

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211281Orig1s000

PRODUCT QUALITY REVIEW(S)



QUALITY ASSESSMENT



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

NDA 211281

OPQ Review #1

Drug Name/Dosage Form	Pizensy (lactitol) for oral solution
Strength	10 g per unit-dose (b) (4) 280 g, 560 g
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Braintree Laboratories, Inc.; Braintree, MA
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	June 29, 2018	OPQ
Amendment	November 21, 2018	OPQ
Amendment	February 22, 2019	ONDP
Amendment	March 28, 2019	ONDP
Amendment	May 2, 2019	ONDP
Amendment	May 15, 2019	ONDP
Amendment	June 4, 2019	ONDP
Amendment	August 7, 2019	ONDP
Amendment	September 9, 2019	ONDP

Quality Review Team

DISCIPLINE	REVIEWER	Secondary Assessment
Drug Substance	Friedrich Burnett	Donna Christner
Drug Product and Labeling	Zhengfang Ge	Moo-Jhong Rhee
Process	Sydney Choi	Nallaperumal Chidambaram
Microbiology	Sydney Choi	Nallaperumal Chidambaram
Facilities	Sydney Choi	Nallaperumal Chidambaram
Regulatory Business Process Manager	Oumou Barry	N/A
Application Technical Lead	Hitesh Shroff	N/A
Environmental Analysis (EA)	Zhengfang Ge	Moo-Jhong Rhee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Active	Reviewed by Dr. Friedrich Burnett on July 23, 2019, and deemed adequate	LOA: February 21, 2017
	Type II		Active	Reviewed by Dr. Friedrich Burnett on July 13, 2019, and deemed adequate	LOA: September 7, 2017	
	Type III		Active	Not reviewed, Information provided in NDA	LOA February 2, 2017	
	Type III		Active	Not reviewed, Information provided in NDA	LOA January 31, 2017	
	Type III		Active	Not reviewed, Information provided in NDA	LOA March 10, 2017	
	Type III		Active	Not reviewed, Information provided in NDA	LOA January 31, 2017	
	Type III		Active	Not reviewed, Information provided in NDA	LOA February 2, 2017	
	Type III		Active	Not reviewed, Information provided in NDA	LOA April 20, 2017	
	Type III		Active	Not reviewed, Information provided in NDA	LOA February 9, 2017	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	118906	From the same applicant and for the same indication
NDA	19011	GoLyteLy



QUALITY ASSESSMENT



NDA	19797	NuLytely
NDA	202811	Linzess
NDA	208745	Trulance

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 adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product, Pizensy (lactitol), for oral solution.

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

The Office of Process and Facilities (OPF) has made a final overall “Approval” recommendation for the facilities involved in this application.

The label/labeling issues have been satisfactorily resolved from the CMC perspective.

Therefore, from the OPQ perspective, this NDA is recommended for **Approval**.

II. Summary of Quality Assessments

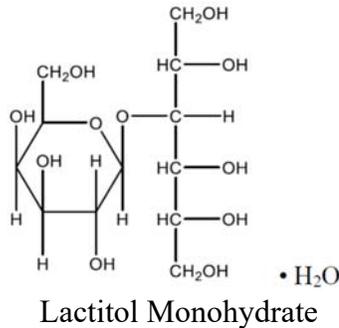
A. Product Overview

Lactitol for oral solution is a simple monosaccharide sugar alcohol and a synthetic derivative of lactose. The drug product is supplied as a powder without any excipients. The drug product does not contain any preservatives or anti-oxidants.

Proposed Indication(s) including Intended Patient Population	Lactitol for oral solution is an osmotic laxative indicated for the treatment of chronic idiopathic constipation (CIC) in adults
Duration of Treatment	As needed
Maximum Daily Dose	(b) (4)
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Lactitol monohydrate is the drug substance in the drug product. Lactitol monohydrate is a synthetic monosaccharide sugar derivative of lactose. It is a white to off-white crystalline powder. It is highly soluble in water, but poorly absorbed BCS Class III compound. It is sparingly soluble in alcohol. No polymorphs of lactitol monohydrate are identified. It is a chiral compound containing 9 chiral centers with optical rotation of +13.5° to +15.5°. Its molecular formula is $C_{12}H_{24}O_{11} \cdot H_2O$ and its molecular weight is 362.33.



Manufacturing: Lactitol monohydrate is manufactured by (b) (4) (DMF (b) (4)) and by (b) (4) (DMF (b) (4)). The complete CMC information regarding raw materials, manufacturing process, (b) (4) characterization, stability, storage and container closure is provided in their DMFs. The Letters of Authorization were also submitted by lactitol monohydrate manufactures.

The identity, purity and quality of lactitol monohydrate are controlled by the specification, which includes description by visual examination, identification by comparison of IR spectrum with a USP standard, assay, related compounds, optical rotation, (b) (4) content and microbial limits.

