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RESEARCH**

APPLICATION NUMBER:

208745Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 12, 2017
From	Joette M. Meyer, Pharm.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 208745
Supplement#	
Applicant	Synergy Pharmaceuticals, Inc.
Date of Submission	January 29, 2016
PDUFA Goal Date	January 29, 2017
Proprietary Name / Non-Proprietary Name	Trulance® (plecanatide)
Dosage form(s) / Strength(s)	3 mg* tablets
Applicant Proposed Indication(s)/Population(s)	Treatment of chronic idiopathic constipation (CIC) in adults
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of chronic idiopathic constipation (CIC) in adults

* the NDA contained data to support (b) (4) a 3 mg (b) (4) tablet strength; during the review cycle the sponsor

(b) (4)

Benefit-Risk Assessment

All disciplines recommend approval of plecanatide 3 mg once daily for the treatment of chronic idiopathic constipation (CIC) in adults. I agree with this recommendation. The following is a summary of the recommendations/conclusions excerpted from each of the respective reviews, followed by a summary of labeling and postmarketing requirements/postmarketing commitments.

The benefit risk framework (BRF), found as an attachment, summarizes the clinical reviewer's BRF and also reflects the cross-discipline team leader's (CDTL) additional considerations and those of other review disciplines. The overall conclusions do not differ from those of the primary clinical reviewer.

Review Disciplines	Recommendations/Conclusions by Discipline (reviewer names and date of final review in DARRTS)
OPQ	Application Technical Lead (ATL) (Hitesh Shroff), 10/6/16: Not ready for approval: The Office of Process and Facilities (OPF) has <i>not</i> made a final overall "Approval" recommendation for the facilities involved in this application as of this review. The label/labeling issues have <i>not</i> been

	<p>completely resolved as of this review. The ATL review includes the following other reviews:</p> <p>Drug Substance (Martin Haber), 9/30/16: Overall, for the drug substance, the chemistry, manufacturing and controls information provided in this application is satisfactory and the recommendation is Approval.</p> <p>Drug Product (Zhengfang Ge), 9/30/16: This application has provided adequate information on the drug product [(b) (4)] 3 mg [(b) (4)] tablets] to assure the identity, strength, purity, and quality with proper raw material controls, satisfactory specification, adequate packaging, and enough stability data to grant the proposed 24 months expiration dating period. Based on assay, plecanatide tablets are stable after been crushed and placed in the dosing agents (applesauce and water) for 30 minutes. No significant degradation is expected. Since the alternative dosing materials will be consumed immediately after the preparation, the applicant's justification is acceptable. Therefore, this NDA is recommended for approval from the drug product perspective.</p> <p>Process/Microbiology (Bo Jiang): The application is recommended for approval from manufacturing process aspect.</p> <p>Environmental Analysis (Raanan Bloom), 10/3/16: The claim for the categorical exclusion for the Environmental Assessment is granted.</p> <p>Facilities (Juandria Williams), 10/4/16: The overall recommendation is pending until the [(b) (4)] pre-approval inspection and associated package is complete and has been evaluated.</p> <p>Biopharmaceutics (Kalpana Paudel), 9/29/16: The dissolution method and acceptance criterion, bridging of the capsule to tablet formulation were reviewed and found acceptable. The biowaiver request was not needed. Results of an in-use stability study support four alternative administration methods to disperse a tablet in applesauce, dissolve a tablet in water for oral ingestion and to dissolve a tablet in water with administration through nasogastric and gastric feeding tubes.</p> <p><i>Addenda:</i> Labeling (Moo-Jhong Ree), October 18, 2016: The outstanding labeling deficiencies were noted to be adequately addressed by the sponsor.</p>
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	<p>Facilities (Juandria Williams), 11/22/16: The inspection of (b) (4) occurred 10/24/16. The investigator found no significant observations and subsequently classified the inspection NAI; no 483 was issued to the firm.</p> <p>There appear to be no significant or outstanding risks to the manufacturing process or final product based on the individual and composite evaluation of the listed facilities' inspectional history, relevant experience, and capabilities. The facilities are determined acceptable to support approval of NDA 208745.</p> <p><i>CDTL Comment: An addendum from the ATL is pending at the time of this review.</i></p>
OBP	<p>Haoheng Yan/Fred Mills, 10/11/16:</p> <p>Plecanatide is a guanylate cyclase-C (GC-C) agonist and is structurally related to the endogenous proteins uroguanylin, differing in one amino acid, and guanylin. Due to the structural similarity, there is a theoretical immunogenicity concern for depletion of the endogenous proteins if patients develop cross-reacting anti-plecanatide antibodies.</p> <p>Linaclotide, approved in 2012, is also a GC-C agonist and a structural analog of endogenous guanylin. Linaclotide was approved with no immunogenicity assay or clinical data (PMRs were issued for the assay and the clinical data). With this precedent, the plecanatide NDA was filed with only an antidrug antibody (ADA) screening assay and no clinical immunogenicity data. It was agreed the clinical data would be submitted during the review cycle.</p> <p>During the review, the applicant informed FDA that they faced ongoing technical issues with the immunogenicity assay. Multiple assay deficiencies were communicated between FDA and the applicant during the review cycle.</p> <p>(b) (4)</p> <p>(b) (4) Overall, the ADA assay needs more development work before it can be appropriately validated for detection of ADA response.</p> <p><i>CDTL Comment: Six PMRs related to assay development will be issued. See Postmarketing Requirements section.</i></p>
Pharmacology Toxicology	<p>Eddie Ng/David Joseph, 10/18/16:</p> <p>There are no novel excipients and the excipients used appear safe. The impurities are considered qualified at the proposed limits in the drug product. Plecanatide was not found to be genotoxic and had no effect on fertility or reproductive function in male or female mice.</p>

