CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211281Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 11, 2020
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 211281
Product Name and Strength:	Pizensy (lactitol) for oral solution, 10 g
Applicant/Sponsor Name:	Braintree Laboratories, Inc (Braintree)
FDA Received Date:	February 7, 2020
OSE RCM #:	2018-1413-5
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader (Acting):	Ashleigh Lowery, Pharm.D., BCCCP

1 PURPOSE OF MEMORANDUM

We reviewed the revised carton labeling and container labels (Appendix A) received on February 7, 2020, for Pizensy (lactitol) for oral solution to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised labels and labeling are acceptable and we have no additional recommendations at this time.

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[a] Abraham, S. Label and Labeling Review for Lactitol (NDA 211281) Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 FEB 5 . RCM No.: 2018-1413-4.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 11, 2020

To: Andrew Kelleher, Regulatory Project Manager, (DGIEP)

Joette Meyer, Associate Director for Labeling, (DGIEP)

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader, OPDP

Subject: OPDP Labeling Comments for PIZENSY (lactitol) for oral solution

NDA: 211281

In response to DGIEP's consult request dated December 7, 2019, OPDP has reviewed the proposed product labeling (PI) for the original NDA submission for Pizensy.

OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DGIEP on February 4, 2020, and are provided below.

Thank you for your consult. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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MEETA N PATEL
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Review

Date:	October 10, 2019
Reviewer:	Michelle Hines, PharmD Division of Pharmacovigilance I (DPV-I)
Team Leader (Acting):	Ann Biehl, PharmD DPV-I
Deputy Division Director:	Monica Muñoz, PharmD, PhD, BCPS DPV-I
Product Name:	Pizensy (lactitol)
Subject:	All adverse events
Application Type/Number:	NDA 211281
Applicant:	Braintree Laboratories Inc.
OSE RCM #:	2019-1849

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1 INTRODUCTION

This review, completed by the Division of Pharmacovigilance I (DPV-I) in response to a consult from the Division of Gastroenterology and Inborn Errors Products (DGIEP), contains an evaluation of the FDA Adverse Event Reporting System (FAERS) database for all adverse events with lactitol through September 22, 2019, and foreign postmarketing safety information with lactitol. This review will inform DGIEP as they determine the acceptability of product labeling submitted for NDA 211281 Pizensy (lactitol monohydrate).

1.1 BACKGROUND AND REGULATORY HISTORY

Lactitol, an osmotic laxative for oral use, is a minimally absorbed, colonically metabolized, synthetic derivative of the milk sugar lactose.[1] Lactitol is a New Chemical Entity as described in 21 CFR 314.108. On September 3, 1985, Importal (lactitol) was registered in Switzerland by Novartis Consumer Health S.A. and was subsequently marketed in other European countries.

On June 29, 2018, the applicant submitted NDA 211281 to FDA to support the approval of lactitol for use in patients with chronic idiopathic constipation (CIC). To support the postmarketing safety experience of lactitol, the applicant submitted the European Medicines Agency (EMA) Final Assessment Report for lactitol, which reviewed the postmarketing experience of lactitol in Europe over the period of October 1, 2009, to September 30, 2012.

On February 1, 2019, DGIEP completed the filing review for NDA 211281 and requested additional postmarketing information related to cardiovascular safety data.[a] On April 2, 2019, in response to the February 1, 2019, filing review, the applicant submitted the Periodic Safety Update Report (PSUR) for lactitol covering the period of October 1, 2012, to September 23, 2015.

On September 4, 2019, DGIEP consulted DPV-I to review the FAERS database for all adverse events with lactitol and foreign postmarketing safety information for lactitol.

On September 5, 2019, DPV-I issued an information request (IR) for complete individual case report (ICR) narratives for reports summarized in the Final Assessment Report (covering the period of October 1, 2009, to September 30, 2012) and PSUR (covering the period of October 1, 2012, to September 23, 2015) for lactitol that the applicant submitted to FDA in support of NDA 211281. On September 13, 2019, the applicant responded to the September 5, 2019, IR and stated that no additional information is available for the events beyond what is contained in the report. The applicant further commented that the gastrointestinal adverse events in the report are consistent with the applicant's phase 3 clinical trials experience, and the unlisted adverse events primarily represent possible hypersensitivity reactions, dosing errors, and cases of lack of efficacy.

[a] DGIEP was particularly interested in cardiovascular safety data to inform their assessment of whether lactitol can affect the QT interval at the intended dose to determine whether the effect of lactitol on QT prolongation can be addressed through labeling or whether a thorough QT/QTc study will be required.

1.2 APPLICANT'S PROPOSED LABELING FOR LACTITOL

The applicant initially submitted proposed labeling for lactitol on February 22, 2019; on August 7, 2019, the applicant updated portions of the proposed labeling, including the format for listing adverse events in *Postmarketing Experience* and the addition of (b) (4) to CONTRAINDICATIONS. Of note, the contraindication for (b) (4) of the proposed labeling.

1.2.1 Applicant's Proposed Labeling for Lactitol from February 22, 2019

The proposed *Postmarketing Experience* section for lactitol from February 22, 2019,[2] is reproduced below.

> **6.2 Postmarketing Experience**
> The following adverse reactions have been identified during post-approval use of lactitol outside the United States. Because these reactions are reported voluntarily, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure.

SOC	Adverse Reaction Term
(b) (4)	

1.2.2 Applicant's Proposed Labeling for Lactitol from August 7, 2019

Portions of the proposed HIGHLIGHTS OF PRESCRIBING INFORMATION section and the complete proposed *Postmarketing Experience* section for lactitol from August 7, 2019,[1] are reproduced below.

> **----------CONTRAINDICATIONS----------**
> PIZENSY is contraindicated in the following conditions:
> - Mechanical gastrointestinal obstruction (4)
> - (b) (4)
> - Galactosemia (4)
>
> (b) (4)

2 METHODS AND MATERIALS

2.1 FAERS DATABASE

DPV-I searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of search	September 23, 2019
Time period of search	All reports through September 22, 2019
Search type	Quick Query
Product Active Ingredients	Lactitol; Lactitol monohydrate
* See **Appendix A** for a description of the FAERS database.	

2.2 FINAL ASSESSMENT REPORT FOR LACTITOL COVERING THE PERIOD OCTOBER 1, 2009, TO SEPTEMBER 30, 2012

DPV-I reviewed the Final Assessment Report[3] for postmarketing adverse events reported with lactitol in Europe; this report was prepared by EMA and summarizes the PSUR for lactitol for the period of October 1, 2009, to September 30, 2012.

[b] The applicant lists 22 events within the table, however the text above the table states that there were 20 serious adverse events reported.

2.3 PSUR FOR LACTITOL COVERING THE PERIOD OCTOBER 1, 2012, TO SEPTEMBER 23, 2015

DPV-I reviewed the PSUR[4] for postmarketing adverse events reported with lactitol; the PSUR was prepared by a sponsor[c] for lactitol in Europe and summarizes the postmarketing safety of lactitol for the period of October 1, 2012, to September 23, 2015.

2.4 CAUSALITY ASSESSMENT

We assessed adverse events in report narratives identified from our search of the FAERS database (described in **Table 1**); the Final Assessment Report for lactitol covering the period October 1, 2009, to September 30, 2012; and the PSUR for lactitol covering the period October 1, 2012, to September 23, 2015; for a causal relationship with lactitol using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) system as shown below in **Table 2**. Reports were excluded from the case series if they were "unlikely" or "unassessable."

Table 2. Causality Classification and Criteria Based on the WHO-UMC System

Causality Term	Assessment Criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon • Rechallenge satisfactory, if necessary
Probable	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanation
Unassessable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

[c] The sponsor for lactitol that prepared the PSUR covering the period October 1, 2012, to September 23, 2015, is different from the sponsor that prepared the PSUR covering the period October 1, 2009, to September 30, 2012.

3 RESULTS

3.1 FAERS DATABASE

Our search of the FAERS database described in **Table 1** yielded 58 foreign reports; of these, we determined that 30 reports had an unassessable causal relationship between lactitol and the reported event(s), and 27 were duplicate reports. The remaining one case of an adverse event with lactitol is discussed below, and **Appendix B** contains a line listing of the case.

FAERS case 4137098, hospitalization, Switzerland, 2004: A physician reported that an 83-year-old woman with a history of chronic renal insufficiency (baseline serum creatinine 92 micromoles [umol] per liter [L], normal range not provided) was initiated on colchicine 0.5 milligrams (mg) daily for gout. Her concomitant medications included torsemide 20 mg daily, which was initiated "years ago," and the following medications, which were initiated "months ago:" enalapril/hydrochlorothiazide (HCTZ) daily, lactitol 10 grams daily, and naproxen 1,500 mg (frequency not reported). Two months after initiating colchicine, the patient increased the dose to 1 mg daily. After the colchicine dose increase, the patient experienced diarrhea 2 to 3 times daily for 1 month, decreased appetite for several weeks, and joint pain. She was evaluated by her physician, who discontinued colchicine, lactitol, and naproxen and admitted the patient to the hospital for deterioration in her general physical condition. Upon admission, the patient had a serum creatinine of 163 umol/L and was diagnosed with acute renal insufficiency with maintained diuresis; enalapril/HCTZ and torsemide were discontinued. Approximately 24 hours after discontinuation of colchicine, lactitol, and naproxen, the patient's diarrhea improved. The patient's serum creatinine returned to baseline (96 umol/L) 3 days after hospital admission. The patient tolerated reinitiation of colchicine 0.5 mg daily for chronic gout.