The batch analyses data of the drug substance utilized in the Phase III clinical studies and also stability studies were provided showing they were within the specification. A retest period of (b) (4) months was proposed and granted when stored in (b) (4). The drug substance DMF (b) (4) and DMF (b) (4) were reviewed by Dr. Friedrich Burnett and deemed adequate from the CMC perspective. (See **the Drug Substance** review)

The drug substance, lactitol monohydrate, manufactured by (b) (4) and by (b) (4) is adequately controlled to conform to the requirements (specification) to produce the drug product, Pizensy (lactitol) for oral solution.

Drug Product:

The drug product, Pizensy (lactitol) for oral solution, is supplied as lactitol powder in 10 g single-dose (b) (4) 280 g multi-dose HDPE bottle and 560 g multi-dose HDPE

bottle. 10 g of lactitol is equivalent to 10.5 g of lactitol monohydrate. There are no preservatives or anti-oxidants in the drug product. The cap of the multi-dose bottle is used to measure 10 g of lactitol. The drug product is dissolved in 4 oz to 8 oz of water, juice or beverage (coffee, tea, soda, etc.) for oral administration.

The drug product specification includes description by visual method, identification by comparison of IR spectrum with a USP standard, (b) (4), assay, impurities and degradants. The in-house, non-compendial methods for assay, (b) (4) and impurities and degradants are validated.

The applicant has performed stability testing on multiple batches of the drug product packaged in (b) (4) 14 oz bottle and 26 oz bottle manufactured using the drug substance manufactured from both (b) (4). Based on the satisfactory stability data of long-term stability at 25°C and accelerated stability at 40°C, the proposed 24-month of expiration dating period is granted when packaged in the proposed container closure system at 25°C per drug product reviewer, Dr. Zhengfang Ge (see the **Drug Product** review).

Manufacturing:

The drug product is manufactured by Braintree Laboratories, Inc.; MA. As lactitol monohydrate is the only ingredient in the drug product, the drug product manufacturing process includes (b) (4)

(b) (4) assessed and controlled. The master batch record indicated that the proposed drug product commercial production batch size is (b) (4) kg. The drug product manufacturing process, in-process controls, drug product release tests and executed batch records were reviewed and deemed satisfactory. The microbial limits tests are performed on each of batch of the bulk drug substance. Therefore, the applicant's proposal for not testing microbial purity of the finished drug product deemed acceptable. (See **Manufacturing Integrated Assessment**)

Facilities:

The Office of Process and Facilities (OPF) has made an "Adequate" recommendation for all drug substance and drug product manufacturing and testing facilities. (See the **Manufacturing Integrated Assessment** review)

Environmental Assessment:

The applicant claims a categorical exclusion from the requirement to prepare an Environmental Assessment statement under 21CFR 25.15(d) and 25.31(b). Under 21 CFR 25.31(b), a categorical exclusion exists for action on an NDA, an abbreviated application or a supplement to such applications where the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. Braintree Laboratories, Inc. also states that to its knowledge no extraordinary circumstances exist, as defined in 21 CFR § 25.21. Lactitol is considered as a GRAS. Braintree Laboratories anticipates that peak distribution of the drug product over the five years following approval will be about (b) (4) kg/yr.

Based on a worst-case estimation where (b) (4) % of ingested lactitol survives to excretion with stool, an expected introduction concentration (EIC) of about (b) (4) ppb can be calculated, well below the 1 ppb limit. As reported in the Purac Biochem b.v. GRAS petition, any lactitol that escapes into the waste stream is rapidly biodegradable as demonstrated by biodegradation testing and no aquatic toxicity was observed. Therefore, claim of a categorical exclusion from the requirements of an environmental assessment (EA) was deemed acceptable. (See the **Drug Product** review)

Labeling:

The proposed label/labeling is satisfactory from the CMC perspective. (See the **Labeling** review).

- C. **Post Approval Commitment:** None
- D. **Lifecycle Management Considerations:** None
- E. **Special Product Quality Labeling Recommendations:** None
- F. **Final Risk Assessment (see Attachment I)**
- G. **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
September 16, 2019

**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: 2019.09.16 12:10:17 -04'00'

LABEL FOR NDA 211281

I. PI

1. Highlights of Prescribing Information



Item	Information Provided in NDA	Reviewer's Assessment
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))		
Proprietary name and established name	(b) (4) (lactitol monohydrate, NF)	Not Adequate (b) (4) is not approved per DMEPA Established name should be (lactitol) for oral solution.
Dosage form, route of administration	Powder for Oral Solution	Not Adequate Dosage form and administration route should be: for oral solution

		Name and dosage form should be expressed as: Tradename (lactitol, NF) for oral solution
Controlled drug substance symbol (if applicable)	N/A	
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))		
Summary of the dosage form and strength	(b) (4) is a white to off-white crystalline powder for oral solution, (b) (4) (b) (4)	Not Adequate (b) (4) The strength should be provided in terms of lactitol instead of lactitol monohydrate

This section is not adequate.

