

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208745Orig1s000

**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)**

Application Type	NDA
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Reviewer Name(s)	Jacqueline Sheppard, PharmD
Acting DRISK Team Leader	Robert Pratt, PharmD
Acting Deputy Division Director	Jamie Wilkins Parker, PharmD
Review Completion Date	November 9, 2016
Subject	Evaluation to determine if a REMS is necessary
Established Name (Proposed) Trade Name Applicant	Plecanatide Trulance Synergy Pharmaceuticals, Inc
Therapeutic Class Formulation(s) Dosing Regimen	Guanylate cyclase agonist Oral tablet 3 mg daily

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Trulance (plecanatide) is necessary to ensure the benefits of this product outweigh its risks. Synergy Pharmaceuticals Inc. submitted a New Drug Application (NDA 208745) for plecanatide with the proposed indication of treatment of chronic idiopathic constipation (CIC). The risk associated with the use of plecanatide is severe diarrhea including potentially fatal diarrhea in children. The Sponsor did not submit a proposed REMS or risk management plan with this application. Of note, plecanatide was studied in both 3 mg and 6 mg doses for the treatment of CIC, however during the course of the review the Sponsor elected to seek approval for only the 3 mg strength (b) (4)

(b) (4)

DRISK and the Division of Gastroenterology and Inborn Errors Products (DGIEP) agree that a REMS is not needed to ensure the benefits of plecanatide outweigh its risks. Plecanatide was effective in increasing the frequency of complete spontaneous bowel movements (CSBM) and complete bowel movements (CBM) in patients with CIC and the side effect profile is similar to other GC-C agonists including the risk of severe diarrhea. Therefore, based on the available data, a REMS is not necessary for plecanatide to ensure the benefits outweigh its risks.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Trulance (plecanatide) is necessary to ensure the benefits of this product outweigh its risks. Synergy Pharmaceuticals Inc. submitted a New Drug Application NDA 208745 for plecanatide with the proposed indication of treatment of chronic idiopathic constipation (CIC). This application is under review in the division of Gastroenterology and Inborn Errors Products (DGIEP). The sponsor did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Plecanatide, a synthetic analogue of the uroguanylin peptide, is a new molecular entity (NME) that functions as an agonist of the guanylate cyclase-C (GC-C) receptor. GC-C receptors are involved in the regulation of fluid and electrolyte transport and in the maintenance of GI acidity. By the agonism of the GC-C receptors, plecanatide affects the sodium/potassium ion efflux and increases the secretion of fluid in the intestinal lumen. This mechanism is predicted to increase the frequency of bowel movements and improve stool consistency. Plecanatide's proposed indication is the treatment of chronic idiopathic constipation (CIC) in adults.

The proposed dosage form of plecanatide is an oral tablet. Tablets would be available in a 3 mg strength. The proposed dosage is 3 mg daily taken with or without food. Plecanatide will most likely be administered in an outpatient or long-term care setting. The duration of treatment for CIC is long-term.

Plecanatide is not part of a drug class that has a REMS. However, the other GC-C agonist currently marketed in the United States, linaclotide, has a boxed warning for a contraindication in pediatric patients due to deaths in juvenile mice. Plecanatide is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 208745 relevant to this review:

- 01/29/2016: NDA 208745 submitted for treatment of chronic idiopathic constipation received.
- 04/13/2016: Filing Review communication where the Agency requested the Sponsor submit a Medication Guide (MG) for plecanatide using linaclotide as the template.
- 06/08/2016: Sponsor submitted updated labeling including a Medication Guide in response to Agency's April 13, 2016 filing Review communication.
- 07/14/2016: Mid-cycle teleconference (b) (4)
(b) (4)
(b) (4) It was
communicated that a REMS will not be necessary to ensure that benefits of the drug outweigh the risks.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Chronic idiopathic constipation is a common disorder that affects 12-19% of North Americans. CIC is defined as active constipation symptoms within the last three months with at least two other symptoms during 25% of defecations. Associated symptoms include stool frequency of less than 3 per week, straining at stool, feelings of incomplete evacuation, need for digital manipulation, or rectal pressure or pain.¹ Multiple studies have demonstrated living with chronic constipation reduces patients' quality of life.²

¹ Lacy B, Levenick J and Crowell, M. (2012) Recent advances in the management of difficult constipation. *Current gastroenterology reports*, 14(4), 306-312.

² Lacy B, Levenick J and Crowell, M. (2012) Recent advances in the management of difficult constipation. *Current gastroenterology reports*, 14(4), 306-312.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

First line treatments for CIC include increased dietary fiber consumption, increased exercise, increased water consumption, and bowel habit training which typically result in partial relief. Over-the-counter (OTC) laxatives are not suitable for long-term use by patients with CIC as they are recommended for periodic use only. Frequently, patients with CIC have regular, chronic use of laxatives leading to adverse events including dependency, tolerance, electrolyte imbalance, and melanosis coli.