Reviewer's comment: This case describes an elderly patient with chronic renal insufficiency on concomitant lactitol who experienced diarrhea with a probable causal association with colchicine use. The case had a serious outcome of hospitalization, and it is possible that volume depletion associated with diarrhea contributed to the patient's acute renal insufficiency. The colchicine labeling states that the most common adverse reaction is diarrhea (23 percent).[5] *It is possible that continued use of lactitol contributed to the severity of the patient's diarrhea.*

3.2 FINAL ASSESSMENT REPORT FOR LACTITOL COVERING THE PERIOD OCTOBER 1, 2009, TO SEPTEMBER 30, 2012

The Final Assessment Report for lactitol encompassed 20 ICRs with lactitol during the reporting period; of these, 14 were non-serious, and 6 were serious. The Final Assessment Report included narratives for the six serious reports; of these, DPV-I determined that four were unassessable. The remaining two serious cases are summarized in **Section 3.2.1**.

3.2.1 Summary of Serious Cases from Final Assessment Report

NOV-RA-2012-(b) (6) (Novartis CHPA (b) (6)), other serious outcome, Netherlands: A 4-year-old boy with a history of epilepsy who had been free of seizures for 3 years experienced an epileptic seizure 36 hours after taking Importal (667 mg lactitol, 5 milliliters [mL] twice daily for 2 days) for constipation. Lactitol was withdrawn and the patient recovered.

Reviewer's comment: This case describes the event seizure with a temporal relationship to lactitol administration. The case contains insufficient information to determine whether the event "decreased absorption of concomitant oral medication" is described—the case does not report whether the child was taking oral antiepileptic medication for seizure prevention or whether the child experienced diarrhea after initiating lactitol therapy for constipation. It is possible that expedited colonic transit of antiepileptic medication resulted in decreased intestinal medication absorption and seizure, or that diarrhea resulted in electrolyte derangements and seizure. However, the case has limited information to determine the etiology of the patient's seizure.

NOV-RA-2012-(b) (6) (Novartis CHPA (b) (6)), hospitalization, Italy: A 78-year-old woman took Portolac (lactitol), Tavor (lorazepam), and Tachidol (acetaminophen/codeine) and subsequently experienced confusion, decreased serum potassium (laboratory value not reported), diarrhea, disorientation, and hyponatremia (laboratory value not reported) "caused by drug abuse." The "suspect drugs" (not specified) were withdrawn, the patient was rehydrated, and her condition improved. The event had a serious outcome of hospitalization.

Reviewer's comment: This case describes a possible causal association between the events confusion, diarrhea, disorientation, and hyponatremia and lactitol use. Diarrhea is included in the applicant's proposed labeling for lactitol; severe diarrhea can cause hyponatremia, and hyponatremia can be associated with confusion or disorientation. The FDA-approved labeling for lorazepam lists confusion and disorientation in ADVERSE REACTIONS *and includes a boxed warning for profound sedation with concomitant use of benzodiazepines and other central nervous system depressants such as opiates (e.g., codeine). The case narrative contains insufficient information to determine whether the events confusion or disorientation are more likely to be attributed to concomitant lorazepam or acetaminophen/codeine use or sequelae of diarrhea/hyponatremia.*

3.2.2 PTs Reported in Non-serious ICRs in Final Assessment Report

The Preferred Terms (PTs) from the 14 non-serious ICRs are listed in **Table 3** below. The narratives for these 14 reports were not available for review; therefore, DPV-I could not assess the reported events for a causal relationship with lactitol use.

Table 3. Preferred Terms from Non-serious Individual Case Reports from the Final Assessment Report for Lactitol from October 1, 2009, to September 30, 2012[*,†] (N=14)

Preferred Term	Number of Reports	Term Encompassed in Proposed Labeling for Lactitol[‡] (Yes/No), Section[§] *(DPV-I Reviewer Comment)*
Immune system disorders		
Swollen tongue	2	(b) (4)
Edema mouth	1	
Lip swelling	1	
Gastrointestinal disorders		
Abdominal distension	3	
Abdominal discomfort	2	

Table 3. Preferred Terms from Non-serious Individual Case Reports from the Final Assessment Report for Lactitol from October 1, 2009, to September 30, 2012[*,†] (N=14)		
Preferred Term	**Number of Reports**	**Term Encompassed in Proposed Labeling for Lactitol[‡] (Yes/No), Section[§] *(DPV-I Reviewer Comment)***
Abdominal pain upper	1	(b) (4)
Constipation	1	
Diarrhoea	1	
Dyspepsia	1	
Flatulence	1	
Lip pruritus	1	
Nausea	1	
Oral pruritus	1	
Psychiatric disorders		
Intentional drug misuse	2	
Injury, poisoning, and procedural complications		
Overdose	3	
Incorrect drug administration duration	1	
General disorders and administration site conditions		
Drug ineffective	5	
Therapeutic response decreased	2	
Condition aggravated	1	
No adverse reaction	1	
Skin and subcutaneous tissue disorders		
Pruritus	1	

* A report can include one or more PTs.
† The narratives for the 14 non-serious reports were not available for review; therefore, DPV-I could not assess these adverse events for a causal relationship with lactitol use.
‡ DPV-I reviewer compared PTs to the applicant's proposed labeling for lactitol submitted to FDA on February 22, 2019.
§ Abbreviations: CT=*Clinical Trials Experience*, PM=*Postmarketing Experience*

*Reviewer's comment: The ICR narratives for non-serious events were not available to assess; therefore, we were unable to evaluate the causal association between the adverse events represented in **Table 3** and lactitol use. Of note, **Table 3** lists multiple PTs that can describe hypersensitivity events (i.e., Edema mouth, Lip swelling, Swollen tongue, Lip pruritus, Oral pruritus); however, we cannot determine the number of ICRs that these events represent or the potential causal association of lactitol with these events.*

3.3 PSUR FOR LACTITOL COVERING THE PERIOD OCTOBER 1, 2012, TO SEPTEMBER 23, 2015

The PSUR for lactitol encompassed 11 ICRs with lactitol during the reporting period; of these, 9 were non-serious, and 2 were serious. The PSUR included narratives for the two serious ICRs and one non-serious ICR; DPV-I determined that the events described in these three ICR narratives had an unassessable or unlikely causal relationship to lactitol use.

Furthermore, the PSUR briefly described five ICRs of rash (n=3) or pruritus (n=2) that occurred prior to the reporting period (i.e., these were reported during the period of September 3, 1985, to September 30, 2009); this information is summarized in **Section 3.3.1**.

3.3.1 Summary of Reports of Rash from PSUR

The five ICRs of rash (n=3) or pruritus (n=2) that are described in the PSUR are summarized below. The two reports of pruritus had serious outcomes.

- One case of rash and pruritus occurred in a 6.5-month-old infant. The treatment continued and after the second sachet was administered, the adverse reaction "increased." Lactitol was discontinued, and the patient had a complete recovery within 1 week.
    - *Reviewer's comment: The events described in this case have a possible causal relationship to lactitol administration because the narrative suggests positive rechallenge and positive dechallenge with lactitol.*
- One report of lactitol overdose in a child or infant also reported rash.
- One report of rash occurred in a 67-year-old patient.
- One serious report of pruritus was an adult patient who experienced bullous dermatitis.
- One serious report of pruritus was an adult patient who experienced maculopapular rash and urticaria, and was treated with intravenous hydrocortisone 50 mg and intramuscular chlorpheniramine.

Reviewer's comment: The above five reports contain terms that can describe hypersensitivity events (i.e., rash, pruritus, bullous dermatitis, maculopapular rash, urticaria). DPV-I assigned a possible causal role of lactitol to the case of rash and pruritus in a 6.5-month-old infant, and the remaining four reports had unassessable causality for lactitol.

3.3.2 PTs Reported in Non-serious ICRs in PSUR

The PTs from the nine non-serious ICRs are listed in **Table 4** below. Of the nine reports, the narratives for eight were not available for review, therefore DPV-I could not assess the events reported in these ICRs for a causal relationship with lactitol use. The one remaining ICR described intentional product misuse in a hospitalized patient who received lactitol via enema rather than orally; no adverse event was reported in association with this administration.

Table 4. Preferred Terms from Non-serious Individual Case Reports from the Periodic Safety Update Report for Lactitol from October 1, 2012, to September 23, 2015[*,†] (N=9)

Preferred Term	**Number of Reports**	**Term Encompassed in Proposed Labeling for Lactitol[‡] (Yes/No), Section[§] *(DPV-I Reviewer Comment)***
Gastrointestinal disorders		
Diarrhoea	3	(b) (4)
Abdominal distension	2	
Abdominal pain	1	
Breath odour	1	
Dyspepsia	1	

Table 4. Preferred Terms from Non-serious Individual Case Reports from the Periodic Safety Update Report for Lactitol from October 1, 2012, to September 23, 2015[*,†] (N=9)		
Preferred Term	**Number of Reports**	**Term Encompassed in Proposed Labeling for Lactitol[‡] (Yes/No), Section[§] *(DPV-I Reviewer Comment)***
Flatulence	1	(b) (4)
Haematochezia	1	
Painful defecation	1	
Vomiting	1	
General disorders and administration site conditions		
Drug ineffective	1	
No adverse event	1	
Hepatobiliary disorders		
Jaundice	1	
Injury, poisoning, and procedural complications		
Intentional product misuse[‖]	1	
Skin and subcutaneous tissue disorders		
Urticaria	1	

* A report can include one or more PTs.
† Of the nine non-serious ICRs, the narratives for eight were not available for review, therefore DPV-I could not assess the events reported in these ICRs for a causal relationship with lactitol use.
‡ DPV-I reviewer compared PTs to the applicant's proposed labeling for lactitol submitted to FDA on February 22, 2019.
§ Abbreviations: CT=*Clinical Trials Experience*, PM=*Postmarketing Experience*
‖ The narrative for one non-serious ICR described intentional product misuse in a hospitalized patient who received lactitol via enema rather than orally; no adverse event was reported in association with this administration.