- Name and dosage form should be displayed in the title as:

TRADENAME (lactitol) for oral solution

- The dosage form and strength should be displayed as:

-
-
-

(b) (4)

Section 2 Dosage and Administration

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))		
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	<ul style="list-style-type: none"> The multi dose bottles are equipped with a cap (b) (4) The unit dose (b) (4) contain 10.5 grams of (b) (4) each. (b) (4) 	<p>Not Adequate</p> <p>The drug product strength should be provided in lactitol 10 g</p>

This section is not adequate.

- Change “the recommended dose of (b) (4) is 21 g orally once daily ...” to “the recommended dose of Tradename is 20 g (equivalent to 21 g of lactitol monohydrate) orally once daily ...”
- Change “reduce the dosage to 10.5 g...” to “reduce the dosage to 10 g...”
- Change “The unit dose (b) (4) contain 10.5 g ...” to “The unit dose packets contain 10 g ...”

3. Section 3 Dosage Forms and Strengths

(b) (4) is a white to off-white crystalline powder supplied as:

- 294 grams of lactitol in multi-dose bottles
- 588 grams of lactitol in multi-dose bottles
- 10.5 grams of lactitol in unit-dose (b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))		
Available dosage forms	For Oral Solution	Adequate
Strengths: in metric system	<ul style="list-style-type: none"> • 294 grams of lactitol in multi-dose bottles • 588 grams of lactitol in multi-dose bottles • 10.5 grams of lactitol in unit-dose (b) (4) 	<p>Per OPQ labeling committee decision, strength should be changed to:</p> <p>Unit (b) (4) 10 g Bottles: 279 g (for 14 oz bottle), 559 g (for 26 oz bottle)</p>
Active moiety expression of strength with equivalence statement (if applicable)	N/A	<p>Adequate</p> <p>The active ingredient is in the form of lactitol monohydrate. The salt equivalence statement does not apply.</p>
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	white to off white crystalline powder	Adequate

This section is not adequate.

- **The lactitol quantities should be displayed as 279 g, 559 g, and 10 g in the 14 oz, 26 oz bottles, and (b) (4) respectively.**

1. Section 11 Description

Lactitol is an osmotic laxative for oral use;

(b) (4)

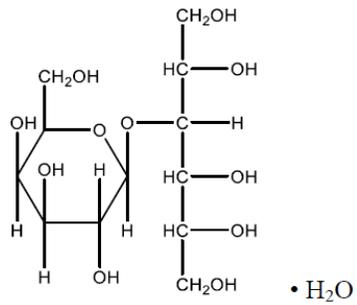
(b) (4)

Lactitol is a simple monosaccharide sugar alcohol

(b) (4)

(b) (4) It is a dry, free flowing powder, readily soluble in aqueous solutions. As shown by the structure diagrams, it is an analog of the disaccharide lactulose.

Lactitol



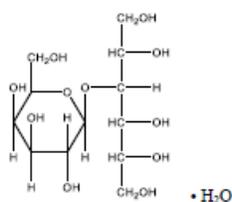
ABLEEZE (lactitol for oral solution) is available in unit dose (b) (4) or multi-dose bottles. There are no inactive ingredients.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))		
Proprietary name and established name	(b) (4) (lactitol for oral solution)	Not Adequate The proposed tradename (b) (4) is not acceptable per DMEPA. “for oral solution” should be moved outside of parenthesis
Dosage form and route of administration	For oral solution	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	N/A	Not Adequate (b) (4)
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	No inactive in the drug product	Adequate
Statement of being sterile (if applicable)	N/A	Adequate
Pharmacological/ therapeutic class	osmotic laxative	Adequate
Chemical name, structural formula, molecular weight	Not provided	Not Adequate Add “Its chemical name is 4-O-β-d-Galactopyranosyl-d-glucitol lactitol. It is supplied as lactitol monohydrate with molecular formula C₁₂H₂₄O₁₁ · H₂O and molecular weight 362.34”

If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	dry, free flowing powder, readily soluble in aqueous solutions	Adequate

This section is not adequate. The following revision should be made:

- “for oral solution” should be moved out of the parenthesis for the established name
- Add “Its chemical name is 4-*O*-β-d-Galactopyranosyl-d-glucitol lactitol. It is supplied as lactitol monohydrate. 10 g lactitol is equivalent to 10.5 g lactitol monohydrate with the following molecular structure ...



Molecular Formula $C_{12}H_{24}O_{11} \cdot H_2O$

Molecular Weight 362.34

2. Section 16 How Supplied/Storage and Handling

16 HOW SUPPLIED/STORAGE AND HANDLING

(b) (4) is supplied in a white to off-white crystalline powder, for oral administration following reconstitution. (b) (4) is available in three sizes:

- (b) (4) multi-dose bottle of 294 grams lactitol (NDC 52268-600-01)
- (b) (4) multi-dose bottle of 588 grams lactitol (NDC 52268-600-02)
- Carton of 28 (b) (4) packets containing 10.5 grams lactitol each (NDC 52268-600-03)

The cap on each bottle is marked (b) (4) and may be used to measure the appropriate (b) (4) dose. Each bottle contains a white desiccant packet printed “Do Not Eat.”

