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Pizensy® (Lactitol) attempts to loosen the market in its treatment for Chronic Idiopathic Constipation

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Chronic idiopathic constipation (CIC) is a bowel disorder defined by the American College of Gastroenterology as the infrequent, difficult, or incomplete passage of stool.[1] It is one of the most common gastrointestinal disorders affecting approximately 14% of the population worldwide with a prevalence as high as 27% in North America.[2] CIC is a functional gastrointestinal disorder (FGID) in which there is usually no demonstrable underlying physiological abnormality. It is thought to be more common in women, elderly people, and those of lower socioeconomic status.[1] Constipation can negatively impact a patient's quality of life and interfere in a person's normal daily routine.

According to the American Gastroenterological Association (AGA), constipation can be classified into three clinical subgroups; normal transit constipation, slow transit constipation, and outlet dysfunction.[3] The first subgroup, normal transit constipation, is the most common subgroup and characterized by preserving normal colonic transit time between 20 and 72 hours. Slow transit constipation presents with a transit time of five or more days and is most often caused by slow peristalsis of the colon due to neurologic dysfunction of smooth muscle. Outlet dysfunction is associated with incomplete rectal evacuation due to incomplete relaxation of the anal sphincter or a structural obstruction in the rectum. About 50% of the patient population with outlet dysfunction also have concurrent slow transit constipation.3 Identifying the etiology of a patients' constipation can help tailor therapy and optimize results.[1] Tools like the Bristol Stool Form Scale (BSFS), which utilizes a noninvasive approach to classifying the patient's constipation by identifying the stool size and consistency, may aid a patient and their healthcare provider in forming a treatment plan for the patient.[4] Patients may report symptoms of abdominal pain, bloating, hard stools, infrequent bowel movements, and feelings or sensations of incomplete evacuation with CIC.[5]

As of 2016, Rome IV standards are the most updated classification of Functional Gastrointestinal Disorders (FGIDs). Per Rome IV measures for CIC, a patient must meet specific diagnostic criteria.[4] These include symptom onset at least six months before diagnosis, with symptoms present for at least the past three months, loose stools rarely present without the use of laxatives, and not meeting criteria for Irritable Bowel Syndrome (IBS). Additionally, two or more of the following for at least 25% of defecations must be present including straining, lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction/blockage, manual maneuvers to facilitate defecation, and fewer than three spontaneous bowel movements per week.[4]

There are multiple FDA approved products for the treatment of CIC.[5,6] Many groups and organizations have provided recommendations for the treatment of constipation, but no standardized guidelines have gained acceptance for general medical practice. Generally, most organizations agree the first option in the treatment of constipation is to begin with dietary and lifestyle adjustments with increased fiber intake and adequate hydration. If lifestyle changes do not work, supplementation with an osmotic laxative (magnesium hydroxide or polyethylene glycol), a stool softener (docusate), or a bulk forming agent (psyllium) is recommended. If these agents fail to relieve CIC, the organizations then suggest supplementing these agents with a stimulant laxative (bisacodyl or glycerol suppositories) or an enema. Other agents such as lubiprostone and linaclotide should be considered when symptoms do not respond to the previously mentioned strategies. Finally, if all measures of symptom relief fail, then surgery is utilized as a last resort to treat the identified disorder.

Pizensy® (lactitol), received FDA approval in February 2020 as an osmotic laxative option for the pharmacological treatment of chronic constipation categorized as either slow or normal transit.[5,6] Treatment of CIC is primarily aimed at producing more frequent bowel movements and improving stool consistency. The purpose of this article is to evaluate the clinical safety and efficacy of lactitol in the treatment of adult patients with chronic idiopathic constipation.

