

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**211281Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Division of Risk Management (DRISK)**  
**Office of Medication Error Prevention and Risk Management (OMEPRM)**  
**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

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**Application Type** NDA  
**Application Number** 211281  
**PDUFA Goal Date** February 21, 2020  
**OSE RCM #** 2018-1599

**Reviewer Name** Yasmeen Abou-Sayed, PharmD  
**Team Leader** Donella Fitzgerald, PharmD  
**Deputy Division Director** Jamie Wilkins, PharmD, MPH  
**Review Completion Date** December 9, 2019  
**Subject** Evaluation of Need for a REMS

**Established Name** Lactitol monohydrate  
**Trade Name** Pizensy  
**Name of Applicant** Braintree Laboratories, Inc.  
**Therapeutic Class** Osmotic laxative  
**Formulation(s)** Powder for reconstitution for oral solution

**Dosing Regimen**



(b) (4)

**Table of Contents**

EXECUTIVE SUMMARY ..... 3

1 Introduction ..... 3

2 Background ..... 3

    2.1 Product Information ..... 3

    2.2 Regulatory History..... 4

3 Therapeutic Context and Treatment Options ..... 4

    3.1 Description of the Medical Condition ..... 4

    3.2 Description of Current Treatment Options ..... 4

4 Benefit Assessment ..... 6

5 Risk Assessment & Safe-Use Conditions ..... 7

    5.1 Adverse events of special interest..... 8

        5.1.1 Hypertension..... 9

6 Expected Postmarket Use..... 10

7 Risk Management Activities Proposed by the Applicant..... 10

8 Discussion of Need for a REMS..... 10

9 Conclusion & Recommendations..... 11

10 Appendices ..... 11

    10.1 References..... 11

## EXECUTIVE SUMMARY

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This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Pizensy (lactitol) is necessary to ensure the benefits outweigh its risks. Braintree Laboratories Inc. submitted a New Drug Application (NDA) 211281 for lactitol with the proposed indication for the treatment of chronic idiopathic constipation (CIC) in adults. The risks associated with lactitol include hypertension. The applicant did not submit a proposed REMS or risk management plan with this application.

Division of Risk Management (DRISK) has determined that a REMS is not needed to ensure the benefits of lactitol outweigh its risks. The potential risk of hypertension seen with lactitol therapy appears to be spurious, without a plausible explanation for why it may occur.<sup>1</sup> No other serious risks have been associated with lactitol in the clinical development program, or post-marketing experience in Europe.

## 1 Introduction

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This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Pizensy (lactitol) is necessary to ensure the benefits outweigh its risks. Braintree Laboratories Inc. submitted a New Drug Application 211281 under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for lactitol with the proposed indication for the treatment of chronic idiopathic constipation (CIC) in adults. This application is under review in the Division of Gastroenterology and Inborn Errors Products (DGIEP). The applicant did not submit a proposed REMS or risk management plan with this application.

## 2 Background

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### 2.1 PRODUCT INFORMATION

Lactitol is a new molecular entity (NME)<sup>a</sup>, and is a minimally absorbed, colonically metabolized sugar alcohol, designed as an osmotic laxative.<sup>2</sup> Lactitol is a synthetic derivative of lactose and consists of galactose and sorbitol linked through a glycoside bond. Because it is minimally absorbed, it promotes the delivery of extra fluid to the colon, thereby encouraging a bowel movement. The proposed indication is for the treatment of chronic idiopathic constipation (CIC) in adults. The product is formulated as a powder for reconstitution for oral administration for daily, chronic use.<sup>b</sup> The Applicant's proposed labeling includes the following dosage and administration recommendations:

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<sup>a</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

<sup>b</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

Lactitol has been marketed since 1985 in European countries for the treatment of constipation as well as hyperammonemia which occurs with hepatic encephalopathy.<sup>3</sup> It is also currently available in the US as a low-calorie sweetener food additive and has been 'generally recognized as safe' in that context.<sup>4</sup>