	<p>In young juvenile mice (1- to 2-week-old mice), plecanatide increased fluid secretion into the intestines as a consequence of stimulation of GC-C resulting in mortality in some mice within the first 24 hours, apparently due to dehydration.</p> <p>The Executive CAC Committee concluded the 2-year mouse and rat carcinogenicity studies were adequate and there were no treatment-related neoplasms.</p> <p>From a nonclinical standpoint, there are no approvability issues. The findings in juvenile mice and clinical relevance to pediatric patients are described in labeling.</p> <p>David Joseph (Secondary Review), 10/2/16: There are no nonclinical issues which preclude the approval of Trulance. I concur with the recommendations related to approvability, stated in the Pharmacology/Toxicology review by Dr. Yuk-Chow Ng.</p> <p>Abigail Jacobs (Tertiary Review), 10/13/16: I concur that there are no pharm-tox related approval issues.</p>
Clinical	<p>Lesley Hanes / Laurie Muldowney, 10/12/16:</p> <p>This review concludes that this application contains sufficient evidence to support the approval of plecanatide 3 mg for the treatment of chronic idiopathic constipation (CIC).</p> <p>The application included two adequate and well-controlled, phase 3 clinical studies which demonstrated that the primary endpoint of the proportion of patients who were overall complete spontaneous bowel movement (CSBM) responders was significantly greater than placebo for both the plecanatide 3 mg and 6 mg treatment groups ($p < 0.001$). Improvements in CSBM responder rates were seen as early as Week 1 with improvement maintained through Week 12.</p> <p>Additionally, three main secondary endpoint results of weekly CSBMs and spontaneous bowel movements (SBMs) frequency and stool consistency were clinically meaningful and statistically significant.</p> <p>Overall, the safety profile of plecanatide treatment appears to be acceptable. Patients in the 3 mg plecanatide group had less reports of adverse events, particularly gastrointestinal (GI)-related, than patients in the 6 mg group. Although the 6 mg plecanatide group experiences efficacy benefit, it did not show a clear efficacy advantage over the 3 mg plecanatide group. However, the 6 mg plecanatide dosage may be less well tolerated due to GI adverse reactions.</p> <p>(b) (4)</p> <p>(b) (4)</p> <p>(b) (4) . Hence, (b) (4)</p> <p>(b) (4) the 3 mg dose is recommended for approval.</p>