*Reviewer's comment: The ICR narratives for non-serious events were not available to assess; therefore, we were unable to evaluate the causal association between the adverse events represented in **Table 4** and lactitol use. Of note, **Table 4** lists one PT that can describe hypersensitivity events (i.e., Urticaria); this PT is reflective of one single ICR.*

4 DISCUSSION

This review, completed by DPV-I in response to a consult from DGIEP, contains an evaluation of the following: all adverse events with lactitol in the FAERS database through September 22, 2019; the EMA Final Assessment Report for lactitol, which reviewed the postmarketing experience of lactitol in Europe over the period of October 1, 2009, to September 30, 2012; and the PSUR for lactitol, which covered the period of October 1, 2012, to September 23, 2015. This review will inform DGIEP as they determine the acceptability of product labeling submitted for NDA 211281 lactitol monohydrate.

The proposed *Postmarketing Experience* section for lactitol submitted to FDA on February 22, 2019, lists (b) (6); in contrast, the August 7, 2019, version of the applicant's proposed *Postmarketing Experience* section lists (b) (6)

(b) (6)

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(b) (4)

We reviewed adverse event tabulations from non-serious ICRs within the EMA Final Assessment Report of lactitol for the period October 1, 2009, to September 30, 2012, and the PSUR for lactitol for the period of October 1, 2012, to September 23, 2015. We were unable to assess the adverse events from non-serious ICRs for a causal association with lactitol because narratives for non-serious ICRs were not available. Furthermore, the adverse event tabulation tables do not reflect whether lactitol was a suspect or concomitant drug in the report. Many of the PTs reported with non-serious ICRs represent labeled gastrointestinal adverse events or terms that do not inform potential safety issues with lactitol. Of note, we identified multiple PTs that can describe hypersensitivity events (i.e., Edema mouth, Lip swelling, Swollen tongue, Lip pruritus, Oral pruritus, Urticaria); however, the lack of ICR narratives precluded our evaluation of lactitol causality for non-serious reports of hypersensitivity events.

5 RECOMMENDATIONS

DPV-I provides recommendations that pertain to the *Postmarketing Experience* section of the applicant's proposed lactitol labeling from February 22, 2019, and August 7, 2019.

- We recommend labeling the following events in *Postmarketing Experience*:
  - hypersensitivity events, including rash and pruritus
- DPV-I does not agree with the applicant's inclusion of the following terms in the *Postmarketing Experience* section of the lactitol labeling at this time: (b) (4) (b) (4)
- DPV-I recommends removal of the following information that was included in the August 7, 2019, version of the *Postmarketing Experience* section: (b) (4) (b) (4)

DPV-I recommends continued pharmacovigilance for cases that suggest decreased absorption or therapeutic effect of concomitant oral medications or serious sequelae of severe diarrhea with lactitol.

6 REFERENCES

(b) (4)

3. Final Assessment Report for Lactitol. October 1, 2009, to September 30, 2012. EMA Procedure Number AT/H/PSUR/0019/002. Available within Summary of Clinical Safety: \\cdsesub1\evsprod\nda211281\0001\m2\27-clin-sum\summary-clin-safety.pdf

4. Periodic Safety Update Report for Lactitol. October 1, 2012, to September 23, 2015. Available at \\cdsesub1\evsprod\nda211281\0017\m1\us\periodic-safety-update-report-af15sc005.pdf. Appendices available at \\cdsesub1\evsprod\nda211281\0030\m1\us\psur-2015---appendices-3a-3c.pdf

5. Colcrys (colchicine) [package insert]. Philadelphia, PA: AR Scientific, Inc.; Label revised July 2009.

7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

7.2 APPENDIX B. FAERS LINE LISTING OF CASE OF ADVERSE EVENTS WITH LACTITOL

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	5/10/2004	4137098	1	CH-ROCHE-366248	Expedited	83	Female	Switzerland	Hospitalized

*Per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A case can have more than one serious outcome.

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/s/

MICHELLE C HINES
10/10/2019 02:43:06 PM

ANN J BIEHL
10/10/2019 03:40:49 PM

MONICA MUNOZ
10/10/2019 03:57:15 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF METABOLISM & ENDOCRINOLOGY PRODUCTS

Date: July 18, 2019

From: Suchitra Balakrishnan, MD. PhD.
Division of Metabolism and Endocrinology Products (DMEP) /CDER

Through: Mitra Rauschecker, MD
Acting Clinical Team Leader
DMEP/CDER

Lisa Yanoff, MD.
Acting Division Director
DMEP /CDER

To: Andrew Kelleher (RPM),
Division of Gastroenterology and Inborn Errors of Metabolism Products (DGIEP)

Subject: RE: Consult request for Lactitol, NDA 211281

This memo provides responses to the consult received on March 22, 2019 regarding labelling of Lactitol for use in patients with diabetes.

- DGIEP consult request
- EDR link to the submission and Sponsor's response to Information request dated April 1, 2019

BACKGROUND

Braintree (hereafter referred to as the sponsor) has submitted a new drug application (NDA) for Lactitol (BLI400, Proposed trade name- (b) (4) Lactitol is a sugar alcohol synthetic derivative of lactose that consists of galactose and sorbitol linked through a glycoside bond. Lactitol is minimally absorbed and exerts an osmotic effect, causing the influx of water into the small intestine leading to a laxative effect in the colon.

Lactitol has been marketed outside of the United States (Importal, Osmolac etc.), including Europe as a treatment for constipation and for treatment of hyperammonemia which occurs with

hepatic encephalopathy (HE) in adults and pediatric patients. It is also approved for use as an excipient with other prescription drugs, and as a food additive/low calorie artificial sweetener.

The proposed indication for this product is for the treatment of chronic idiopathic constipation (CIC) in adults. The recommended dosage of is 20 grams (equivalent to 21 grams of lactitol monohydrate) orally once daily, preferably with meals.

The sponsor proposes the following language in Section 8, Special Populations:

8.6 Diabetes
(b) (4) *has negligible caloric values (2 kcal/g or 8.5 kJ/g) and has no effect on insulin secretion and blood glucose levels. Therefore, lactitol may also be administered to diabetic patients.*

Specific trials in diabetic patients have not been conducted. There were 122 patients with a history of diabetes who were enrolled in the clinical trials. DGIEP requested DMEP input on the labelling language, and whether chronic administration of the product would raise safety concerns for diabetic patients.

Applicable Clinical Information:

Clinical Pharmacology:
Lactitol is minimally absorbed systemically following oral administration. Following a single oral dose of 21 grams of (b) (4) in healthy adult subjects under fed conditions, the mean ±SD peak serum concentration (Cmax) was 776±253 ng/mL, the serum lactitol was not detectable at 24 hours after administration, and the mean ±SD area under the serum drug concentration over time curve (AUC) was 6,019 ±1,711 ng*hr/mL. The Cmax and AUC values increased greater than 2-fold under fasted conditions compared to fed conditions.

In clinical study of CIC patients receiving 21grams of (b) (4) for 6 months, serum lactitol concentrations ranged from 26 to 5500 ng/mL over the course of the study.

No formal pharmacodynamic studies have been conducted with (b) (4)

Clinical trial data:
Three Phase 3 studies in constipated adult patients, including two double-blind studies, were conducted in support of this New Drug Application. Study BLI400-301 evaluated daily treatment with 21g BLI400 laxative or 48ug Amitiza for 12 weeks (3 months) and Study BLI400-302 compared daily treatment with 21g BLI400 to placebo for 6 months (24 weeks).
Study BLI400-303 was a 1 year open-label study where patients were instructed to take 21g BLI400 each day. There were 834 patients in the BLI400 safety population with a collective BLI400 exposure of about 425 years. The safety population included 206 patients age 65 or over, 60 of whom were 75 years of age or more. The most common adverse reactions that were more frequent with BLI400 compared to placebo were flatulence (6.8% vs 2.6%) and diarrhea (5.6% vs. 2.9%)

The sponsor reports that no adverse events were unusually frequent in the sub-group of 122 diabetic patients enrolled in the phase 3 studies, and laboratory results and trends were similar to the general safety population. In response to an Information request dated April 1, 2019, the sponsor confirmed that HbA1c and FPG were not collected in Phase 3 studies. They also did not conduct any clinical pharmacology PK/PD or other clinical study in which glucose or insulin were measured post dosing. They cited evidence from the published literature to conclude that lactitol has a low glycemic index, with little or no effect on glucose, insulin and C-peptide in healthy volunteers[1, 2]. In a study by Natah, et al., 25 grams of glucose, lactitol or xylitol were administered to 8 non-obese men aged approximately 25 years. Blood samples were collected every 30 minutes over 3 hours for measurement of glucose, insulin and C-peptide. There was no rise in plasma glucose, insulin or C-peptide concentrations with lactitol, while there was a small increase after xylitol. In a second study by Shimomura, et al, the effects of a 46 g chocolate that contained approximately 41 grams of sucrose or 19.4 grams of lactitol on blood glucose and insulin were examined, after administration to five healthy males. The sugar containing chocolate raised insulin peaking 30 minutes after administration to a mean of 60 μU/mL versus an increase to less than 10 μU/mL after the lactitol-chocolate. Plasma glucose rose from approximately 90 to 105 mg/dl with the sugar-containing chocolate while there was no change after the lactitol-containing chocolate.