Storage:

Store at 20°C to 25°C (68° to 77°F). Excursions permitted between 15° to 30°C (59° to 86°F). See USP controlled room temperature.

Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))		
Strength of dosage form	Not provided	Not Adequate strengths should be changed to 279 g, 559 g and 10 g (b) (4) and unit (b) (4) respectively.
Available units (e.g., bottles of 100 tablets)	(b) (4) and carton of 28 packets	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	White to off white crystalline powder, for oral administration following reconstitution	Adequate
Special handling (e.g., Dispense in tight and light resistant container as defined in USP)	The cap on each bottle is marked (b) (4) and may be used to measure the appropriate (b) (4) dose. Each bottle contains a white desiccant packet printed "Do Not Eat."	Adequate 10.5 g marked on each measuring line inside of the cap reflects the actual weight of API lactitol monohydrate
Storage conditions	Store at 20°C to 25°C (68° to 77°F). Excursions permitted between 15° to 30°C (59° to 86°F). See USP controlled room temperature.	Adequate
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Not provided	Not Adequate

This section is not adequate. The following revision should be made:

- **Dose strengths should be changed to 279 g, 559 g, and 10 g (b) (4) (b) (4) and unit packet, respectively**
- **Add Manufacturer/distributor name**

II. Labels:

1. Immediate Container Label

Labels for (b) (4) bottles are the same except net weight. The bottle label for the (b) (4) and (b) (4) label are provided below

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	(b) (4)	<p>Not Adequate</p> <p>lactitol is the established name and should be in parenthesis. Dosage form should be provided</p> <p>The name and dosage form should be displayed as: (b) (4) (lactitol, NF) for oral solution</p>
Dosage strength Active moiety expression of strength with equivalence statement (if applicable), if space is available	Only net weight is provided	<p>Not Adequate</p> <p>Strength should be shown as:</p> <p>(b) (4)</p> <p>Add "10 g lactitol is equivalent to 10.5 g lactitol monohydrate" on the side panel</p>
Net contents	294 g and 588 g for bottles 10.5 g for (b) (4)	<p>Not Adequate</p> <p>(b) (4)</p> <p>(b) (4) and 10.5 g for the packet are the net quantity of the drug products should be moved away from the title (e.g. move to the bottom of the front panel).</p>
"Rx only" displayed prominently on the main panel	Provided	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Provided	Adequate
Lot number and expiration date (21 CFR 201.17)	Provided on the bottle, but not on the (b) (4)	<p>Not Adequate</p> <p>Provide lot number and expiration date on the (b) (4)</p>

<p>Storage conditions Special handling, e.g., “Dispense in tight and light resistant container as defined in USP”.</p>	<p>(b) (4)</p>	<p>Not Adequate</p> <p>Change store at room temperature to Store at 20°C to 25°C (68° to 77°F). Excursions permitted between 15° to 30°C (59° to 86°F). See USP controlled room temperature</p> <p>At the end of steps 1 and 2, add (b) (4)</p>
<p>Bar code (21CFR 201.25)</p>	<p>Bar code is provided on the bottles No bar code provided on the (b) (4)</p>	<p>Not Adequate</p> <p>Add bar code on (b) (4)</p>
<p>Name of manufacturer/distributor</p>	<p>Provided</p>	<p>Adequate</p>
<p>And others, if space is available</p>	<p>direction of use is provided</p>	<p>Not Adequate</p> <p>The direction of use on the bottle uses (b) (4)</p> <p>(b) (4) The DMEPA has been informed of this issue and will request the applicant to make appropriate changes to avoid over dosing</p>

This section is not adequate. The following revision should be made:

- 1) The format of the drug product name, dosage form and strength should be presented as follows:**

(b) (4)

Tradename

(lactitol, NF) for oral solution

10 g per packet

Side panel: 10 g lactitol is equivalent to 10.5 g lactitol monohydrate

(b) (4)

Tradename

(lactitol, NF) for oral solution

279 g

Side panel: 279 g lactitol is equivalent to 294 g lactitol monohydrate

(b) (4)

Tradename

(lactitol, NF) for oral solution

559 g

Side panel: 559 g lactitol is equivalent to 588 g lactitol monohydrate

- 2) **At the end of steps 1 and 2 of the direction on the side panel of the bottle, add** (b) (4)
- 3) **Provide lot number and expiration date on** (b) (4)
- 4) **Display the storage condition as: Store at 20°C to 25°C (68° to 77°F). Excursions permitted between 15° to 30°C (59° to 86°F). See USP controlled room temperature**
- 5) **Add bar code on** (b) (4)