	<p>Plecanatide has structural homology to endogenous guanylin/uroguanylin; there is a theoretical concern for the development of guanylin/uroguanylin deficiency. Adverse events suggestive of fluid/volume overload were explored (e.g., congestive heart failure, dyspnea, pulmonary congestion, edema, weight increase, blood pressure increase, hyponatremia, pancreatitis and pancreatic enzyme deficiency). There are no clear signals or obvious differences in the frequency of the potential UPD syndrome adverse events between plecanatide and placebo.</p> <p>Ischemic colitis was identified as a potential risk with other CIC treatments and was assessed during the review. There were no reports of ischemic colitis during plecanatide clinical development.</p>
<p>Clinical Pharmacology</p>	<p>Dilara Jappar/Sue Chih Lee, 10/6/16:</p> <p>The Office of Clinical Pharmacology has found the submission acceptable from a clinical pharmacology standpoint provided a mutual agreement on labeling language is reached between the FDA and the sponsor.</p> <p>A thorough QT study was not conducted. FDA determined a study was not warranted based on limited systemic exposure to plecanatide and the active metabolite (IND 74883, 9/7/14).</p>
<p>Biostatistics</p>	<p>Shahla Farr / Yeh-Fong Chen, 11/2/16:</p> <p>After thorough evaluation and clarifications with the sponsor, the statistical review team concluded that results of the submitted two studies are statistically significance and can be used to support plecanatide's efficacy for the indication of Chronic Idiopathic Constipation (CIC) in adults.</p>
	<p>Sarrit Kovacs/Elektra Papadopoulos, 12/5/16</p> <p>The review concludes that the evidence submitted by the applicant is sufficient to demonstrate that the CSBM stool frequency, SBM stool frequency, and stool consistency pre-specified secondary endpoints are suitable for inclusion in labeling claims in the context of use. However, the three daily symptom scores (abdominal pain, abdominal discomfort, and abdominal bloating) were not pre-specified in the endpoint testing hierarchy and were not Type I error controlled. This reviewer discussed this with the Clinical review team and these endpoints are not part of the CIC disease definition, therefore, the abdominal symptom instruments were not reviewed for their adequacy to support labeling claims.</p> <p>With regard to the straining PRO instrument, the qualitative patient data generally supported the relevance and meaningfulness of the straining concept and severity. The COA Staff defer to DGIEP regarding the review of the clinical data to support the pre-specified secondary endpoint labeling claims (i.e., review of the cumulative distribution function [CDF] plots showing separation between treatment arms at the meaningful responder thresholds).</p>

	<p>The reviewer believes that the four pre-specified secondary endpoints are suitable for inclusion in the label, based on the modest but consistent separation between treatment arms at the meaningful responder thresholds across both studies.</p> <p><i>CDTL Comment:</i> <i>In reviewing data related to the straining endpoint, the clinical team determined that small but meaningful, clinical differences between the 3 mg plecanatide and placebo groups were evident in the distinct CDF plot curves, which showed the reduction in straining scores averaged over 12 weeks, as anchored by the cross-validated, Patient Global Assessment constipation severity score. Therefore, the clinical team recommends including “improvement ... in the amount of straining” in labeling and further defining straining as the “amount of time pushing or physical effort to pass stool”.</i></p>
OSI	<p>Susan Leibenhaut/Susan Thompson, 9/16/16:</p> <p>Six clinical investigator (CI) sites, a contract research organization (CRO) and the sponsor were inspected for this application. Two CI sites have the final classification of voluntary action indicated (VAI), and the violations cited are not considered to have an impact on data integrity. The four other clinical site inspections have classifications of no action indicated (NAI). Both the sponsor and CRO sites have the classifications of NAI.</p> <p>During the process of selecting clinical sites for inspection, it was noted that two CI sites that participated in Protocol SP304203-03 were classified as Official Action Indicated (OAI) for previous inspections conducted as a result of complaints.^{1,2} It was communicated to the review division that the data from these sites be considered unreliable and be removed from the label.</p> <p>Because all inspected sites, the sponsor, and the CRO did not have issues with data integrity and reliability, it is considered that the studies appear to have been conducted adequately, and the data generated by the studies, except for the two sites noted above, appear acceptable in support of the respective indication.</p>
OSE/DMEPA	<p>Matt Barlow//Mishale Mistry, Proprietary name, 9/8/16:</p> <p>The proposed proprietary name, Trulance, was found to be conditionally acceptable (letter to the sponsor, 5/12/16). Our re-assessment did not identify any names that represent a potential source of drug name confusion. Therefore, we maintain that the proposed proprietary name is acceptable from a promotional and safety perspective.</p> <p>Sherly Abraham/Mishale Mistry, Label and Labeling Review, 12/2/16:</p>