Pharmacology

Mechanism of Action

Lactitol is a minimally absorbed sugar alcohol, used as an osmotic laxative.[7] It is a synthetic derivative of lactose and con-

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sists of galactose and sorbitol linked through a glycoside bond. Because it is minimally absorbed in the small intestine, it exerts its osmotic effect by causing an influx of water into the small intestine leading to a laxative effect in the colon, thereby softening the stool and encouraging a bowel movement.[7]

Pharmacokinetics

After a 20 mg single oral dose of lactitol is administered, non-fasting adult patients reach peak serum concentration (Tmax) in 3.6 ± 1.2 hours.[7] If taken under fasting conditions, both the maximum plasma concentration (Cmax) and overall systemic absorption (AUC) of lactitol values increase greater than two-fold compared to fed conditions. During clinical trial evaluation, it was discovered that the mean half-life for lactitol is 2.4 hours and is generally minimally absorbed in the small intestine. Unabsorbed lactitol is degraded into organic acids in the colon and excreted in the feces.[7]

Table 1 | Select Lactitol Pharmacokinetics[7]

Absorption	
T_{max}[a]	3.6 ± 1.2 hours
Cmax[b]	776 ± 253 ng/mL
AUC[c]	6,019 ± 1,771 ng*hr/mL
Distribution	
No information available	
Metabolism	
No information available	
Elimination	
Half-life	2.4 hours

[a]Time to maximum plasma concentration; [b]Maximum plasma concentration; [c]Area under the curve
*Cmax and AUC values increase greater than 2-fold under fasted conditions compared to fed conditions.

CLINICAL TRIALS

The following section will review two phase III trials (NCT02481947, NCT02819297) conducted by Braintree Laboratories to evaluate the safety and efficacy of lactitol. Both trials had the same inclusion and exclusion criteria as well as the same primary efficacy endpoint. Trial NCT02481947 assessed the efficacy of lactitol compared to lubiprostone, another commonly prescribed medication used for constipation. Trial NCT02481947 evaluated the efficacy of lactitol compared to placebo. The results of these trials are summarized in **Table 2**.

Study NCT02481947

The efficacy of lactitol for CIC was studied in a phase III double-blind, randomized, multicenter clinical study by Braintree Laboratories, (NCT02481947).[8] This study included 459 subjects comparing lactitol 20g once daily versus lubiprostone 24 mcg twice daily for 12 weeks. The study aimed to establish non-inferiority of lactitol to lubiprostone for the in the treatment on CIC. Patients included were ages 18 to 87 years, 80% female, with 66% identified as white, and 29% black. Patients were required to meet modified Rome II criteria, same diagnostic criteria for CIC as Rome IV previously mentioned, for at least 12 weeks in the preceding 12 months. Additionally, patients were required to report at least one of the following symptoms: straining, lumpy or hard stools, and a sensation of incomplete evacuation for at least 25% of defecations. Patients who met these criteria were also required to demonstrate the following: on average have less than three complete spontaneous bowel movements (CSBMs) over the two-week screening period, had no more than one SBM with a BSFS of 6, or no SBMs with a BSFS of 7. 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. Additionally, subjects were provided bisacodyl 5 mg 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 four days. Exclusion criteria included those who experienced loose stools in the absence of laxative use for greater than 25% of bowel movements, patients who met the Rome II criteria for IBS, subjects with known or suspected gastrointestinal obstruction or bowel perforation, patients who had major surgery within 30 days of the start of the trial, subjects taking laxatives or prokinetic agents, subjects who were pregnant or lactating, patients who were taking narcotic analgesics known to cause constipation, and subjects with clinically significant cardiac complications defined prior to the start of the study.[8]

The primary efficacy endpoint was the proportion of subjects who were weekly responders for at least nine out of 12 weeks, with at least three of those weeks occurring in the last four weeks of treatment.[7,8] A weekly responder was defined as having ≥ 3 complete spontaneous bowel movements and an increase from baseline of > 1 CSBM for that given week. The baseline average of CSBMs at the start of the trial in the lactitol group was 1.9 and in the lubiprostone group was 2.3. Patients reported taking a dose of lactitol on 83% of eligible study days. Compliance rates were similar between both treatment groups. The most frequently reported baseline concomitant medication in both groups were anti-hypertensive agents (18.7% in the lactitol group and 17.5% in the lubiprostone group). Information provided by patients after each bowel movement using an electronic diary was utilized. To demonstrate non-inferiority of lactitol to lubiprostone, a pre-established margin of -12.6% was determined by the manufacturer based on prior studies comparing a different agent, linaclotide and placebo.[7,8]