2. Carton Label

Carton is proposed for the carton of 28 (b) (4) not for the bottle

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	(b) (4)	<p>Not Adequate</p> <p>The name, dosage form and strength should be displayed as:</p> <p>Tradename (lactitol, NF) for oral solution 10 g per packet</p>
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	Not provided	<p>Not Adequate</p> <ul style="list-style-type: none"> (b) (4)
Net quantity of dosage form	This carton contains 28 (b) (4) packets	Adequate
"Rx only" displayed prominently on the main panel	Provided	Adequate
Lot number and expiration date	Not Provided	<p>Not Adequate</p> <ul style="list-style-type: none"> Provide lot number and expiration date
Storage conditions Special handling, e.g., "Dispense in tight and light resistant container as defined in USP".	<p>Keep the medication out of the reach of children.</p> <p>(b) (4)</p>	<p>Not Adequate</p> <ul style="list-style-type: none"> (b) (4) <p>Store at 20°C to 25°C (68° to 77°F). Excursions permitted between 15° to 30°C (59° to 86°F). See USP controlled room temperature</p>
Bar code (21CFR 201.25)	Provided	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Provided	Adequate
Manufacturer/distributor's name	Provided	Adequate
Quantitative ingredient information (injectables)	N/A	
Statement of being sterile (if applicable)	N/A	
"See package insert for dosage information"	Not provided	<p>Not Adequate</p> <ul style="list-style-type: none"> Add "See package insert for dosage information"

"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Provided	Adequate
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This section is not adequate. The following revision should be made:

- 1) The format of the drug product title should be presented in the (b) (4) carton label as follows:

**Tradename (lactitol, NF) for oral solution
10 g per packet**

- 2) Add "10 g lactitol is equivalent to 10.5 g lactitol monohydrate" on the side panel of the (b) (4) carton label
- 3) Provide lot number and expiration date on the carton label for the packet box
- 4) Display the storage condition on the immediate container as: Store at 20°C to 25°C (68° to 77°F). Excursions permitted between 15° to 30°C (59° to 86°F). See USP controlled room temperature
- 5) Add "See package insert for dosage information" on the (b) (4) carton

List of Deficiencies:

A. Regarding PI

I. Highlights of Prescribing Information

- Name and dosage form should be displayed in the highlight title as:

TRADENAME (lactitol) for oral solution

- The dosage form and strength should be displayed as:
 - (b) (4) bottle containing (b) (4) grams of lactitol
 - (b) (4) bottle containing (b) (4) grams of lactitol
 - 28 packets per box containing 10 grams of lactitol each packet

II. Full Prescribing Information

For Section 2, "Dosage and Administration"

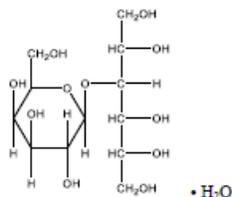
- Change “the recommended dose of (b) (4) is 21 g orally once daily ...” to “the recommended dose of Tradename is 20 g (equivalent to 21 g of lactitol monohydrate) orally once daily ...”
- Change “reduce the dosage to 10.5 g...” to “reduce the dosage to 10 g...”
- Change “The unit dose (b) (4) contain 10.5 g ...” to “The unit dose packets contain 10 g ...”

For Section 3, “DOSAGE FORMS AND STRENGTHS”

The lactitol quantities should be displayed as 279 g, 559 g and 10 g in the (b) (4) (b) (4) bottles, and unit packet, respectively.

For Section 11, “DESCRIPTION”

- “for oral solution” should be moved out of the parenthesis for the established name
- Add “Its chemical name is 4-*O*-β-d-Galactopyranosyl-d-glucitol lactitol. It is supplied as lactitol monohydrate. 10 g lactitol is equivalent to 10.5 g lactitol monohydrate with the following molecular structure ...”



Molecular Formula $C_{12}H_{24}O_{11} \cdot H_2O$

Molecular Weight 362.34

For Section 16, “HOW SUPPLIED/STORAGE AND HANDLING”

- Dose strengths should be changed to 279 g, 559 g and 10 g for (b) (4) (b) (4) bottle, and unit packet, respectively.
- Add Manufacturer/distributor name

B. Regarding Container/Carton Labels:

For Container Labels:

- 1) The format of the drug product name, dosage form and strength should be presented as follows:

(b) (4)

Tradename
(lactitol, NF) for oral solution
10 g per packet

Side panel: 10 g lactitol is equivalent to 10.5 g lactitol monohydrate

(b) (4) :

Tradename
(lactitol, NF) for oral solution
279 g

Side panel: 279 g lactitol is equivalent to 294 g lactitol monohydrate

(b) (4) :

Tradename
(lactitol, NF) for oral solution
559 g

Side panel: 559 g lactitol is equivalent to 588 g lactitol monohydrate

- 2) At the end of “Step 2” of the direction on the side panel of the bottle, add “
”
- 3) Display the storage condition as: Store at 20°C to 25°C (68° to 77°F). Excursions permitted between 15° to 30°C (59° to 86°F). See USP controlled room temperature
- 4) Provide lot number and expiration date on (b) (4)
- 5) Add bar code on (b) (4)