¹<http://www.accessdata.fda.gov/scripts/SDA/sdDetailNavigation.cfm?sd=clinicalinvestigatorsdisqualificationproceedings&id=1E2A9A1BD59D686CE053554DA8C0B073&rownum=126>

² <http://www.fda.gov/iceci/enforcementactions/warningletters/2016/ucm493102.htm>

	<p>On June 8, 2016, the Applicant proposed alternative administration instructions for adult patients with swallowing difficulties. The tablets can be crushed and administered orally either in applesauce or with water, or administered with water via a nasogastric or gastric feeding tube. We identified areas in the Prescribing Information that can be improved to clarify the alternate dosing information for adult patients with swallowing difficulties. Additionally, we identified areas in the container labels and carton labeling that can be improved.</p> <p><i>CDTL Comment:</i> <i>The carton/container labeling submitted by the sponsor on 1/3/17 was found to be acceptable by DMEPA.</i></p>
<p>OSE/DRISK</p>	<p>Jacqueline Sheppard/Jamie Wilkins, 11/10/16:</p> <p>The sponsor did not submit a proposed REMS or risk management plan with this application.</p> <p>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.</p>
<p>DMPP</p>	<p>Karen Dowdy / Marcia Britt Williams, 9/19/16</p> <p><i>CDTL Comment:</i> <i>DMPP provided edits to the Medication Guide on 9/19/16 and 12/9/16.</i></p>
<p>DPMH</p>	<p>Carolyn Yancey/Mona Khurana (Pediatrics), 10/20/16:</p> <p>Pediatrics: Trulance (plecanatide) triggers PREA as a new active ingredient, new indication, new dosage form, new dosing regimen, and new route of administration. In the NDA, the applicant submitted the initial Pediatric Study Plan (iPSP), agreed upon 2/6/15. Based upon a recommendation from the Pediatric Review Committee (PeRC) on 9/26/16, the sponsor was asked to revise the pediatric plan to align with linaclotide, the other drug in this pharmacologic class. The agreed-upon iPSP includes a partial waiver of pediatric patients less than 2 years of age. The FDA will require that plecanatide not be studied in pediatric patients less than 6 years of age until the postmarketing requirement (PMR) to characterize GC-C mRNA expression in duodenal and colonic mucosal biopsies in pediatric patients 0 to 6 years undergoing diagnostic gastrointestinal endoscopies as part of their medical care is submitted and reviewed under NDA 202811 Linzess (linaclotide).</p> <p>The applicant will also be required to characterize GCC mRNA expression in duodenal and colonic mucosal biopsies in pediatric patients undergoing diagnostic gastrointestinal endoscopies as part of their medical care. As this</p>

	<p>study is not treatment dependent, both sponsors should consider collaboration to collect the necessary data.</p> <p>Christos Mastroyannis/Tamara Johnson (Maternal Health), 11/10/16:</p> <p>Maternal Health: The review provides recommended revisions and structuring of existing information related to the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections in labeling in order to provide clinically relevant information for prescribing decisions and to comply with current PLLR regulatory requirements.</p> <p>The applicant should conduct a milk-only lactation study in patients, using a validated assay, in order to appropriately inform the lactation section of labeling.</p> <p><i>CDTL Comment:</i> <i>For additional details on the required pediatric and lactation studies, see Postmarketing Requirements section below.</i></p>
OPDP	<p>Adewale Adeleye/Kathleen Klemm, 9/21/16: OPDP provided comments on the proposed PI and OPDP/DMPP provided comments on the proposed Medication Guide. OPDP had no comments on the proposed carton/container labeling.</p>