In the United States, lubiprostone and linaclotide are approved to treat CIC. Lubiprostone is a calcium channel activator available as an oral capsule taken twice daily with food or water. The agent may cause dyspnea within an hour of dosing. Linaclotide is a GC-C agonist available as an oral capsule taken daily on an empty stomach. The agent has a boxed warning for pediatric use as it is contraindicated in children up to the age of 6 and should be avoided in patients 6-17 years of age due to causing deaths due to dehydration in juvenile mice. Both products are contraindicated in patients with known or suspected mechanical bowel obstructions.

The Applicant states that plecanatide, a GC-C agonist similar to linaclotide, would broaden the treatment landscape and offer an alternative treatment option for patients with CIC.

Table 1: Summary of Pharmaceutical Treatment Options for CIC

Established Name (Trade Name)	Year of Approval	Class	Dosing/Administration	Important Safety and Tolerability Issues	Risk Management Approaches/ Boxed Warning, Medication Guide
Lubiprostone (Amitiza)	2006	Chloride channel activator	24 mcg orally twice daily with food and water	-CI in patients with known or suspected mechanical GI obstruction -may cause dyspnea	
Linaclotide (Linzess)	2012	GC-C agonist	145 mg orally daily	-CI in patients under age 6, avoid use in patients 6-17 years of age -CI in patients with known or suspected mechanical GI obstruction -may cause severe diarrhea	-Boxed Warning -Medication Guide

4 Benefit Assessment

The efficacy and safety of plecanatide for the treatment of CIC in adults was demonstrated in two phase three randomized, double-blind, placebo-controlled trials. Both studies evaluated the efficacy and safety of oral plecanatide 3 mg and 6 mg tablets in patients with CIC. The two studies were conducted concurrently in the same geographic area, with the same drug, and the same protocol. The primary endpoint of the pooled study was the durable overall complete spontaneous bowel movement (CSBM) responder rate. This was defined as a patient who has greater or equal to 3 CSBM in a given week and an increase from baseline of at least 1 CSBM in the same week for at least 9 of the 12 treatment weeks. Secondary endpoints include change from baseline in stool consistency, mean number of spontaneous bowel movements, and daily reported constipation symptoms including abdominal discomfort, bloating, and/or pain. An additional phase three, open label safety study (SP 304203-01) was conducted with a safety population of 1782 patients with up to two weeks of dosing.

During review of the NDA, the Office of Scientific Integrity (OSI) determined that data from two specific sites (#362 and #402) may pose data integrity issues due to past FDA violations. As a result, a decision was made at mid-cycle meeting that data from these sites should be considered unreliable and the data was removed from the efficacy and safety analysis. Furthermore, it was noted that there were 164 duplicate patients that were randomized more than one time in the primary safety pool studies. These duplicate patients, except for the 44 patients identified as index patients, were removed from the safety analysis. Additionally during the midcycle teleconference, the Sponsor elected to seek approval for only the 3 mg strength (b) (4)

(b) (4)

The two phase 3 efficacy studies (Studies SP304203-00 and SP304203-03) randomized patients 18 to 80 years old to receive placebo, plecanatide 3 mg, or plecanatide 6 mg daily over a 12-week treatment period. In study SP304203-00, which randomized 453 patients to the 3 mg treatment group and 452 patients to placebo, the proportion of CSBM responders over Weeks 1 – 12 was significantly greater in patients receiving plecanatide compared to placebo (21.0% in the 3 mg group, versus 10.2 %, in the placebo, $p < 0.001$). Similarly, in Study SP304203-03, which randomized 443 patients to the 3 mg treatment group and 445 patients to placebo, the proportion of CSBM responders over Weeks 1 – 12 was significantly greater in patients receiving plecanatide compared to placebo (20.5% in the 3 mg group, versus 13.0 %, in the placebo, $p < 0.003$). Therefore, for the primary endpoint analysis, the results of the pooled analysis are highly statistically significant for the plecanatide treatment arm compared to placebo. The 3 mg plecanatide treatment was also clinically meaningful and statistically significantly more effective than placebo for the secondary endpoints of weekly CSBM and SBM frequency, and stool consistency. The clinical reviewer concluded that the increases in the stool frequency, via the increase in number of CSBMs and SBMs in a week, may have clinical meaningfulness to many patients who suffer from CIC.