For (b) (4) Carton Labels:

- 1) **The format of the drug product title should be presented as follows:**

**Tradename (lactitol, NF) for oral solution
10 g per packet**

**Side panel: 10 g lactitol is equivalent to 10.5 g lactitol
monohydrate**

- 2) **Provide lot number and expiration date**
- 3) **Display the storage condition as: Store at 20°C to 25°C (68° to 77°F).
Excursions permitted between 15° to 30°C (59° to 86°F). See USP
controlled room temperature**
- 4) **Add “See package insert for dosage information”**

Overall Assessment and Recommendation:

The labeling and labels are **not** deemed ready for approval in its present form per 21 CFR 314.125 (b)(6) from the CMC labeling perspective until the deficiencies are satisfactorily resolved.

Primary Labeling Reviewer Name and Date:

Zhengfang Ge, Ph. D.

*Reviewer, BRANCH V/DIVISION II
OFFICE OF NEW DRUG PRODUCT*

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

I agree with Dr. Ge’s assessment on the labeling/labels, and concur with her recommendation that this NDA is not ready for approval in its present form until the outstanding issues are satisfactorily resolved.

Moo-Jhong Rhee, Ph. D.

*Branch Chief, BRANCH V/DIVISION II
OFFICE OF NEW DRUG PRODUCT*



Zhengfang
Ge

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Moo Jhong
Rhee

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Memorandum

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

Date: July 18, 2019

From: Zhengfang Ge, Ph.D.
ONDP/Division II/Branch V

Through: Moo-Jhong Rhee, Ph.D.
Chief, ONDP/Division II/Branch V

To: Labeling Review #1 of NDA 211281: Tradename (lactitol, NF) for oral solution

Subject: Labeling Deficiencies

In labeling review #1, it was concluded that the strength of the drug product should be expressed in terms of lactitol with an equivalence statement of “10 g lactitol is equivalent to 10.5 g lactitol monohydrate” from a strict scientific perspective since the drug product contains only active ingredient lactitol monohydrate.

Concerning about a potential restrict of generic products, the labeling committee recommends using lactitol only in the labeling without indicating the active ingredient of various hydrate forms of lactitol (anhydrous, monohydrate, or dihydrate), see the attached email from Mr. J. Abdus-Samad in OPPQ dated 18-July-2019. Based on the recommendation, the strength of the drug product will be expressed in terms of lactitol without a quantitative equivalence statement to lactitol monohydrate. The molecular structure and molecular weight of lactitol instead of lactitol monohydrate will be provided in section 11 of PI. The deficiencies listed in labeling review #1 are revised as below:

List of Deficiencies in Labeling Review #1:

A. Regarding PI

I. Highlights of Prescribing Information

- Name and dosage form should be displayed in the highlight title as:

TRADENAME (lactitol, NF) for oral solution

- The dosage form and strength should be displayed as:

For oral solution:

- 279 grams of lactitol in multi-dose bottles
- 559 grams of lactitol in multi-dose bottles
- 10 grams of lactitol in unit-dose (b) (4)

II. Full Prescribing Information

For Section 2, “Dosage and Administration”

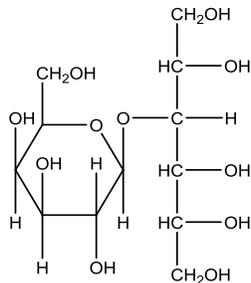
- Change “the recommended dose of Tradename is 21 g orally once daily ...” to “the recommended dose of Tradename is 20 g orally once daily ...”
- Change “reduce the dosage to 10.5 g...” to “reduce the dosage to 10 g...”

For Section 3, “DOSAGE FORMS AND STRENGTHS”

The lactitol strengths should be displayed as 279 g, 559 g and 10 g respectively.

For Section 11, “DESCRIPTION”

- “for oral solution” should be moved out of the parenthesis for the established name
- Add chemical name 4-*O*-β-d-Galactopyranosyl-d-glucitol lactitol.
- Remove equivalence statement “10 g lactitol is equivalent to 10.5 g lactitol monohydrate”
- Display molecular structure for lactitol instead of lactitol monohydrate as below



Molecular Formula C₁₂H₂₄O₁₁

Molecular Weight 344.31

For Section 16, “HOW SUPPLIED/STORAGE AND HANDLING”

- Dose strengths should be changed to 279 g, 559 g and 10 g respectively.
- Add Manufacturer/distributor name

B. Regarding Container/Carton Labels:

For Container Labels:

- 1) The format of the drug product name, dosage form and strength should be presented as follows:

(b) (4)

Tradename
(lactitol, NF) for oral solution
10 g per unit-dose (b) (4)

(b) (4)

Tradename
(lactitol, NF) for oral solution
279 g

(b) (4) :