Labeling

Prescribing Information

Below is a summary of the substantive issues discussed during the review. Comments from the review team and consultants (e.g., DMEPA, Maternal Health, Pediatrics, and OPDP) have been incorporated. At the time of this review, the PI is considered to be substantially complete and a version was provided to the sponsor on December 9, 2016. A response was received from the sponsor on December 22, 2016 and comments from the team were sent to the sponsor on January 9, 2017. A teleconference with the sponsor was held January 10, 2017 where verbal agreement was reached on the Prescribing Information (PI) and Medication Guide (MG).

The review team has ensured the PI and MG are aligned with current labeling regulations (21 CFR 201.57), PLR labeling guidances, the Selected Requirements for Prescribing Information (SRPI), and best labeling practices.

The following is a summary of the substantive revisions made to the PI by section.

In general, the information in the PI follows that of Linzess (linaclotide).

HIGHLIGHTS

In general, revisions to this section were made in alignment with the revisions in the Full Prescribing Information and will not be described here, see below.

The Established Pharmacologic Class (EPC) is “guanylate cyclase-C (GC-C) agonist.” Plecanatide is an analog of the endogenous human uroguanylin peptide, and both are GC-C agonists. The mechanism of action of plecanatide is the same as Linzess (linaclotide), an analog of guanylin.

FULL PRESCRIBING INFORMATION

Boxed Warning

The subject of the warning is the nonclinical findings of death in young juvenile mice. The title of the warnings is: **RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS**

Plecanatide has not been studied clinically in pediatric patients. There is a theoretical concern for severe dehydration in pediatric patients, particularly in pediatric patients less than 2 years of age, based on the nonclinical findings of death due to severe dehydration in young juvenile mice. Deaths were observed in young juvenile mice 1 to 2 weeks old (human age equivalent of approximately 1 month to less than 2 years). Although there were no deaths in older juvenile mice at least 3 weeks old, given the deaths in younger mice and the lack of clinical safety and efficacy data in pediatric patients, plecanatide is contraindicated in patients less than 6 years of age and should be avoided in patients 6 years to less than 18 years of age. Due to similar nonclinical study findings during the development of linaclotide, linaclotide is also contraindicated for patients less than 6 years of age and recommended to be avoided in patients 6 years to less than 18 years of age.

DPMH recommends that the upper pediatric age be “less than 18 years of age”, to reflect the ages studied in the clinical trials, rather than (b) (4) (definition of pediatric patient, according to the regulations) throughout labeling.

1 INDICATIONS AND USAGE

The indication specifies that plecanatide is indicated in adults for the treatment of chronic idiopathic constipation (CIC).

2 DOSAGE AND ADMINISTRATION

The recommended dosage of plecanatide is 3 mg taken orally once daily.

(b) (4)



Plecanatide can be taken with or without food. In a pharmacokinetic/pharmacodynamic study, subjects who received either a low-fat, low calorie (LF-LC) meal or a high fat, high calorie (HF-HC) meal reported looser stools than fasted subjects up to 24 hours after a single dose of plecanatide 9 mg (3 times the recommended dose). Although these results were statistically significant, the sponsor did not consider this difference between fed and fasted subjects to be clinically significant. In addition, the dose tested was 3 times higher than the recommended dose. In clinical studies, plecanatide was administered with or without food.

During the review, the sponsor submitted information to allow for the tablets to be crushed and administered orally either in applesauce or with water or administered with water via a nasogastric or gastric feeding tube. This information was found to be adequate by the OPQ biopharmaceutics and drug product reviewers. Therefore, this section allows for crushing and mixing the tablets for adult patients with swallowing difficulties. Only applesauce or water will be allowed, as other soft foods/liquids were not studied. This information has also been incorporated into the Medication Guide.