Reviewer's Assessment:
There is no published data or clinical study conducted by the sponsor in diabetic patients evaluating effects on glucose, insulin, or C-peptide. HbA1c or fasting plasma glucose were not collected in the clinical studies. Therefore, the available data does adequately not support the statement that lactitol may also be administered to diabetic patients. However, the available information (this included information in the sponsor's submission regarding post-marketing experience outside of the US) does not suggest that it is unsafe to administer in diabetic patients.

I conducted a limited search of the literature for systematic reviews and meta-analyses regarding concerns about weight gain and risk for Type 2 DM with nonnutritive sweeteners. The information available to date is conflicting and further research is needed to fully characterize the risk[3,4, 5, 6] . In addition, limited information is available about the sugar alcohols like lactitol and xylitol.

We agree with deletion of Section 8.6 based on best labeling practices. In addition, it is reasonable to stay silent on the use of this product in patients with diabetes. Data submitted by

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[1] Natah SS, Hussien KR, Tuominen JA, Koivisto VA. Metabolic response to lactitol and xylitol in healthy men. Am J Clin Nutr. 1997 Apr;65(4):947-50.

[2] Shimomura Y, Maeda K, Nagasaki M, Matsuo Y, Murakami T, Bajotto G, Sato J, Seino T, Kamiwaki T, Suzuki M. Attenuated response of the serum triglyceride concentration to ingestion of a chocolate containing polydextrose and lactitol in place of sugar. Biosci Biotechnol Biochem. 2005 Oct;69(10):1819-23.

[3] Nonnutritive sweeteners and cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies. *CMAJ* 2017 July 17;189:E929-39.

[4] Does low-energy sweetener consumption affect energy intake and body weight? A systematic review, including metaanalyses, of the evidence from human and animal studies; International Journal of Obesity (2016) 40, 381–394

[5] Metabolic effects of non-nutritive sweeteners. Physiology & Behavior 152 (2015) 450–455

[6] Non-nutritive sweeteners: Review and update. Nutrition 29 (2013) 1293-1299

the sponsor was not adequate to clearly rule out an effect on insulin and glucose metabolism in patients with diabetes mellitus, but the theoretical risk is minor given the published data that (b) (4) has negligible caloric values (2 kcal/g or 8.5 kJ/g) and has no effect on insulin secretion and blood glucose levels in healthy volunteers.

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUCHITRA M BALAKRISHNAN
07/18/2019 03:28:15 PM

MITRA RAUSCHECKER
07/18/2019 03:56:05 PM

LISA B YANOFF
07/18/2019 04:38:58 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 10, 2019
Requesting Office or Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Application Type and Number:	NDA 211281
Product Name and Strength:	Lactitol, NF for oral solution, 10g
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Braintree Laboratories, Inc. (Braintree)
FDA Received Dates:	June 29, 2018, November 21, 2018, February 22, 2019, May 2, 2019 and June 4, 2019
OSE RCM #:	2018-1413
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader (Acting):	Idalia E. Rychlik, Pharm.D.

1 REASON FOR REVIEW

As part of the review process for lactitol, we reviewed the proposed lactitol prescribing information (PI), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Information Requests	C
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Other	E-N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance.

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), container labels and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Gastroenterology and Inborn Errors Products (DGIEP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	The previously denied proprietary name, (b) (4) is used throughout the Prescribing Information (PI).	Proposed proprietary name, (b) (4) found unacceptable by DMEPA on April 16, 2019. NDA 211281 is pending; a new name was submitted on May 2, 2019 and is currently under review.	Delete the denied proprietary name, (b) (4) throughout the PI.

Table 2. Identified Issues and Recommendations for Division of Gastroenterology and Inborn Errors Products (DGIEP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	The abbreviation "oz" is used in the PI.	Misinterpretation and confusion over abbreviations may lead to prescribing or administration errors.	Consider replacing the symbol "oz" with its intended meaning "ounce".
3.	The preparation and administration instructions in both the Highlights and Full Prescribing Information provide dosing information (b) (4)	The multi-dose bottle presentation is intended to be administered using the product cap. (b) (4) the intended 10 grams which is demarcated on the dosing cap. This may lead to wrong dose errors.	Express the dose in metric units (i.e., 10 grams or 20 grams) throughout the PI (Highlights, Section 2 Dosage and Administration) which would also be consistent with the demarcation in the measuring (dosing) cup.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The National Drug Code (NDC) number on the unit-dose (b) (4) is missing.	Per 21 CFR 207.33, drug products subject to listing with the FDA must have a unique NDC to identify its labeler, product, and package size and type.	Submit the NDC number ensuring the NDC package code (last 1-2 digits) is different between the containers sizes.
2.	The Unit-dose (b) (4) is referred to as "(b) (4) packet".	Using two different package-type terms (unit-dose (b) (4) and (b) (4) packet) to describe one package may lead to confusion.	Revise the terminology to "unit-dose (b) (4) for consistency with the rest of the PI.

Table 3. Identified Issues and Recommendations for Braintree Laboratories, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Measuring (Dosing) Cup of Bottle Containers:			

Table 3. Identified Issues and Recommendations for Braintree Laboratories, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The product is packaged with a dosing cup (i.e., the cap of the bottle). The demarcation line indicating 10 grams and the labeled '10 grams' on the dosing cup is difficult to read and may be easily overlooked because it is embossed.	The lack of readability and prominence of the line and the labeled 10 grams may lead to wrong dose errors.	We acknowledge your responses and revised container labels to our information requests (IR) dated May 15, 2019 and June 4, 2019. However, your proposed mitigation strategies are not sufficient to mitigate the risk of dosing errors with your product. Therefore, we recommend that you increase the readability and prominence of the (b) (4) fill-line and the corresponding measurement statement of "10 grams". Consider using an alternate color (b) (4) to ensure that this important information is not overlooked. We request that you submit the revised sample for our evaluation.
2.	The metric measurement on the demarcation line is listed as 10.5 grams.	Per Guidance for Industry: Naming of Drug Products Containing Salt Drug Substances. 2013. (available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM379753.pdf), the metric measurement on the demarcation line should be "10 grams".	Revise the measurement statement on the product measuring cap to "10 grams" per recommendation from the Office of Pharmaceutical Quality (OPQ).

Table 3. Identified Issues and Recommendations for Braintree Laboratories, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	All Container Label(s) and Carton Labeling		
3.	The product dosage form statement is missing.	The established name for the product should include the finished dosage form. See Draft Guidance: Container and Carton, April 2013 (lines 336-342, 344-349)[a]	Add the finished dosage form either on the same line as the active ingredient (established name) or directly below the active ingredient (established name). For example: TRADENAME (lactitol, NF for oral solution) TRADENAME (lactitol, NF) for oral solution TRADENAME (lactitol, NF) for oral solution
4.	The established name on the container label and carton labeling is inconsistent with the Prescribing Information (PI).	The established name on the container label and carton labeling should be consistent with PI to avoid dosing confusion.	Revise the established name on container label and carton labeling to be consistent with PI. For example: TRADENAME (lactitol, NF for oral solution) TRADENAME (lactitol, NF) for oral solution

[a]Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

Table 3. Identified Issues and Recommendations for Braintree Laboratories, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			TRADENAME (lactitol, NF) for oral solution
5.	The statement of the recommended or usual dosage is missing from the side panel.	The statement of the recommended or usual dosage is required per 21 CFR 201.55.	Include the following statement on the side panel: "Recommended Dosage: See prescribing information."
6.	The product storage information is presented as (b) (4)	(b) (4)	Remove the bolded statement (b) (4) " from all labeling.
7.	It is unclear where the machine readable product identifier required under the Drug Supply Chain Security Act	DSCSA requires manufacturers and re-packagers, to affix or imprint a product identifier to each package and homogenous case of a	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from:

Table 3. Identified Issues and Recommendations for Braintree Laboratories, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(DSCSA)[b] is located on the label.	product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively.	https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.
8.	The dosing information on the side panel instructions are (b) (4)	The multi-dose bottle presentation is intended to be administered using the product cap. (b) (4) the intended 10 grams which is demarcated on the dosing cap. This may lead to wrong dose errors.	Revise the directions on the side panel to express the dose in metric units (i.e., 10 grams or 20 grams) which would also be consistent with the demarcation in the measuring (dosing) cup.
9.	The lot number statement is missing.	The lot number statement is required as per 21 CFR 201.10(i)(1)	Include the lot number statement.
10.	The expiration date statement is missing.	The expiration date should be clearly defined to minimize confusion and risk for deteriorated drug medication errors.	The expiration date should be on the side panel in the format specified below. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-