Tradename
(lactitol, NF) for oral solution
559 g

- 2) **Display the storage condition as: Store at 20°C to 25°C (68° to 77°F). Excursions permitted between 15° to 30°C (59° to 86°F). See USP controlled room temperature**
- 3) **Provide lot number and expiration date on (b) (4)**
- 4) **Add bar code on (b) (4)**

For (b) (4) Carton Labels:

- 1) **The format of the drug product title should be presented as follows:**

Tradename (lactitol, NF) for oral solution
10 g per unit-dose (b) (4)

- 2) **Provide lot number and expiration date**
- 3) **Display the storage condition as: Store at 20°C to 25°C (68° to 77°F). Excursions permitted between 15° to 30°C (59° to 86°F). See USP controlled room temperature**
- 4) **Add “See package insert for dosage information”**

Regarding Measuring Cap of the bottle containers:

Change the “10.5 g” on the measuring cap to “10 g”

Recommendation:

The labeling and labels are **not** ready for approval in its present form per 21 CFR 314.125 (b)(6) from the CMC labeling perspective until the above deficiencies are satisfactorily resolved.

Attachment:

From: [Abdus-Samad, Jibril](#)
To: [Ge, Zhengfang](#)
Cc: [Shroff, Hitesh](#); [Rhee, Moo Jhong](#); [Meyer, Joette M](#)
Subject: RE: Strength of lactitol powder, NDA 211281
Date: Thursday, July 18, 2019 1:02:59 PM
Attachments: [image012.png](#)

Hi Zhengfang,

Thank you for contacting the PQL Mailbox. Here is our response. Feel free to call me if any questions.

-

NF and USP monograph Labeling Requirements

Lactitol has NF excipient monograph, but no USP drug substance, and no USP drug product monograph.

The NF excipient monograph for Lactitol has a labeling statement requirement to indicate whether it is the monohydrate, the dihydrate, or the anhydrous form. The label on the Lactitol excipient container must comply. If this Lactitol for Oral Solution product is approved..., we then expect the NF excipient monograph to transfer to a USP drug substance monograph, in which case the labeling requirements would transfer as well. However, the labeling requirements for an NF excipient monograph, as well as a USP drug substance monograph do not carry over to the USP drug product monograph.

While there is inconsistency in existing USP monographs with regard to labeling the hydration state, we anticipate that the drug product monograph will have a statement such as “**DEFINITION:** Lactitol contains NLT x % and NMT y % of Lactitol (C₁₂H₂₄O₁₁).”

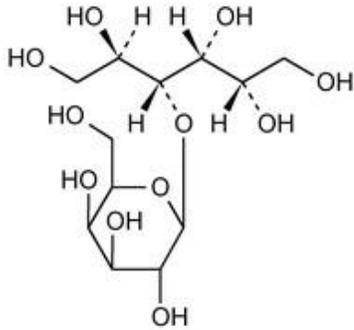
ANDA Perspective

- Including the lactitol monohydrate information may restrict a potential generic to this proposed product to using only lactitol monohydrate when it is possible to meet the requirements of a Lactitol drug product by using the various forms of Lactitol (anhydrous, monohydrate, or dihydrate).
- It may be helpful to clearly mention the hydration state in the RLD application submission in the Description and Composition. David Claffey and I participated in an OGD-led Work Group regarding excipients that looked at some issues similar to this one. The WG decision was to comply with the USP requirement to label all ingredients based on the USP established name (e.g. Lactitol) as required per FDCA and include the hydration information in the RLD application submission in the Description and Composition. Although the WG dealt mainly with excipients and this Lactitol issue is for an active ingredient, the same rules apply regarding naming and labeling requirements.

Recommendation

OPPQ recommends not including the hydration state in the Lactitol for Oral Solution drug product label and labeling unless the labeling clearly indicates that the hydration state is clinically important. (For more information about hydrate forms see the Regulatory Classification of Pharmaceutical Co-Crystals: Guidance for Industry.) The requirement is to label based on the established name of the drug substance, Lactitol, and express the strength as the anhydrous form. Additionally, including this hydration state in the drug product labeling (e.g. 10 g lactitol is equivalent to 10.5 g lactitol monohydrate) may lead to confusion regarding the salt policy, similar to what has occurred in this email chain. Therefore, we also advise against including the equivalency information in the labeling.

Lactitol



[CLICK IMAGE TO ENLARGE](#)

$C_{12}H_{24}O_{11}$ 344.31
 $C_{12}H_{24}O_{11} \cdot H_2O$ 362.34
 $C_{12}H_{24}O_{11} \cdot 2H_2O$ 380.35
4-O- β -D-Galactopyranosyl-D-glucitol [585-86-4].
Monohydrate [81025-04-9].
Dihydrate [81025-03-8].

DEFINITION

Lactitol contains NLT 98.0% and NMT 101.0% of $C_{12}H_{24}O_{11}$, calculated on the anhydrous basis.