## 2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 211281 relevant to this review:

- 11/21/2018: NDA 211281 submission for chronic idiopathic constipation received
- 5/8/2019: A Mid-Cycle communication was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for Pizensy
- 5/21/2019: Major amendment containing a reanalysis of adverse events for phase 3 studies, as requested by the FDA to exclude data from sites associated with misconduct, received
- 6/14/2019: Major amendment acknowledgment letter sent to the applicant; PDUFA goal date extended by 3 months to February 21, 2010

## 3 Therapeutic Context and Treatment Options

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### 3.1 DESCRIPTION OF THE MEDICAL CONDITION

Chronic idiopathic constipation (CIC) is a functional constipation associated with symptoms of straining, lumpy/hard stools, incomplete evacuation, sensation of anorectal obstruction,  $\leq 3$  defecations/week, and requiring manual maneuvers for defecation in greater than 25% of bowel movements. Chronic idiopathic constipation has a prevalence of 14- 20% in the United States and 45% of sufferers report having the condition for 5 years or more.<sup>5,c</sup> Chronic idiopathic constipation has a significant impact on patients. CIC can lead to social isolation since symptoms are associated with eating. Additionally, there may be fear that symptoms will recur, and patients experience frustration due to the lack of effective therapies and lack of empathy of family and friends for this distressing condition.<sup>2,d</sup> The agency recognizes a need for additional treatment options for patients with CIC.<sup>5</sup>

### 3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

There are multiple FDA approved products for the treatment of CIC (Table 1). The use of polyethylene glycol (PEG) is one of the mainstays of treatment. However, the label for PEG recommends use be limited to 7 days, a significant limitation due to the chronic nature of CIC where years of treatment may prove necessary. Biofeedback is effective for patients with pelvic floor dyssynergia. Non-FDA approved treatments of uncertain benefit include fiber supplementation and hydration.<sup>6</sup>

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<sup>c</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.

<sup>d</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.

**Table 1 Summary of therapies for chronic idiopathic constipation**

<b>Product Trade Name (Generic)</b>	<b>Indication</b>	<b>Dosing/Administration</b>	<b>Important Safety and Tolerability Issues</b>	<b>Risk Management Approaches/ Boxed Warning, Medication Guide</b>
<b>FDA Approved Treatments</b>				
Polyethylene Glycol OTC 2008	Occasional constipation	17 g dissolved in 4-8 ounces of water. Use once a day, no more than 7 days	May cause loose, watery stools	
Linacotide 2012	Chronic idiopathic constipation (CIC) in adults	145 mcg capsules once daily orally	Diarrhea	Boxed warning for severe diarrhea in children
Lubiprostone 2006	CIC in adults	24 mcg capsules twice daily orally	Nausea Diarrhea Syncope Dyspnea Not to be used in setting of bowel obstruction	
Plecanatide 2017	CIC in adults	3 mg capsule oral once daily	Diarrhea	Boxed warning for risk of serious dehydration in children. Contraindicated in children < 6 years of age.
Prucalopride 2018	CIC in adults	2 mg oral once daily	Suicidal ideation and behavior	Medication Guide
<b>Other Treatments</b>				
Biofeedback may be effective in patients with pelvic floor dyssynergia.				
Fiber supplements and hydration are widely recommended but of uncertain benefit.				

## 4 Benefit Assessment

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The efficacy of lactitol for CIC was studied in two phase 3 studies, Study 301 (National Clinical Trial [NCT] 02481947) and Study 302 (NCT02819297). Both studies were designed as double-blind, randomized, multicenter clinical trials and enrolled adults who averaged less than 3 spontaneous bowel movements per week during a 14-day screening period. Additionally, subjects were provided bisacodyl 5mg tablets to use as rescue medication and were instructed to take 5-10 mg if they experienced severe discomfort or had not had a bowel movement in 4 days.

Study 301 evaluated daily treatment with 21 gm lactitol versus 48 mcg of lubiprostone for 12 weeks and enrolled 459 subjects, in order to demonstrate non-inferiority of lactitol. The primary efficacy endpoint was the proportion of subjects who were weekly responders for at least 9 out of 12 weeks, with at least 3 of those weeks occurring in the last 4 weeks of treatment. A weekly responder was defined as having  $\geq 3$  complete spontaneous bowel movements (CSBMs) and an increase from baseline of  $> 1$  CSBM for that given week. A predetermined margin of -12.6% was specified by the Applicant, to demonstrate non-inferiority of lactitol to lubiprostone. The -12.6% margin was not based on comparisons between the active comparator and placebo and was not met based on the results in the trial. Based on the intent to treat (ITT) population, which excluded subjects from a site currently under investigation for fraudulent results, 47 subjects were responders on lactitol (21.1%), and 57 subjects responded to lubiprostone (25.7%). This treatment margin of -4.6, with a 95% confidence interval ranging from -12.5 to 3.3, barely excluded the non-inferiority margin.