Based on the intent to treat (ITT) population, 21.1% were responders on lactitol vs 25.7% of patients taking lubiprostone [-4.6 %; 95% CI -12.5 to 3.3; p = 0.016]).[8] The estimated change in number of CSBMs per week from baseline were lower for the lactitol group compared to the lubiprostone group at every week during the 12-week treatment period. The lubiprostone group had a mean increase of 0.9 CSBM/week from baseline to Week 12 over the lactitol group. Rescue medication use with bisacodyl was permitted during the trial and was accounted for in the primary endpoint analysis. Patients in the lactitol group and patients in the lubiprostone group took an estimated average of 1.3 bisacodyl doses per week during the 12-week treatment period. The FDA review-team for this study determined that the study results were inconclusive and that the primary endpoint analysis cannot be relied on to establish efficacy of lactitol on its own. This was due to the study observers choosing the non-inferiority margin based on trial results from the drug linaclotide rather than the active comparator lubiprostone and placebo. The FDA review-team of this clinical study asked the manufacturer to provide additional information to support the efficacy of lactitol based on clinical trials from other countries where the drug has been widely marketed for over 30 years in the treatment of CIC. The outcomes of these external studies demonstrated the efficacy of lactitol through an increased amount of bowel movements per week as well as

Table 2 | Primary Endpoints from Lactitol Phase III Trials[7-9]

Trial	Trial Design	Primary Outcome	Intervention	Change (P-Value)
NCT02481947	Phase III double-blind, randomized, multicenter clinical study	Proportion of subjects who are weekly responders for at least 9 out of 12 weeks	Lactitol 20 mg vs Lubiprostone 24 mcg	- 4.6% (p = 0.016)
NCT02819297	Phase III double-blind, randomized, multicenter clinical study	Proportion of subjects who are weekly responders for at least 9 out of 12 weeks	Lactitol 20 mg vs Placebo	12.2% (p < 0.001)

improvement in stool consistency in patients, which was deemed satisfactory by the FDA review-team for it to gain approval. Reviewers appointed by the FDA including a Nonclinical Reviewer, Clinical Pharmacology Reviewer, Clinical Reviewer, Statistical Reviewer, and Division Deputy Director. The results of these studies are talked about further in depth in the discussion section.[8,9]

Study NCT02819297

The efficacy of lactitol was evaluated in another phase III, double-blind, randomized, placebo-controlled, multicenter clinical study (NCT02819297) by Braintree Laboratories.[8] This study compared daily treatment with lactitol 20 g once daily versus placebo for 24 weeks. This study included 594 subjects observed over a 24-weeks. Patients who developed persistent diarrhea or loose stools were allowed to reduce their dosage lactitol to 10g once daily. Patient demographics as well as inclusion/exclusion criteria for this trial were the same as in Study NCT02481947 above.8 Patients reported taking a dose of lactitol on 77% of eligible study days. The most frequently reported drug classes of baseline concomitant medications in both groups were anti- hypertensive agents (29.2% in the lactitol group and 29.7% in the placebo group) and lipid- modifying agents (21.6% in the lactitol group and 19.5% in the placebo group). The primary endpoint, which only looked at responders over the first 12 weeks of treatment, was the proportion of subjects who were weekly responders for at least nine out of 12 weeks, with at least three of those weeks occurring in the last four weeks of treatment. A weekly responder was defined as having ≥ 3 complete spontaneous bowel movements and an increase from baseline of > 1 CSBM for that given week. A secondary endpoint exploring overall drug response from weeks 13-24 was established to explore the longer-term efficacy of lactitol.