Respectfully,
Jibril

LCDR Jibril Abdus-Samad, PharmD
Policy Lead
FDA/CDER/OPQ/OPPQ/DRGS/Compendial Operations and Standards Branch
301-796-2196



Zhengfang
Ge

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Moo Jhong
Rhee

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Memorandum

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

Date: Aug 9, 2019

From: Zhengfang Ge, Ph.D.
ONDP/Division II/Branch V

Through: Moo-Jhong Rhee, Ph.D.
Chief, ONDP/Division II/Branch V

To: Labeling Review of NDA 211281: Tradename (lactitol) for oral solution

Subject: Final Recommendation for Labeling/Labels

The labeling review #1 has noted the following issues:

A. Regarding PI

I. Highlights of Prescribing Information

- Name and dosage form should be displayed in the highlight title as:

TRADENAME (lactitol) for oral solution

- The dosage form and strength should be displayed as:

For oral solution:

- 279 grams of lactitol in multi-dose bottles
- 559 grams of lactitol in multi-dose bottles
- 10 grams of lactitol in unit-dose (b) (4)

II. Full Prescribing Information

For Section 2, “Dosage and Administration”

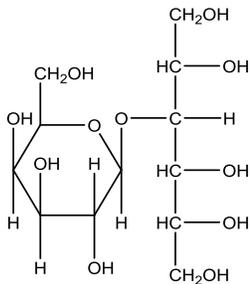
- Change “the recommended dose of Tradename is 21 g orally once daily ...” to “the recommended dose of Tradename is 20 g orally once daily ...”
- Change “reduce the dosage to 10.5 g...” to “reduce the dosage to 10 g...”

For Section 3, “DOSAGE FORMS AND STRENGTHS”

The lactitol strengths should be displayed as 279 g, 559 g and 10 g respectively.

For Section 11, “DESCRIPTION”

- “for oral solution” should be moved out of the parenthesis for the established name
- Add chemical name 4-*O*-β-d-Galactopyranosyl-d-glucitol lactitol.
- Remove equivalence statement “10 g lactitol is equivalent to 10.5 g lactitol monohydrate”
- Display molecular structure for lactitol instead of lactitol monohydrate as below



Molecular Formula C₁₂H₂₄O₁₁

Molecular Weight 344.31

For Section 16, “HOW SUPPLIED/STORAGE AND HANDLING”

- Dose strengths should be changed to 279 g, 559 g and 10 g respectively.
- Add Manufacturer/distributor name

B. Regarding Container/Carton Labels:

For Container Labels:

- 1) The format of the drug product name, dosage form and strength should be presented as follows:

(b) (4)

**Tradename
(lactitol) for oral solution
10 g per unit-dose (b) (4)**

(b) (4)

**Tradename
(lactitol) for oral solution
279 g**

(b) (4)

**Tradename
(lactitol) for oral solution
559 g**

- 2) **Display the storage condition as: Store at 20°C to 25°C (68° to 77°F). Excursions permitted between 15° to 30°C (59° to 86°F). See USP controlled room temperature**
- 3) **Provide lot number and expiration date on (b) (4)**
- 4) **Add bar code on (b) (4)**

For (b) (4) Carton Labels:

- 1) **The format of the drug product title should be presented as follows:**

**Tradename (lactitol) for oral solution
10 g per unit-dose (b) (4)**

- 2) **Provide lot number and expiration date**
- 3) **Display the storage condition as: Store at 20°C to 25°C (68° to 77°F). Excursions permitted between 15° to 30°C (59° to 86°F). See USP controlled room temperature**
- 4) **Add “See package insert for dosage information”**

Regarding Measuring Cap of the bottle containers:

Change the “10.5 g” on the measuring cap to “10 g”

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

The above requests have been implemented in the revised labeling. The applicant proposed to round the 279 g and 559 g for 14 oz bottle and 26 oz bottle to 280g and 560 g, respectively, which are deemed acceptable. The revised container/carton labels are satisfactory and provided in the **Attachment**.

Recommendation:

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

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page



Zhengfang
Ge

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Moo Jhong
Rhee

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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment – NDA 211281

a) Drug Product: Lactitol for oral solution, 10 g, 280 g and 560 g

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
Assay	Drug substance, manufacturing process	Low	The purity of the drug substance is controlled by drug substance and drug product release and stability specification.	The assay of the drug product is within the acceptance limits during release and stability testing of multiple batches. None	None
(b) (4)	Manufacturing process	Low	(b) (4) is assessed during the drug product (b) (4) process. In addition, it is also controlled per USP (b) (4) in the drug product specification.	All drug product batches met the proposed (b) (4) specification. None	None
(b) (4)	Drug substance, manufacturing process	Low	The (b) (4) of the drug substance is controlled in drug substance and drug product release and stability specification.	The (b) (4) in the drug product is within the acceptance limits during release and stability testing of multiple batches. None	None