Upon performing further analyses to assess the robustness of study 301, the clinical reviewer determined the study was not adequate to stand alone as a trial to support efficacy, based on the Applicant's choice to set the non-inferiority margin on data from a different drug (linaclotide, versus the lubiprostone used in the study), and the study results were marginal. Additionally, the Applicant had not performed a placebo-controlled study at the time of Study 301, and therefore did not have an appropriate comparator population. However, as lactitol has been marketed in other countries for over 30 years as a treatment for constipation, there are several publications on placebo-controlled and active-controlled efficacy trials with lactitol in CIC. It was decided that those publications, along with a comparison of the lactitol arm from Study 301 to placebo arms from other trials in CIC provided supportive information on the efficacy of lactitol.<sup>6</sup>

Study 302 compared daily treatment with 21 gm lactitol versus placebo for 24 weeks in 623 subjects. The primary endpoint was the proportion of subjects who were weekly responders for at least 9 weeks out of the first 12 week treatment period, with at least 3 of those weeks occurring in the last 4 weeks of the first 12-week treatment period. A weekly responder was defined as having  $\geq 3$  CSBMs and an increase from baseline of  $> 1$  CSBM for that given week. Of note, rescue medication use was accounted for in the primary endpoint analysis, with a CSBM 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. The ITT population as determined by the clinical reviewer was reduced to 594 subjects, due to study site misconduct at one of the sites, a loss of data due to a fire at a second site, two subjects who enrolled at multiple sites, and missing baseline data on other subjects. In the ITT, 25.1% of the

subjects on lactitol were found to be responders (n = 73) versus 12.9% of subjects on placebo (n=39), and the difference in treatment effect was found to be statistically significant (p<0.001).

Overall, the clinical reviewer has concluded, based on the collective evidence from studies 301 and 302, combined with published literature, lactitol demonstrated efficacy for the treatment of CIC in adults.<sup>e</sup>

## 5 Risk Assessment & Safe-Use Conditions

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The safety review for lactitol was based on the three phase 3 trials, the previously described studies 301 and 302, in addition to data collected from Study 303.<sup>7</sup> Study 303 (NCT02819310) was a long-term, open-label, uncontrolled study designed to assess the safety of lactitol and enrolled 298 subjects. Because of the varying study designs (placebo-controlled, active comparator, long-term open-label uncontrolled), safety findings were evaluated in each trial by the clinical reviewer independently. There were 807 patients treated with lactitol in the phase 3 trials. 698 (86%) of those patients were exposed to lactitol for 3 months, 473 (59%) were exposed to lactitol for 6 months and 220 (27%) were exposed to lactitol for 12 months.

In study 301, the most common adverse events (AEs) in subjects receiving lactitol were flatulence (7.8%), diarrhea (5%), headache (2.3%), blood creatinine phosphokinase increase (2.3%), and abdominal distension (2.3%). All these events occurred at a similar rate to subjects in the lubiprostone group, except for flatulence. This can be attributed to the mechanism of action of lactitol, which is a fermentable carbohydrate. There were two severe AEs (SAEs) in the lactitol group, one death and one instance of cellulitis. The death occurred in a female patient with history of schizophrenia and ongoing depression. The patient completed study treatment with lactitol and was found dead in her apartment two weeks after completing the study treatment, on the day she was scheduled for her 98 day follow up phone call. Her death was ascribed by the coroner as “natural, sudden unexplained death in schizophrenia.” The principal investigator reported this death as unrelated to lactitol, and the clinical reviewer concurred.<sup>1</sup> The cellulitis occurred in a 57-year-old female, with a history of diabetes who presented to the ER with high blood sugar and lower extremity edema. The cellulitis event appears to be unrelated to lactitol.<sup>1</sup>