[b]The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

Table 3. Identified Issues and Recommendations for Braintree Laboratories, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
11.	The principal display panel contains the following undefined statements: code (XX-XXXX) and the date (November 2018).	The PDP should only display the most important product information to prevent medication error. It is unclear what code (XX-XXXX) and the date (November 2018) stand for and why they are located on the PDP.	Define the code (XX-XXXX) and date (November 2018).
Container Labels (Multi-dose bottles)			
1.	The image of the measuring cap and demarcated line labeled “10 grams” in Step 2 lacks readability and prominence.	We acknowledge your revised container labels to our information requests dated May 15, 2019 and June 4, 2019. The proposed label is insufficient to mitigate	Revise the Step 2 in the dosing schematic to include a prominent and readable depiction the 10-gram fill-line within the measuring cap. Refer to our recommendations for the Measuring (Dosing) Cup

Table 3. Identified Issues and Recommendations for Braintree Laboratories, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		potential dosing errors which may occur due to the current dosing cap and 10-gram fill-line presentation.	of Bottle Containers above to align the dosing cup image and depiction of the 10 g demarcation line.
2.	The strength presentation statement is missing.	The strength presentation is required as per 21 CFR 201.15(a)(6).	Include the following strength statement to the primary display panel. For example, (b) (4) Tradename (lactitol, NF) for oral solution 279 g (b) (4) Tradename (lactitol, NF) for oral solution 559 g
(b) (4) Carton Labeling			
1.	There are two barcodes (e.g. linear barcode) presented on labeling.	The drug barcode is often used as an additional verification before drug administration in the inpatient setting. Duplicate and/or unnecessary barcodes may result in product selection errors. It is unclear what the purpose of the additional barcode is.	Please explain the purpose of the additional barcode.
2.	The strength presentation statement is missing.	The strength presentation is required as per 21 CFR 201.15(a)(6).	Add the strength presentation statement below proprietary name, established name and dosage form. The strength presentation should read "10 grams per unit-dose (b) (4)

Table 3. Identified Issues and Recommendations for Braintree Laboratories, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	Unit-dose (b) (4) are referred to as "(b) (4) packet" which is inconsistent with the PI.	The package term should be consistent with the Prescribing Information. Using two different terms to describe one package may lead to confusion.	Change the package term from "(b) (4) packet" to "unit-dose (b) (4) to be consistent with the PI.
4.	The net contents statement references "1 Patient booklet" which includes "Patient Instructions" and "Full Prescribing Information".	Typically, the Full Prescribing Information is intended for healthcare providers. The labeling submitted on June 29, 2018 does not contain any additional "Patient Instructions".	Please clarify if you intend to include "Patient Instructions" with the product. If so, please submit your proposed labeling.
5.	The carton containing 28 unit-dose (b) (4) packets uses the same NDC as the individual unit dose (b) (4) packet.	The carton containing 28 unit-dose (b) (4) packets should not use the same NDC as the individual unit dose (b) (4) packet to avoid product package confusion.	The carton containing 28 unit-dose (b) (4) uses the same NDC as the individual unit dose (b) (4) packet. The container label of one unit and the carton labeling of 28 should have different NDC package codes (last 2 digits of the NDC). Revise the NDC numbers so that the carton labeling and vial labels use a different NDC package code.
Unit Dose (b) (4) label			
	The strength presentation statement is missing.	The strength presentation is required as per 21 CFR 201.15(a)(6).	Add the strength presentation statement below proprietary name, established name and dosage form. The strength presentation should read "10 g per unit-dose (b) (4) packet".
	The National Drug Code (NDC) number is missing.	Per 21 CFR 207.33, drug products subject to listing with the FDA must have a	Submit the NDC number ensuring the NDC package code

Table 3. Identified Issues and Recommendations for Braintree Laboratories, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		unique NDC to identify its labeler, product, and package size and type.	(last 1-2 digits) are different between the containers sizes.

4 CONCLUSION

Our evaluation of the proposed lactitol prescribing information, container labels and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Braintree Laboratories, Inc so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED
APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for lactitol that Braintree Laboratories, Inc. (Braintree) submitted on June 29, 2018.

Table 3. Relevant Product Information for lactitol	
Initial Approval Date	N/A
Active Ingredient	lactitol
Indication	(b) (4) is indicated for the treatment of chronic idiopathic constipation (CIC) in adults.
Route of Administration	Oral
Dosage Form	For oral solution
Strength	10 g
Dose and Frequency	The recommended adult dosage is 20 grams (b) (4) orally once daily, preferably with meals. Dosage is reduced to 10 grams (b) (4) once daily for persistent loose stools.
How Supplied	(b) (4) is supplied in a white to off-white crystalline powder for oral administration following reconstitution and available in three sizes: 1) (b) (4) multi-dose bottle of 279 grams lactitol 2) (b) (4) multi-dose bottle of 559 grams lactitol 3) Carton of 28 unit-dose (b) (4) containing 10 grams lactitol each (2 packets per dose).
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.
Reference Listed Drug/Reference Product	None

APPENDIX C. INFORMATION REQUESTS:

Information request and response from Braintree and Labeling/Container-Carton Draft received on May 15, 2019:

We refer to the prescribing information submitted on February 22, 2019 and product samples received on March 28, 2019 for NDA 211281. We note, that the recommended adult dose of lactitol is 21 grams, with a possible dose reduction to 10.5 grams, once daily (b) (4) **within the administration information throughout the PI. The product's dosing cap has a demarcation line at the dosing interval** (b) (4) (b) (4) **Please explain your plan to mitigate the potential for these wrong dose errors.**

An additional illustration will be added to the bottle label to more clearly instruct the consumer on the 10.5 g fill line demarcation (similar to attached picture of cap). The illustration would have a larger arrow pointing to the white inner cap which is the fill line.

The narrative below the illustration will be expanded to read (b) (4)

(b) (4)

We believe these additions will mitigate the potential for wrong dose errors.

(b) (4)

Information request and response from Brain tree and Labeling/Container-Carton Draft Labeling/Container-Carton Draft received on June 4, 2019:

We refer to our information request dated May 8, 2019 and your response submitted on May 15, 2019 for NDA 211281 (lactitol, NF).

In your response you stated that an additional illustration will be added to the bottle label to more clearly instruct the consumer to the 10.5 gram fill line demarcation with a larger arrow pointing to the white inner cap and a narrative below the illustration. Please submit the proposed revised labels and labeling for our review by May 23, 2019.

(b) (4)


(b) (4)

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following lactitol labels and labeling submitted by Braintree Laboratories, Inc. (Braintree).

- Container labels received on May 2, 2019
- Carton labeling received on May 2, 2019
- Prescribing information (not imaged) received on February 22, 2019

F.2 Label and Labeling Images

Prescribing information (not imaged)

\\cdsesub1\evsprod\nda211281\0010\m1\us\bli400fpidraft-revised-per-filing-review-comments.pdf

Container labels:

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

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

SHERLY ABRAHAM
07/10/2019 10:31:39 AM

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07/10/2019 10:48:31 AM

Clinical Inspection Summary

Date	June 21, 2019
From	Susan Leibenhaut, M.D., OSI/DCCE/GCPAB Susan Thompson, M.D., Team Leader, OSI/DCCE/GCPAB Kassa Ayalew, M.D., M.P.H., Branch Chief, OSI/DCCE/GCPAB
To	Irena Lavine, M.D., Medical Officer, DGIEP
NDA #	211281
Applicant	Braintree Laboratories, Inc.
Drug	Lactitol monohydrate
NME	Yes
Division Classification	Constipation
Proposed Indication	Treatment for adult constipation
Consultation Request Date	January 15, 2019
Summary Goal Date	June 28, 2019
Action Goal Date	November 20, 2019
PDUFA Date	November 20, 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Inspections for this NDA were conducted at four clinical investigator (CI) sites and the sponsor. Although inspectional observations were noted at the two clinical investigator sites (Drs. Idalia Acosta and M.A. Mahmud), the findings are unlikely to have a significant impact on overall results. No significant regulatory findings or data integrity issues were noted. The study data generated by these sites and the sponsor are acceptable in support of the application.

II. BACKGROUND

The sponsor submitted this NDA for BLI400 (lactitol monohydrate), a powder for reconstitution for oral administration intended for the treatment of constipation in adults. BLI400 is a member of the pharmaceutical class of osmotic laxatives. It is not absorbed but is metabolized by colonic microbes into D-galactose and D-sorbitol, which are fermentable to organic acids including lactic, formic, propionic, butyric, and acetic acids. Lactitol has been marketed since at least 1985 in Europe and other regions as a syrup or powder for the treatment of constipation in adults.

Drug: lactitol monohydrate

Studies– Protocol numbers and titles for all studies that were inspected

1. Protocol BLI400-301 entitled "A Safety and Efficacy Evaluation of BLI400 Laxative vs Amitiza (Lubiprostone) in Adults with Constipation"

Number of subjects: 459 subjects
Number of sites: 49 sites
Number of countries where subjects were enrolled: USA only
Dates that study was conducted: May 5, 2015 to November 16, 2015
Efficacy endpoint: Proportion of subjects who were weekly responders for 9 of the first 12 weeks. Response is defined as complete spontaneous bowel movement (CSBM). CSBM is defined as a bowel movement that occurred with no rescue laxative use in the previous 24 hours. A weekly responder was a subject who had ≥ 3 CSBMs and an increase from baseline of > 1 CSBM in that week. At least 3 of the 9 weeks had to occur during Weeks 9 to12

2. Protocol BLI400-302 entitled "A Safety and Efficacy Evaluation of BLI400 Laxative in Constipated Adults"

Number of subjects: 623 subjects
Number of sites: 51 sites
Number of countries where subjects were enrolled: USA only
Dates that study was conducted: June 7, 2016 to June 19, 2017
Efficacy endpoint: Proportion of subjects who were weekly responders for 9 of the first 12 weeks of treatment, with at least 3 of those weeks occurring during Weeks 9 to12 of treatment. A weekly responder was a subject who had ≥ 3 CSBMs and an increase from baseline of > 1 CSBM in that week. A CSBM was defined as a bowel movement that occurred with no rescue laxative use in the previous 24 hours and that was accompanied by a sense of complete evacuation.