In the primary endpoint analysis, there were 291 patients allocated to the lactitol group and 303 to the placebo group. Information provided by patients after each bowel movement using an electronic diary was utilized. The baseline average of CSBMs at the start of the trial in the lactitol group was 2.1 and in the placebo group was 1.0. Efficacy was assessed based on the first 12 weeks of the six-month treatment period for the 594 patients. Over the first 12-week course of treatment, patients treated with lactitol (25.1%) achieved a significantly greater efficacy response compared to placebo (12.9%) [12.2%; 95% CI 6.0-18.5; p < 0.001]. Of the patients in the lactitol group, 74 of 291 patients at least temporarily reduced their dose to 10g once daily. Improvements in the mean frequency of CSBMs/week were seen at Week 1 with improvement generally maintained through Week 12. The lactitol group had a mean increase of 0.8 CSBM/week from baseline to Week 12 over the placebo group. Rescue medication use with bisacodyl was permitted during the trial and was accounted for in the primary endpoint analysis. Patients in the lactitol group and patients in the lubiprostone group took an estimated average of 1.7 bisacodyl doses per week during the 12-week treatment period. The use of rescue medication was generally similar between the groups. A responder subgroup analysis based on Weeks 13 to 24 of the treatment period was conducted. Patients treated with lactitol (24.4%) achieved a greater efficacy response compared to placebo (16.2%), but the estimated treatment effect was slightly smaller compared to that of the first 12 weeks [8.2%; 95% CI 1.8-14.7; p < 0.001].[8]

Adverse Events and Drug Interactions

Studies NCT02481947 and NCT02819297 included a safety component to assess the side effect profile of lactitol.[7,8] Patients in the lactitol group reported adverse effects including upper respiratory tract infection (9%), flatulence (8%), diarrhea (4%), increased blood creatine phosphokinase (4%), abdominal distention (3%), and increased blood pressure (3%). Another phase III study which included 298 patients found similar adverse effects as studies NCT02481947 and NCT02819297, however, also saw additional adverse effects recorded in the lactitol treatment group including urinary tract infection (5%) and abdominal pain (3%) over a one-year period.[7,8]

In patients with known or suspected mechanical gastrointestinal obstruction, lactitol is contraindicated. It is recommended that other oral medication be taken at least two hours before or two hours after the administration of lactitol due to incidence of reduced absorption of other oral medication when taken together.[7]

Dosage and Administration

The FDA recommended adult dose of lactitol is 20g by mouth once daily for the treatment of CIC categorized as either slow or normal transit.[7] Patients may reduce the dose to 10 g once daily by mouth if they experience persistent loose stools. The drug is available in powder form in a multi-dose bottle. Lactitol 20g dose should be dissolved in 8 oz of water, juice, coffee, tea, or

soda. The multi-dose bottles of lactitol are available in 280 g or 560 g bottles. Lactitol is also available in 10 g unit dose packets. The entire contents of one or two packets, depending on dose, is mixed with the preferred beverage and drunk in its entirety as stated before.[7]

Special Populations

There are no human studies completed in pregnant women, therefor data is inadequate to assess for any drug associated birth defects. In animal studies with rats and rabbits, did not show any evidence of harm to the fetus. It is currently unknown as to the effect of lactitol on lactation. Lactitol is a minimal systemically absorbed so there is thought that any clinically relevant outcomes in the breastfed infant are not likely.[7] No dose adjustments in renal or hepatic impairment are required. The safety and efficacy of lactitol has not been established in pediatric patients, but the manufacturer has established that pediatric postmarketing studies will begin in late 2020.[7]

Clinical Implications

Trials NCT02481947 and NCT02819297 were conducted to assess the efficacy of lactitol. These trials were appropriately designed, appropriately conducted, with comparisons to placebo or a fair active comparator in lubiprostone. The inclusion and exclusion criteria for both trials appear adequate in the study's design, and representative of the CIC population. The duration of treatment and outcome of the placebo-controlled trial provided data that is applicable in using this agent as a treatment option, but for a disease state such as CIC which can distress a patient throughout their lifetime, longer study periods would be appropriate. Study NCT02819297 even showed 74 of the 291(~25%) lactitol treated patients temporarily reduced their dose to 10 g daily due to persistently loose stools due to efficacy of lactitol.[8]