In study 302, the most common adverse events, as compared to placebo, are shown in table 2:

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<sup>e</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

Table 2 – Adverse events reported in the ITT population of Study 302 with a higher incidence than placebo

<b>Adverse Event</b>	<b>Lactitol (N=291) n (%)</b>	<b>Placebo (N=302) n (%)</b>
<b>Upper respiratory tract infection</b>	25 (8.6)	19 (6.3)
<b>Flatulence</b>	23 (7.9)	8 (2.6)
<b>Diarrhea</b>	13 (4.5)	9 (3.0)
<b>Blood creatine phosphokinase increased</b>	12 (4.1)	9 (3.0)
<b>Abdominal distension</b>	10 (3.4)	2 (0.7)
<b>Back pain</b>	7 (2.4)	3 (1.0)
<b>Gastroenteritis</b>	7 (2.4)	2 (0.7)

The frequency of common AEs between lactitol and placebo were generally similar, except for flatulence, diarrhea, and abdominal distension. This can be attributed to the mechanism of action of lactitol. SAEs occurred in 8 lactitol subjects in this study. Six of the patient's SAEs were in the gastrointestinal system, and included abdominal pain, diarrhea, abdominal distension, and flatulence. The other two SAEs were related to hypertension and are described further below.

In study 303 findings, the most frequent common AEs were diarrhea (7.7%), flatulence (5.4%), urinary tract infection (5.4%), abdominal pain (2.7%), abdominal distension (2.3%), and upper respiratory infection (2.3%). A total of 16 (5.4%) subjects reported SAEs; the two types of events related to lactitol treatment were 4 subjects with flatulence and 3 with diarrhea. None of the remaining SAEs were related to study drug.

Lactitol was discontinued by 2.3% of patients in study 301 for various reasons unrelated to study drug. In study 302, 3.8% patients discontinued lactitol for AEs similar to the most common AEs reported overall (i.e. flatulence, stomach cramps, diarrhea, etc.). In study 303, 4.4% of subjects discontinued due to AEs, also for reasons similar to the most common AEs reported (flatulence, diarrhea, nausea, and abdominal pain).

In addition to the safety information submitted in the NDA, DGIEP requested the Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur's Assessment from the European Medicines Agency (EMA) to inquire about post-marketing safety concerns.<sup>8</sup> The EMA PRAC's assessment did not provide information that would change the overall evaluation of benefit-risk for lactitol.

## **5.1 ADVERSE EVENTS OF SPECIAL INTEREST**

### 5.1.1 Hypertension

Although the percentages are small, there was an imbalance of patients with hypertension and increased blood pressure in the lactitol treatment group compared to the placebo in Study 302. In addition, there was a relatively high frequency of patients with hypertension and related terms in Study 303, although the absence of controlled data for this longer trial (up to 1-year duration) makes it difficult to determine if a safety signal is present for this common AE in the general population. The events of hypertension, blood pressure increased, and blood pressure systolic increased for the three phase 3 trials are shown below in Table 3:

**Table 3: Blood Pressure Related Treatment Emergent Adverse Events in studies 301, 302, 303**

Preferred term	Lactitol (301, 302, 303) n = 814	Placebo (Study 302) n = 302	Amitiza (Study 301) n = 222
Hypertension	13	1	1
Blood pressure increased	6	1	0
Blood pressure systolic increased	1	0	0

In study 302, a 68-year-old female had a cerebrovascular accident, 2 weeks after discontinuing the study medication. The patient enrolled in the study with elevated blood pressure, which subsequently elevated through the study. This continued elevation makes it plausible that lactitol contributed to her SAE, however her blood pressure after discontinuing lactitol is unknown, and a complete cardiac history is unavailable for the subject. The second SAE in study 302 was an incident of elevated blood pressure in a 71-year-old male who enrolled in the study with a history of hypertension and was hospitalized during the course of the study for elevated blood pressure, secondary to poor compliance with his blood pressure medication. This incident was determined to be unlikely related to study drug.

