) (4)
Mott's Natural Applesauce 3 mg tablet 6 mg tablet				
Musselman's Unsweetened Applesauce 3 mg tablet 6 mg tablet				
Water solution 3 mg tablet 6 mg tablet				

The results presented in Table 20 confirm that Plecanatide Tablets, 3 mg, prepared according to the alternative dosing procedures included in the proposed medication guide, meet the proposed drug product specifications (3.2.P.5.1) for assay.

The results of in-use-study of crushed Plecanatide on applesauce are acceptable, and support the medication guide instructions that Plecanatide Tablets should be administered "right away" once prepared in any of the listed alternative dosing vehicles. The proposed alternative dosing instructions state that administration of the prepared dose occurs immediately following preparation of the dosing material (water or applesauce).

Reviewer's Assessment:

The Applicant's conclusion is acceptable

List of Deficiencies:

N/A



Primary Biopharmaceutics Reviewer Name and Date: Kalpana Paudel, Ph.D. 09/26/2016

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

I concur. 09/27/16

Tien-Mien Chen, Ph.D.

DB/ONDP/OPQ



Tien Mien
Chen

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Rankin g	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
Assay	Formulation, Raw materials, Process Parameters, Scale/equipmen t	L	<p>Assay is determined by a validated HPLC method.</p> <p>Critical manufacturing process steps were identified and controlled.</p> <p>The long term and accelerated stability studies show that the assay is consistent during the time tested.</p>	<p>The dose strength of the drug product is expected to be within the specification for oral administration during the entire shelf life from product quality perspective.</p> <p>None</p>	None
Impurities	Raw materials, process parameters,	M	<p>The related substances/ impurities are fully characterized and controlled by DS specification and DP specification. The test results during the stability studies are within the specification. The impurities are assessed by validated HPLC methods.</p>	<p>The degradation/impurities of the drug product are expected to be controlled and the drug product is safe for oral administration during the entire shelf life from product quality perspective.</p> <p>Low</p>	None
Water Content	(b) (4)				

			(b) (4)		
Dissolution	Formulation, raw materials, process parameters	L	No significant changes were observed in the dissolution results during the long term and accelerated stability studies.	None	None

ATTACHMENT II: List of Deficiencies for Complete Response

A. Labeling Deficiencies

1. PI

#16 How Supplied/Storage and Handling

- “Do not remove the desiccant packet from the bottle” should be added

#17 Patient counseling information

- Manufacturer information [e.g., name and location of business (street address, city, state and zip code)] is required in labeling and should be located after section 17 patient counseling information

- B. Process/Facility:** There has *not* been an “Approval” recommendation from the Office of Process and Facility

ATTACHMENT III: Analytical Method Validation Report



DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

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Division of Pharmaceutical Analysis
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Date: July 5, 2016

To: Zhengfang Ge, Method Verification Requestor
Danuta Gromek-Wood, Method Verification Requestor
Truong Quach, Method Verification Project Manager
Moo Jhong Rhee, ONDP

Through: Michael Trehy, Ph.D., Lab Chief, Branch II, CDER/OPQ/OTR/DPA, CDER/OPQ/OTR/DPA

From: Janie D. Dunn, Ph.D., Kui Zeng, Ph.D., Chemist, CDER/OPQ/OTR/DPA

Subject: Method Verification for NDA 208745: Plecanatide Tablets, 3 mg and 6 mg

Michael L. Trehy - S

Digitally signed by Michael L. Trehy - S
DN: c=US, o=U.S. Government, ou=FDA, ou=OPQ, ou=OTR, ou=Branch II, cn=Michael L. Trehy - S
Date: 2016.07.20 11:47:49 -0500

The methods underwent a paper-based review by an expert in the area of HPLC, UPLC, and HPLC-MS/MS. Analytical testing was not performed.

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

- 3.2.P.5.2. Analytical Procedures, Determination of Plecanatide Related Substances in Plecanatide Tablets by UPLC
- 3.2.P.5.2. Analytical Procedures, Plecanatide Placebo, 0.3 mg, 1 mg, 3 mg, 6 mg, and 9 mg Tablets: Identification by LC/MS/MS

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to this ID method.

- 3.2.P.5.2. Analytical Procedures, Plecanatide Placebo, 0.3 mg, 1 mg, 3 mg, 6 mg, and 9 mg Tablets: Identification by LC/MS/MS

(b) (4)

OVERALL ASSESSMENT AND SIGNATURES:

From the the quality perspective this NDA is not deemed ready for approval at this time in its present form per 21 CFR 314.125(b)(6) and 21 CFR 314.125(b)(13).

Application Technical Lead Name and Date:

Hitesh Shroff
Division of New Drug Products II, Branch V

1 Document History

Document History		
Author: Integrated Quality Assessment Team, and Don Henry.		
<p>Clearance Statement: This document is sponsored by the Integrated Quality Assessment Team.</p> <p>Jorge Rondon (OPRO/OE), Don Henry (OPRP/OE), and the Integrated Quality Assessment Team have cleared this template for use.</p>	<p>This process (CDER OPQ Integrated Quality Assessment Template) will be reviewed at the following intervals and changes to the work aid will be captured as needed:</p> <p>This process will be reviewed approximately 150 days from date issued (February 18, 2016).</p>	
Version	Summary of Changes Issued	Date
03	Content update	02/18/2016



Hitesh
Shroff

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