Sites were chosen based on enrollment, inspectional history, and number of INDs in the OSI database. A total of two clinical sites were chosen for each study above. The sponsor was inspected because this product is considered a new molecular entity to the U.S. FDA and because there were issues with the eDiary compliance in Study BLI400-302 (discussed below). Note that consult from OND to OSI had the number of subjects for Sites 27 and 36 for Study BLI400-301 switched. The correct number is contained in the body of the review for each site below.

III. RESULTS (by site):

1. **Ian Lustbader, M.D,**
   Manhattan Medical Research,215 Lexington Avenue, 21st Floor, New York, NY 10016

At this site, for Protocol BLI400-301, there were 13 subjects screened, 10 subjects were randomized, and 8 subjects completed the study. A total of 10 subject records were reviewed. The records were reviewed for informed consent process, staff training, test article accountability, efficacy parameters, protocol deviations, concomitant medications, eligibility criteria, and adverse events. Source documents for protocol adherence and data verification were compared to line listings from the NDA. No significant deviations or discrepancies were noted, and no Form 483 was issued. . There was no evidence of under reporting of adverse events.

The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

2. **Carlos Ramos, M.D.**
   A+ Research, Inc.,8660 West Flagler Street, Suite 111,Miami, FL 33144

At this site, for Protocol BLI400-301, there were 14 subjects screened, 14 subjects were randomized, and 13 subjects completed the study. One subject withdrew. The records for all 14 randomized subjects were reviewed. The records were reviewed for informed consent process, staff training, test article accountability, efficacy parameters, protocol deviations, concomitant medications, eligibility criteria, and adverse events. Source documents for protocol adherence and data verification were compared to line listings from the NDA. No significant deviations or discrepancies were noted, and no Form 483 was issued. There was no evidence of under reporting of adverse events.

The study appears to have been conducted adequately at this site and the data generated by this site may be used in support of the respective indication.

3. **Idalia Acosta, M.D.**
   San Marcus Research Clinic, Inc. 5941 NW 173 Drive, Suite 1, Miami, FL 33015

For Protocol BLI400-302 at this site, 35 subjects were screened, 26 subjects were randomized and received test article, and 24 subjects completed the study. Subject (b) (6) withdrew. A total of 14 subjects' records were reviewed. The data in the line listings was compared with the source documents. Except for Observation 1 noted below, there were no discrepancies noted between the line listings and source

documents and eDiary data at the CI site.

A Form FDA 483, Inspectional Observations, was issued at the close of the inspection for the following violations:

1. The investigator failed to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation. Specifically, the CI failed to retain complete diaries for 4 of 26 enrolled subjects. The eDiary was used by each subject to report their bowel movements, intake of study medication, and rescue medication, if any. The entries were used for primary and secondary endpoints determination for this investigational product. For these four subjects, the date of the last bowel movement (efficacy) entry was at least four months before the date of the last visit as noted in the source documents.

Subject # and arm	Date of first OV# per NDA listing	Date of Last OV per Source	Date of Last OV per eCRF	Date of Last Diary Entry
(b) (6) Placebo	(b) (6)	(b) (6) (Visit 8)	(b) (6) (Visit 8)	(b) (6) (Before Visit 4)
(b) (6) Placebo	(b) (6)	(b) (6) (Visit 8*)	(b) (6) (Visit 8*)	(b) (6)
(b) (6) BLI400	(b) (6)	(b) (6) (Visit 8)	(b) (6) (Visit 8)	(b) (6)
(b) (6) Placebo	(b) (6)	(b) (6) (Visit 8)	(b) (6) (Visit 8)	(b) (6)

OV = Office visit

*EIR states that the last OV was (b) (6). This date is the date of the telephone contact as per protocol. The last OV was (b) (6) The source and the eCRF agree.

<u>Reviewer note:</u> The clinical investigator was cited for the fact that the date of last visit according to source documents was more than four months after the date of the last office visit for four subjects. Subject (b) (6) (placebo) entered values in the diary up to Week 4 of the study, whereas the other three subjects (Subject (b) (6) [placebo], Subject (b) (6) [BLI4000], and Subject (b) (6) [Placebo]) had not completed any efficacy assessments after the screening period. These missing values were reported by the sponsor in the line listings submitted to the NDA. Subjects (b) (6) and (b) (6) were reported by the sponsor in the clinical study report as being excluded from the per protocol population because there was no efficacy data entered after screening. An additional subject at this site, Subject (b) (6) [Placebo] was also reported by the sponsor as having no efficacy data after screening but continued in the study. (Last Diary entry (b) (6); last office visit in the eCRF datasets (b) (6)). All subjects except (b) (6) had been identified by the sponsor as having participated in the study but had not been compliant with data entry. This finding of an additional subject who was not excluded from the PPP raised the questions of whether data was entered by the subjects and then lost or not analyzed, whether the site or sponsor were aware of the issues, and why subjects were not educated as to diary entry or withdrawn from the study. This issue will be further assessed during the sponsor inspection. The sponsor also

responded to this observation stating that the subjects did not complete the diary assessments.

These results were communicated to the review division on April 12, 2019. Additional analyses of the dates of last visit and dates of last diary entry were conducted by the review division to determine the magnitude (how many subjects were involved) and significance (at what visit did the diary entries cease) of the issue. An Information Request was sent to the sponsor to determine the cause and significance of the finding. This was also further discussed during the sponsor inspection.

2. An investigation was not conducted in accordance with the signed statement of the investigator. Specifically, there was no documentation that the clinical investigator determined each subject's eligibility for all ten subjects' records reviewed. Furthermore, this responsibility was not delegated nor allowed to be performed by anyone other than the clinical investigator or the sub-investigator as per Protocol Section 4.1 and Delegation Log.

<u>Reviewer note:</u> In her response, the CI noted that she determined eligibility as per protocol. The randomization source document did not require a CI signature. She admits that the lack of signature resulted in inadequate documentation. The corrective action plan includes review of source documents provided by the sponsor so that study activities can be adequately documented.

Dr. Acosta adequately responded to the inspection findings in a letter dated April 18, 2019.

4. M.A. Mahmud, M.D.
Kindred Medical Institute for Clinical Trials, Corona, CA 92879

For Protocol BLI400-302 at this site, 20 subjects were screened, and 18 subjects were randomized and received test article. Seventeen subjects completed the study. One subject withdrew because there was difficulty with blood drawing of this subject. A total of 20 subjects' records were reviewed. The data in the line listings was compared with the source documents. The only discrepancy between the line listings and the eDiary data noted at the CI site was that observed for Subject (b) (6) on (b) (6) in which the eDiary data on the USBs (which served as the site data) and in the online portal show the subject entered nine complete spontaneous bowel movements (CSBMs), but the data listings show only eight CSBMs because the CSBM at time 16:02 was missing (see Observation 2.) There was no underreporting of adverse events.

A Form FDA 483, Inspectional Observations, was issued at the close of the inspection for the following violations:

1. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan because the following protocol violations

were noted:

a. On (b) (6) at Study Visit 2 the CI randomized and dispensed study drug to Subject (b) (6) who did not meet bowel movement (BM) entry criteria of fewer than three complete spontaneous bowel movements (CSBMs) per week and fewer than six spontaneous bowel movement (SBMs) per week during the screening period from (b) (6) to (b) (6). Subject (b) (6) reported having 10 CSBMs in the eDiary on the following dates and times: on (b) (6) at time 20:51; and on (b) (6) at times 08:49, 09:38, 10:24, 10:53, 11:01, 11:55, 15:51, 15:59, and 16:02. Subject (b) (6) was randomized to active treatment and completed study BLI400-302.

Reviewer note: In his response, the CI noted that the protocol required eligibility screening at Visit 1 and that the eDiary was to determine whether the subject could be randomized. Because the eDiary did not provide subject eligibility, the staff called (b) (4) the CRO responsible for the eDiary to determine eligibility. According to exhibits collected during the inspection (Exhibit 11) and the clinical investigator (CI) response, staff at (b) (4) performed a manual "script" and determined that the subject was eligible despite the report of having more than 3 CSBMs during the week. According to Exhibit 10, page 16, the sponsor was aware of this issue as far back was October 2017. This mis-randomization is noted in Listing 16.2.3 as "subject was randomized in error", and the subject was excluded from the mITT and PP populations. This error is attributable to the sponsor, and there will be an IR generated to determine whether the sponsor conducted a root cause analysis concerning this error. Currently, it appears that this is an isolated incident, but it is recommended that the review division review the datasets to determine if additional subjects were randomized that did not meet the eligibility criteria of either fewer than three complete spontaneous bowel movements (CSBMs) per week and fewer than six spontaneous bowel movement (SBMs) per week during the screening period.

b. Subject (b) (6) was assessed on (b) (6) (Study Visit 4), 1 (b) (6), and (b) (6), prior to the subject deciding on (b) (6) to withdraw from the study due to failed blood draw attempts on (b) (6) and (b) (6). The investigator failed to perform the following protocol required early termination visit assessments for Subject (b) (6): physical examination and ECG. In addition, for Subject (b) (6) the investigator failed to conduct the protocol required follow up phone call to assess for new adverse events.