It is important to note that the clinical development program for lactitol was not designed to evaluate blood pressure, nor was there standardization in the measurements of blood pressure. Blood pressure measurements can be affected by proper cuff size and placement, wrapping the cuff over clothing, time of day, and patient position. The study protocols did not specify exclusion criteria for hypertension and many patients had hypertension or risk factors at baseline. The protocols also did not specify the criteria for considering blood pressure changes as AEs. DGIEP sent an information request (IR) to further investigate the potential hypertension safety signal and based on the information provided along with the limitations previously defined, the clinical reviewer determined that there is no plausible mechanism

by which lactitol could cause hypertension and the balance in hypertension AE's is likely a spurious finding.<sup>5,9,f</sup>

## 6 Expected Postmarket Use

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Chronic idiopathic constipation is a common disorder affecting the adult population. Patients are likely to be treated by multiple prescriber types including generalists and mid-level providers in inpatient and outpatient settings.

## 7 Risk Management Activities Proposed by the Applicant

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The Applicant did not propose any risk management activities for lactitol beyond routine pharmacovigilance and labeling.

## 8 Discussion of Need for a REMS

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The Clinical Reviewer recommends approval of lactitol on the basis of the efficacy and safety information currently available.

Chronic idiopathic constipation is a common, long lasting and distressing condition for patients with significant impact on quality of life. Lactitol has been demonstrated to have a positive clinical benefit to treat the symptoms of CIC. The potential risk of hypertension associated with lactitol seems to be a spurious finding, based on a lack of plausibility. Additionally, lactitol is widely used outside the US with no safety restrictions and no significant safety signals identified.

Post marketing experience from the use of lactitol in the United States as a food additive, as well as data available from European marketing of lactitol as a drug, was evaluated by the Division of Pharmacovigilance.<sup>10</sup> Additionally, DGIEP requested the Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur's Assessment from the European Medicines Agency (EMA) to inquire about post-marketing safety concerns.<sup>11</sup> Neither of these assessments provided information that would change the overall evaluation of benefit-risk for lactitol.

Labeling will be used to communicate to prescribers the potential common adverse events associated with lactitol, including hypertension in the table of common adverse events, found in Section 6 of the Prescribing Information.<sup>12</sup> The overall limited risks of lactitol in the setting of a large population likely to benefit from treatment does not require a REMS to ensure that benefits outweigh the risks.

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<sup>f</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

## 9 Conclusion & Recommendations

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Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for lactitol to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

## 10 Appendices

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### 10.1 REFERENCES

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<sup>1</sup> Division of Gastroenterology and Inborn Errors Products. Draft Unireview for Pizensy (lactitol), NDA 211281, October 29, 2019.

<sup>2</sup> Braintree Laboratories, Inc. Clinical Overview for Pizensy, November 21, 2018.

<sup>3</sup> Braintree Laboratories, Inc. Summary of Clinical Efficacy for Pizensy, November 21, 2018.

<sup>4</sup> Faruqi AA, Joshi, C. Lactitol: A Review of its Use in the Treatment of Constipation. International Journal of Recent Advances in Pharmaceutical Research 2012; 2(1): 1-5.

<sup>5</sup> Heidelbaugh JJ, et al. The spectrum of constipation-predominant irritable bowel syndrome and chronic idiopathic constipation: US survey assessing symptoms, care seeking, and disease burden. The American journal of gastroenterology. 2015;110(4):580-587.

<sup>6</sup> Division of Gastroenterology and Inborn Errors Products. Draft Unireview for Pizensy (lactitol), NDA 211281, October 29, 2019.

<sup>7</sup> Braintree Laboratories, Inc. Summary of Clinical Safety for Pizensy, November 21, 2018.

<sup>8</sup> European Medicines Agency (EMA). Final Assessment Report for lactitol, May 13, 2016.

<sup>9</sup> Braintree Laboratories, Inc. Response to FDA Information Request, May 21, 2019.

<sup>10</sup> Hines, Michelle. Division of Pharmacovigilance. Pharmacovigilance Review for NDA 211281 lactitol, October 10, 2019.

<sup>11</sup> European Medicines Agency (EMA). Final Assessment Report for lactitol, May 13, 2016.

<sup>12</sup> Braintree Laboratories, Inc. Proposed Prescribing Information for Pizensy, September 9, 2019.

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