However, trial NCT02481947 had several limitations. In trial NCT02481947 it was mentioned that the non-inferiority margin determined for this study was based off prior studies using the drug linaclotide and not lubiprostone which lead the FDA review-team to ask for additional documentation. The FDA review-team of this clinical study however asked the observer to provide additional information to support the efficacy of lactitol based on clinical trials from other countries where the drug has been widely marketed for over 30 years in the treatment of CIC. The manufacturer subsequently supplied this additional information including trials conducted of this drug outside of the US to support the efficacy of lactitol. These trials included one Belgian study by Vanderdonckt et al which studied the laxative effect of lactitol compared to placebo in an elderly institutionalized population suffering from chronic constipation.[9] The results of this study displayed that patients experienced an increase of approximately two bowel movements per week and a reduction in stool consistency from hard to soft within four weeks of lactitol treatment. Another German based study from Heitland et al compared lactitol to lactulose in an open, randomized comparative study, over a duration of 14 days which demonstrated that patients receiving lactitol experienced at least one bowel movement per day on 75% of the days, compared to 70% of days in patients taking lactulose. Both lactitol and lactulose also demonstrated similar improvements in stool consistency. Additionally, a Chinese study comparing lactitol versus lactulose by Xu et al, demonstrated that the frequency of bowel movements was normalized in 78% of patients in both the lactitol and lactulose groups by day three, and in 95% of patients by day seven. These trials demonstrated improvement with lactitol when compared to placebo, and that efficacy measures when treated with lactitol compared to lactulose were similar or slightly better in the lactitol treatment arm. Ultimately, this corresponding evidence was deemed sufficient by the FDA review-team in favor of lactitol gaining approval by the FDA.[9]

Table 3 | Adverse Drug Reactions[7,8]

Event	Incidence
Upper Respiratory Tract Infection	9%
Flatulence	8%
Urinary Tract Infection	5%
Diarrhea	4%
Increased Creatinine Phosphokinase	4%
Abdominal Distension/Pain	3%
Hypertension	3%
Back Pain	2-3%
Gastroenteritis	2%
Infections	2%

Although these international studies demonstrated the primary efficacy endpoint of study NCT02481947, the duration of treatment could have been extended to establish a longer period of efficacy, as previously mentioned CIC is a lifetime disease; the longest treatment period was four weeks in the Vanderdonckt et al trial.[9] Additionally, the studies involving an active comparator solely compared lactitol to lactulose. There were no trials using the active comparator from study NCT02481947, lubiprostone, or even studies comparing lactitol to a commonly used laxative such as polyethylene glycol despite these pharmacological agents being available in countries outside the United States. These trials and their corresponding evidence were enough to achieve approval, but additional studies are needed to gain a more complete picture as to the efficacy of lactitol.

Lactitol is attempting to gain merit in a class of drugs that already has many options. Currently, osmotic agents are considered a first line pharmacological therapy option for the treatment of CIC, but over-the-counter alternatives such as magnesium hydroxide and polyethylene glycol exist and are some of the mainstays of treatment as commonly used osmotic laxatives.[6] However, the label for PEG recommends use be limited to 7 days for self-treatment, a significant limitation due to the chronic nature of CIC where years of treatment may be necessary.[2] For patients requiring treatment longer than 7 days, lactitol may be implemented as efficacy was proven in trial NCT02819297 for up to 12 weeks. After lack of symptom relief with OTC options a patient may see their provider and be prescribed lactitol. Its main distinguishing feature compared to other prescription laxatives, is that it is the only FDA approved product which the patient can self-titrate based on their own results for stool consistency.8 The self-dose adjustment provides the patient more liberty when administering this medication. Additionally, unlike current prescription treatments (linaclotide and lubiprostone) which are solid oral doses, lactitol is mixed with the patient's fluid of choice, e.g., water,

juice, coffee, tea or soda, and taken once a day at the patient's preferred time, which could improve adherence; including a side effect profile similar to other pharmacological therapies used in practice.[7] However, cost is currently unknown and would have to be considered prior to use based on patient's insurance and payment options. Prescription alternatives lubiprostone and linaclotide have been accessible for as little as $7-$9.5 In European countries such as France, 10 g doses in a 20 dose box can be obtained for the USD equivalent of $3.50.10 Ultimately, trial NCT02481947 showed slightly less efficacious results of lactitol when compared to lubiprostone (21.1% vs 25.7%). However, when gathering results from the international studies and the placebo-controlled trial NCT02819297, lactitol showed over course of treatment that patients had statistically significant improvements in stool frequency and stool consistency.