Reviewer note: In his response, the CI noted that, because the subject withdrew due to difficulties with blood drawings, the site chose not to call the subject back to avoid any undue stress on the subject. This regulatory violation does not have any impact on data integrity.

2. Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation. Specifically, for Subject (b) (6) in Study BLI400-302, source data does not match data reported to the sponsor regarding whether the subject met BM entry criteria at Visit 2. According to the data that Subject (b) (6) entered into the eDiary during the screening period, the subject failed BM entry criteria for the study since the subject reported having more than three

CSBMs per week during the screening period. The subject reported in the eDiary having nine CSBMs on (b) (6). The CI documented on the (b) (6) Visit 2 paper case report form (CRF) that Subject (b) (6) did not screen fail due to the BM entry criteria. The CI documented in the electronic CRF, electronically signed by him on (b) (6), that the subject continued to meet all criteria for randomization at Visit 2 on (b) (6) even though the subject did not meet the eligibility criterion of an average of fewer than three CSBMs per week during the 14-day screening period. On (b) (6), the CI randomized and dispensed study drug to Subject (b) (6), who completed the study.

Reviewer note: In his response, the CI notes that he depended on the eDiary for this information.

Dr. Mahmud adequately responded to the inspection findings in a letter dated March 11, 2019.While inspectional observations were noted, they do not appear to have a significant impact on data reliability or on the rights, safety, or welfare of subjects. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

5. Braintree Laboratories, Inc.
   60 Columbian St. West, Braintree, MA 02184

This sponsor inspection was issued to review the conduct of clinical studies performed in support of NDA 211281. The inspection audited Protocol BLI400-302 and focused on the following clinical investigators: Site 2 (Acosta) and Site 29 (Mahmud).

The inspection reviewed the following: organizational chart, standard operating procedures, quality assurance and clinical operations, study monitoring plans and reports, electronic diary (eDiary) data, guidances and procedures, eDiary alerts, eCRFs, and test article reconciliation. It was requested that the FDA investigator review drug accountability and compare this with eDiary results for some subjects who appeared to have not taken study drug. There were discrepancies found between eDiary entry and drug accountability records. For example, Subject # (b) (6) did not have any reported instances of taking study drug according to the eDiary entries. The eCRF shows Subject # (b) (6) was routinely supplied study drug and brought back used study drug throughout their participation of the study. Overall, the sponsor fulfilled their responsibilities.

Reviewer note: The study sites documented the amount of study drug return within the eCRFs. Therefore, there could potentially be subjects who did not accurately report test article compliance in the eDiary, however, they may have taken all or most doses as per the test article data within the eCRF.

A Form FDA 483, Inspectional Observations, was issued at the end of the inspection because the investigator did not comply with the general investigational plan and was not promptly brought into compliance by the sponsor. Specifically,

the primary endpoint for this study was based on the number of complete spontaneous bowel movements as reported by subjects using an electronic diary. Per the protocol, subjects should be completing their electronic diary daily reporting during the treatment period of the study. However, Study Site #002 had five out of 26 randomized subjects (Subjects (b) (6)) who did not have any documented bowel movement electronic diary data for their entire participation within the treatment period of the study

The issues concerning non-compliance with the eDiary for efficacy assessments and for medication compliance were discussed with the review division on April 12, 2019 after the inspection of Site 002. Information requests were sent to the sponsor requesting medication compliance data based on drug accountability. An analysis of study subjects comparing date of last visit and date of last diary entry was also requested.

The sponsor responded to the IR on May 15, 2019. The sponsor responded to the items listed on the Form FDA 483, inspectional observations, in a letter dated May 23, 2019. They acknowledged the issues and proposed corrective action.

The study appears to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.

{See appended electronic signature page}

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Good Clinical Practice Assessment Branch
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatric and Maternal Health Memorandum

Date: June 13, 2019 **Date Consulted:** December 6, 2018

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne Yao, MD, Director
Division of Pediatric and Maternal Health

To: Andrew Kelleher, Regulatory Project Manager (RPM)
Division of Gastroenterology and Inborn Error Products (DGIEP)

Drug: Lactitol powder for oral solution

NDA: 211281

Proposed Indication: Treatment of chronic idiopathic constipation in adults

Applicant: Braintree Laboratories, Inc.

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- NDA 211281 submitted on November 21, 2018
- Applicant's pregnancy case summary submitted February 28, 2019

Consult Question: DGIEP requests DPMH assistance with the PLLR labeling review for this new molecular entity (NME).

INTRODUCTION

On November 21, 2018, the applicant, Braintree Laboratories, Inc., submitted NDA 211281 for a new molecular entity (NME), lactitol. On December 6, 2018, DGIEP consulted DPMH to provide input on the proper format and content of the *Pregnancy* and *Lactation* subsections of lactitol labeling to be in compliance with the Pregnancy and Lactation Labeling Rule (PLLR).

REGULATORY HISTORY

- Lactitol is an osmotic laxative with a proposed indication for the treatment of chronic idiopathic constipation (CIC) in adults.
- Lactitol has been approved and marketed (Tradenames: Importal, Emportal, Portolac) since 1985 outside of the U.S. by a different sponsor in several countries including Switzerland and the European Union (EU) for the treatment of constipation and for hyperammonemia which occurs with hepatic encephalopathy (HE).
- On February 1, 2019, the Agency sent the applicant an information request (IR) to provide the narratives for cases of lactitol exposure during pregnancy or lactation during clinical trials.
- On February 28, 2019, the Applicant submitted the requested supporting information.

BACKGROUND

Drug Characteristics[1]

- *Description:* minimally absorbed, colonically metabolized sugar alcohol (polyol).
- *Mechanism of action:* osmotic laxative, obligating the influx of water into the small intestine which is delivered to the colon and promotes a bowel movement.
- *Dosage and Administration:* dilute 21 grams in 4-8 oz of water, juice, or other beverage and take once, preferably with meals.
- *Molecular weight:* 362.33 Daltons
- *Bioavailability:* <1% in animal studies
- *Adverse reactions:* diarrhea, flatulence, upper respiratory tract infection, increased blood creatinine phosphokinase, nasopharyngitis, abdominal distension

REVIEW

PREGNANCY

Nonclinical Experience[1]

Oral administration of up to 2,000 mg/kg/day in rats and 1,000 mg/kg/day in rabbits during organogenesis produced no maternal toxicity, no effects on embryo-fetal development and no teratogenicity. Oral administration of up to 500 mg/kg/day in rats during organogenesis through lactation produced no developmental abnormalities or effects on growth, learning and memory, or fertility in the offspring through maturation. No effect was observed on body weights (growth or gestation), sexual maturation, clinical findings, behavior (learning and memory), reproductive performance/fertility indices, GD13 uterine implantation data, and macroscopic findings.

The maximum recommended human dose is approximately 0.35 mg/kg/day, based on a 60-kg body weight. Limited systemic exposure to (b) (4) was achieved in animals during organogenesis (AUC = 9 and 51 mcg•hr/mL in rats and rabbits, respectively, at the highest dose

(b) (4)

levels). Based on AUC, the relative extent of exposure to lactitol in animals compared to humans ranged from 1.53-fold (single oral doses in fed animals) to approximately 66-fold higher (in pregnant rabbits). For more details, refer to the Nonclinical Review by Tamal Chakraborti, PhD.

Clinical Trials

Pregnant women were excluded from lactitol clinical trials. The applicant stated two patients were confirmed to have become pregnant during Braintree-sponsored studies of lactitol (see Table 1 below). Lactitol was discontinued upon the diagnosis of pregnancy in each case.

Table 1: Pregnancy Cases during Lactitol Clinical Trials*

Patient ID	Lactitol Exposure	Gestational timing	Outcome
(b) (6) Study BLI400-303	21 g daily	Preconception to 5 weeks EGA	Term-live birth no complications
(b) (6) Study BLI400-302	10.5 g daily	Preconception to 7 weeks EGA	Term-live birth no complications

*Source: Reviewer's Table

Review of Published Literature

-Applicant's Review: The applicant did not perform a review of published literature relevant to lactitol use during pregnancy. The applicant stated experience with the use of lactitol during pregnancy is limited; however, animal experiments have not shown evidence of a teratogenic potential.[2]

-DPMH's Review: PubMed, Embase, Micromedex[3], TERIS[4], Reprotox[5], and Briggs[6] were searched using "lactitol" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," and "miscarriage." No relevant publications were identified.

Reviewer's Comment

The available human data from two pregnancy cases reported during clinical trials are insufficient to evaluate for any drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Limitations of these data include the small number of exposed cases and the limited duration of drug exposure (lactitol was discontinued early in the 1st trimester at the time of pregnancy diagnosis in both cases). Considering the minimal systemic absorption of lactitol in adults, the amount of fetal exposure is unknown but likely to be low. Therefore, a postmarketing requirement to study the safety of lactitol use in pregnant women is not suggested despite the potential for wide use in women of reproductive potential with CIC.

[2] Lactitol (NDA 211281) Clinical Summary of Safety.
[3] Truven Health Analytics information, http://www micromedexsolutions.com/Accessed 5/6/19.
[4] TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 5/6/19.
[5] Reprotox® Website: www.Reprotox.org. REPROTOX® system Accessed 5/6/19.
[6] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.

LACTATION

Nonclinical Experience

Oral administration of up to 500 mg/kg/day in rats during organogenesis through lactation produced no developmental abnormalities or effects on growth, learning and memory, or fertility in the offspring through maturation. For more details, refer to the Nonclinical Review Tamal Chakraborti, PhD.