5 Risk Assessment & Safe-Use Conditions

The primary safety population included 2627 subjects exposed to either 3 mg, 6 mg, or placebo in the pooled analysis of the two phase three studies. Due to the data integrity issues that arose during review of this application, select safety analyses were performed excluding duplicate patients that enrolled in more than one plecanatide study. Additionally, data from sites #362 and #402 was excluded from analysis. The secondary safety pool was comprised of 2370 patients in a long-term, open-label extension study and 508 patients in two phase 2 studies. For the purpose of this review, an adverse event (AE) was defined as any untoward medical occurrence in subject that might or might not have had a causal relationship with plecanatide. The most commonly occurring adverse reactions associated with plecanatide include was diarrhea (5 %) and sinusitis (1.4%).

5.1 SERIOUS ADVERSE EVENTS (SAEs)

5.1.1 Severe Diarrhea

Plecanatide use was associated with severe diarrhea in 0.6% of patients in the 3 mg plecanatide group compared to 0.3% patients in the placebo group. Sites were instructed to record an AE of diarrhea only if the patient reported the effect was bothersome, had a Bristol Stool Chart (BSFS)³ score of 6 or 7, had a sense of urgency or required treatment or hospitalization. Events were coded as severe if they were medically significant but not immediately life-threatening; disabling; or involved limitations of self-care activities of daily living. Severe diarrhea led to discontinuation in 2.1% of the primary safety pool. The Applicant's proposed labeling includes a statement in the Warnings and Precautions section for severe diarrhea. This warning is also included in the labeling for linaclotide, another agent in the class.

In six separate non-clinical studies, plecanatide was associated with deaths of juvenile mice. Deaths were observed in neonatal mice after a single dose of 1 mg/kg/day at postnatal day 7 and juvenile mice after a single dose of 10 mg/kg at postnatal day 14. These ages correspond to human infants and children under the age of 2. Therefore, plecanatide will be contraindicated in children under the age of six. The Applicant's proposed labeling includes a boxed warning for contraindication in pediatric patients up to 6 years of age due to death from dehydration in juvenile mice and avoidance in pediatric patients age 6 to 17 years of age.

5.1.2 Deaths

One death occurred during the clinical development program for plecanatide. One patient in the 6 mg plecanatide long-term safety study died due to myocardial infarction attributed to recent cocaine abuse in the setting of underlying coronary disease. The patient, a 47 year old male, with a history of substance abuse was hospitalized for acute renal insufficiency and myocardial infarction. He was subsequently discharged and suffered another myocardial infarction which was fatal. The clinical reviewer agrees with the Sponsor that the death was unrelated to the study drug.

6 Expected Postmarket Use

The likely prescribers for plecanatide will be general practitioners and gastroenterologists which are the same prescribers for the existing approved treatments for CIC, lubiprostone and linaclotide.

Plecanatide will be prescribed primarily in outpatient and long-term care settings. A Medication Guide (MG) will be included in the final labeling.

7 Evaluating the Need for a REMS

The pivotal trials showed that plecanatide achieved the primary endpoints and was effective in increasing the frequency of CSBMs and CBMs in patients with CIC. The most important safety concern with plecanatide is severe diarrhea including potentially fatal diarrhea in children. The safety of plecanatide is similar to other treatments for CIC including linaclotide. Linaclotide, approved in 2012,

³ Bristol Stool Chart (BSFS) is a validated measure of stool consistency commonly used in clinical trials.

has a boxed warning for severe diarrhea and is contraindicated in children under the age of 6 due to deaths in juvenile rats. The risk of severe diarrhea including potentially fatal diarrhea in the pediatric population associated with plecanatide will be addressed through a boxed warning, and in the Warnings and Precautions and Contraindications section of the prescribing information. Additionally, plecanatide will have a MG. Therefore, based on the available data the risks of plecanatide a REMS is not necessary to ensure its benefits outweigh the risks.

8 Risk Management Activities Proposed by the Applicant

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

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary for plecanatide to ensure the benefits outweigh the risks. Plecanatide was effective in increasing the frequency of CSBMs and CBMs in patients with CIC. Additionally, the side effect profile is similar to other GC-C agonists including the risk of severe diarrhea. Therefore, based on available data, the safety and risk mitigation approach of plecanatide is similar to other drugs in the class, the risks will be communicated via labeling including the use of a Medication Guide and boxed warning.

Should DGIEP have any concerns or questions, or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 MATERIALS REVIEWED

The following is a list of materials informing this review:

1. Synergy Pharmaceuticals, Inc. Proposed Prescribing Information for plecanatide, dated January 29, 2016.
2. Synergy Pharmaceuticals, Inc. Clinical Overview for plecanatide, dated January 29, 2016.
3. Synergy Pharmaceuticals, Inc. Summary of Clinical Safety for plecanatide, dated January 29, 2016.
4. Hayes, L. DGIEP. Clinical Review for plecanatide [NDA 208745], dated October 12, 2016.
5. Synergy Pharmaceuticals, Inc. Draft Medication Guide for plecanatide, dated June 8, 2016.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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11/09/2016

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11/10/2016