Conclusion

Pizensy® (lactitol), the newly approved osmotic laxative for the management and treatment of symptoms in patients with chronic idiopathic constipation appears to be both efficacious and safe to use in the adult population. Options such as polyethylene glycol and magnesium hydroxide would still be the first line treatment as they are readily available and less expensive compared to lactitol. Further head to head studies with other active comparators as well as the use of this therapy in the pediatric population will likely be needed to fully understand the place in therapy of lactitol.

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Personalized Medicine Corner

Proton Pump Inhibitors and CYP2C19 Pharmacogenetics

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Background

Proton pump inhibitors (PPIs) are a cornerstone in the treatment of gastrointestinal (GI) disease. Patients with gastric ulcers, esophagitis, gastroesophageal reflux disease (GERD) and Helicobacter pylori (H. pylori) infections benefit from the acid suppressing properties of PPIs. They suppress the acid secretion of parietal cells in the gastric mucosa by inhibiting the H+/K+ ATPase proton pump, resulting in a duration of action of up to three days. Patients are at increased risk of side effects from PPIs regimens that cause elevated serum concentrations or long-term therapy. Adverse effects include risk of infections, renal dysfunction, bone fractures and electrolyte imbalances.

Patient Case

AP is a 42-year-old Caucasian woman who initially presented after the holidays with complaints of acid reflux and nausea despite OTC Tums use. She expressed to her physician she believes this was triggered by the food she shared over the holidays with her family. At that time, she was initiated on omeprazole 20 mg daily, with instructions to continue taking OTC Tums for breakthrough symptoms. Upon follow up six months later, AP expresses her symptoms have gotten worse despite PPI treatment. She now sleeps with three pillows at the head of bed and still endorses symptoms despite diet and lifestyle changes. H. Pylori testing was found to be negative, but an upper endoscopy revealed erosive esophagitis. Upon discussion with her physician, CYP2C19 testing was also ordered.

Her pharmacogenetic test results are as follows:

CYP2C19 genotype: *1/*17
CYP2C19 phenotype: Rapid metabolizer(!)

The Role of CYP2C19 in Proton Pump iIhibitor Therapy

The CYP2C19 gene is polymorphic, with alleles categorized into functional groups. A patient may have normal function alleles, increased function, decreased function or no function alleles. First generation PPIs (lansoprazole, omeprazole and pantoprazole) and dexlansoprazole of the second generation, are extensively metabolized by CYP2C19, and thought to be influenced by genetic results. In contrast, the second-generation PPIs esomeprazole and rabeprazole are less dependent on CYP2C19 metabolism and are less influenced by genotype. Poor and intermediate metabolizers are known to have decreased clearance resulting in high serum concentrations, putting these patients at risk of adverse events. Rapid and ultra-rapid metabolizers are the opposite, with increased clearance resulting in risk of therapy failure. The recently published Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for PPIs include therapy recommendations for the first-generation PPIs and dexlansoprazole. CPIC does not make recommendations for esomeprazole and rabeprazole due to the lack of data indicating that CYP2C19 genotype influences their serum concentrations and therapy outcomes.

Therapy Recommendations

AP's pharmacogenetic test results indicate that she is a CYP2C19 rapid metabolizer. We also know that omeprazole is extensively metabolized by CYP2C19, and the standard starting dose is currently ineffective for her. Based on CPIC guideline recommendations, we would increase her dose by 50-100% to effectively treat her erosive esophagitis. Alternatively, an agent less influenced by CYP2C19 genotype such as esomeprazole or rabeprazole may be reasonable to recommend.

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