Clinical Trials

Lactating patients were excluded from lactitol clinical trials. The applicant states there were no reports of infant exposure to lactitol through breastfeeding.

Review of Published Literature

-Applicant's Review: The applicant did not perform a published literature search relevant to lactitol use during lactation. The applicant stated no studies have been conducted to investigate whether lactitol passes into breastmilk; however, as the absorption of lactitol is minimal, the clinical relevance appears to be low.[2]

-DPMH's Review: PubMed, Embase, Micromedex[7], TERIS[8], Reprotox[9], and Briggs[10], *Medications and Mother's Milk*[11], and LactMed[12] were searched using "lactitol" AND "breastfeeding" or "lactation." No relevant publications were identified.

Reviewer's Comment

Systemic exposure to lactitol in the breastfed infant is unlikely because the maternal systemic exposure is minimal. The effect of any exposure to lactitol in the gastrointestinal tract of the breastfed infant is unknown, but not likely to be clinically relevant.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

No adverse effects on fertility were observed in rats after administration of lactitol by oral gavage at doses up to 10 g/kg/day.[13] For more details, refer to the Nonclinical Review by Tamal Chakraborti, PhD.

[7] Truven Health Analytics information, http://www micromedexsolutions.com/Accessed 5/6/19
[8] TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 5/6/19
[9] Reprotox® Website: www.Reprotox.org. REPROTOX® system Accessed 5/6/19
[10] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.
[11] Hale, Thomas (2017) Medications and Mothers' Milk. Amarillo, Texas. Hale Publishing.
[12] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. LactMed is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare providers and nursing women. LactMed provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 5/6/19
[13] Ninomiya H, et al. Reproductive and developmental toxicity studies of lactitol (NS-4) (1)—fertility study in rats by oral administration. 1994, J Toxicol Sci, 19 Suppl 3L429-439.

Review of Published Literature

-Applicant's Review: The applicant did not perform a published literature search relevant to lactitol use and effects on male or female fertility.

-DPMH's Review: PubMed, Embase, Reprotox[5] were searched using, "lactitol" AND "fertility," "infertility," "contraception," and "oral contraceptives." No relevant publications were identified.

DISCUSSION AND CONCLUSIONS

Pregnancy

DPMH recommends subsection 8.1 of labeling state that lactitol is minimally absorbed systemically following oral administration, and it is unknown whether maternal use will result in fetal exposure to the drug. Overall, the available data from two exposure cases during clinical trials are not sufficient to evaluate for any drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Animal studies do not suggest lactitol causes embryo-fetal toxicity.

Lactation

DPMH recommends subsection 8.2 of labeling for lactitol state that there are no data on the presence of lactitol in human milk, the effects on the breastfed infant, or the effects on milk production. It is unknown whether the minimal systemic absorption of lactitol by adults will result in a clinically relevant exposure to breastfed infants. Therefore, DPMH recommends including the following risk/benefit statement for lactation, "the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for lactitol and any potential adverse effects on the breastfed infant from lactitol or from the underlying maternal condition."

Females and Males of Reproductive Potential

DPMH recommends subsection 8.3 of labeling for lactitol be omitted because there are no available human data and animal data do not suggest lactitol adversely effects fertility. Pregnancy testing and contraception headings are not recommended because the available data do not suggest an increased risk of embryo-fetal toxicity or mutagenicity.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR. The labeling recommendations below reflect input from the Clinical Pharmacology and Nonclinical Review Teams. DPMH discussed our labeling recommendations with DGIEP on May 28, 2019. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Lactitol Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Lactitol is minimally absorbed systemically following oral administration *[see Clinical Pharmacology (12.3)]*, and it is unknown whether maternal use will result in fetal exposure to

the drug. Available data from case reports on lactitol use in pregnant women are not sufficient to evaluate for any drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal developmental studies, no effects on embryo-fetal development were observed with oral administration of (b) (4) to rats and rabbits during organogenesis at doses much higher than the maximum recommended human dosage *(see Data).*

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Reproduction studies have been performed in pregnant rats at oral doses of lactitol up to 2000 mg/kg/day (about 0.93 times the recommended daily human dose based on body surface area) and in pregnant rabbits at oral doses up to 1000 mg/kg/day (about 0.93 times the recommended daily human dose based on body surface area) administered during the period of organogenesis. These studies did not reveal any evidence of harm to the fetus due to lactitol.

In a pre-and postnatal development study in rats, lactitol, administered from gestation day 6 to lactation day 20, did not cause any adverse effect on pre and postnatal development up to 2000 mg/kg/day (about 0.93 times the recommended daily human dose based on body surface area).

Lactation

Risk Summary

There are no data on the presence of lactitol in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Lactitol is minimally absorbed systemically following oral administration *[see Clinical Pharmacology (12.3)]*. It is unknown whether the minimal systemic absorption of lactitol by adults will result in a clinically relevant exposure to breastfed infants. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for lactitol and any potential adverse effects on the breastfed infant from lactitol or from the underlying maternal condition.

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/s/

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M E M O R A N D U M

From: Ramy Abdelrahman, MD, Commissioner Fellow

Division of Pediatric and Maternal Health (DPMH)

Through: Hari Cheryl Sachs, MD, Team Leader

John J. Alexander, MD, MPH, Deputy Division Director
DPMH

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug Name: BLI400 Lactitol Monohydrate

NDA (Associated IND): 211281 (118906)

Sponsor: Braintree Laboratories, Inc.

Proposed Indication: Treatment of chronic idiopathic constipation (CIC) in adults

Proposed dosing (adults): 21g per day (powder dissolved in 4 to 8 oz of liquid). May decrease to 10.5g per day if diarrhea / loose stools

Background:

On June 29, 2018, Braintree Laboratories, Inc submitted a 505(b) new drug application (NDA) for their BLI400 (lactitol monohydrate) powder for reconstitution for oral administration which is proposed for use in the treatment of chronic idiopathic constipation (CIC).

BLI400 is a new chemical entity, a minimally absorbed polyol sugar, that is designed as an osmotic laxative. Lactitol has been marketed since 1985 in countries outside the US for the treatment of constipation, as well as for the treatment of hepatic encephalopathy.

Regulatory history:

The following regulatory history was provided by DGIEP:

- On June 17, 2013, IND118906 was submitted by the sponsor.
- On January 14, 2014, an End of Phase 2 (EOP2) meeting was held.
- On March 2014, the sponsor submitted the initial pediatric study plan (iPSP) for their IND.
- On April 2014, DGIEP informed the sponsor that the iPSP submission was materially incomplete and could not be reviewed, recommending that the sponsor submit a revised iPSP within 30 days.
- On May 2014, the sponsor submitted the revised iPSP, however the submission was not coded properly in DARRTS and was not reviewed.
- On June 2016, DGIEP sent an Advice Letter/IR requesting information on the adult program and an update on the status of the iPSP.
- On August 2016 Sponsor responded and acknowledged that no further comment had been received from FDA since the May 2014 submission of the revised iPSP.
- There is no further communication or reviews in DARRTS related to the iPSP.
- On February 2018, the sponsor submitted a PPSR outlining studies for pediatric patients with constipation in ages 6 months and older.
- During the review of the PPSR, the DGIEP identified that there was no agreed iPSP; therefore, the project manager spoke with the sponsor and requested that the sponsor submit a revised iPSP in accordance with the most recent PSP Guidance.
- On May 2018, a revised iPSP was submitted.
- On June 2018, DGIEP issued an Inadequate Letter for the PPSR, outlining concerns for the constipation program, including issues with study design, endpoint selection and treatment duration as well as failure to address other indications (e.g., hepatic encephalopathy).
- Of note, the revised iPSP was submitted before the sponsor received the comments on the PPSR. Consequently, the iPSP has the same deficiencies as the PPSR.

- On June 29, 2018, the NDA was submitted without an agreed iPSP, and no pre-NDA meeting was requested by the sponsor.

Adequacy of the applicant's Pediatric Study Plan:

There were several issues that precluded the agreement of the applicant's iPSP during the filing period

- The sponsor proposed an efficacy study in pediatric patients 6 months and older, (b) (4) (b) (4) Although DGIEP has determined juvenile animal studies are needed to support studies in patients less than 6 years of age, studies in patients 6y and older could be done concurrently.
- The sponsor did not address the extrapolation of efficacy to specific pediatric populations.
- The sponsor proposed to defer protocol submissions and start of pediatric studies until after approval of BLI400 in the adult population has been obtained. Pediatric protocols should be submitted as soon as possible; these could be initiated once available data suggest an acceptable safety profile and clinical benefit of BLI400 in adult patients.
- There were several study design issues including patient population, endpoint selection and treatment duration that need to be addressed.

Recommended Regulatory Action:

The lack of an agreed-upon iPSP is a refuse to file issue for this application. DPMH recommends a refuse to file for this application under 21 CFR 314.101(d) for the following reasons:

- ***The sponsor has submitted the NDA without an Agreed iPSP.***
- ***Sponsor has been aware that an Agreed iPSP is required at the time of NDA submission.***
- ***The proposed indication (CIC) is not a life threating condition, with multiple other treatment options available to adults.***

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RAMY ABDELRAHMAN
08/22/2018

HARI C SACHS
08/22/2018
I agree with these recommendations, noting that the RTF action was also supported by the Pediatric Review Committee (which is distinct from DPMH)

JOHN J ALEXANDER
08/22/2018