3 DOSAGE FORMS AND STRENGTHS

Plecanatide is available as a 3 mg tablet.

4 CONTRAINDICATIONS

Plecanatide is contraindicated in patients less than 6 years of age due to the risk of serious dehydration, as described above. It is also contraindicated in patients with known or suspected mechanical gastrointestinal obstruction, due to the mechanism of action of the drug in the GI tract and risk of serious outcomes.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Dehydration in Pediatric Patients

This subsection provides more details related to the risk of serious dehydration in pediatric patients. In young juvenile mice (1- to 2-week-old mice; human age equivalent of approximately 1 month to less than 2 years of age), plecanatide increased fluid-secretion into the intestines as a consequence of stimulation of guanylate cyclase-C (GC-C), resulting in mortality in some mice within the first 24 hours, apparently due to dehydration. Due to increased intestinal expression of GC-C, patients less than 6 years of age may be more likely than patients 6 years of age and older to develop severe diarrhea and its potentially serious consequences.

This subsection reiterates:

- Plecanatide is contraindicated in patients less than 6 years of age.
- The safety and effectiveness of plecanatide in patients less than 18 years of age have not been established.
- Avoid the use of plecanatide in patients 6 years to less than 18 years of age, given the deaths in younger mice and the lack of clinical safety and efficacy data in pediatric patients.

5.2 Diarrhea

In the adult clinical trials, diarrhea was the most common adverse reaction with severe diarrhea reported in 0.6% of plecanatide-treated patients compared to 0.3% of placebo-treated patients.

Risk mitigation for the development of severe diarrhea is to suspend plecanatide dosing and rehydrate the patient.

6 ADVERSE REACTIONS

During the process of selecting clinical sites for inspection, it was noted that two sites that participated in Protocol SP304203-03 were classified as Official Action Indicated (OAI) for previous inspections conducted as a result of complaints.^{3,4}

Data (both safety and efficacy) from these sites was considered unreliable and was removed from the label.

The safety data described reflect the safety database from the two double-blind, placebo-controlled 12-week clinical studies. Demographic characteristics were comparable between the treatment groups.

The most common adverse reactions (defined as adverse events occurring at a higher rate in the plecanatide group compared to placebo) in the two trials was diarrhea: 5% in the plecanatide 3 mg group and 1% in the placebo group. The majority of reported cases of diarrhea occurred within 4 weeks of treatment initiation. Diarrhea was also the most common adverse reaction leading to discontinuation (2% of plecanatide-treated patients and 0.5% of placebo-treated patients).

Less common adverse reactions included abdominal distension, flatulence, abdominal tenderness, and increased liver biochemical in 5 patients treated with plecanatide 3 mg: 2 patients with ALT greater than 5 to 15 times the upper limit of normal and 3 patients with AST greater than 5 times the upper limit of normal. These laboratory abnormalities were not associated with clinical symptoms and did not meet the criteria for Hy's law.

7 DRUG INTERACTIONS

There are no clinically relevant drug interactions, so this section has been omitted. (b) (4)

(b) (4)

(b) (4)

³<http://www.accessdata.fda.gov/scripts/SDA/sdDetailNavigation.cfm?sd=clinicalinvestigatorsdisqualificationproceedings&id=1E2A9A1BD59D686CE053554DA8C0B073&rownum=126>

⁴ <http://www.fda.gov/iceci/enforcementactions/warningletters/2016/ucm493102.htm>

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Plecanatide was not mutagenic or clastogenic in genetic toxicology assays when evaluated at the highest concentrations of doses tested.

There is no evidence that administration of plecanatide to mice and rabbits during organogenesis causes adverse developmental effects.

No studies of plecanatide have been conducted in pregnant women. Because the drug has not yet been approved, no pharmacovigilance database has been established.

Plecanatide and its active metabolite are not measurable in animal and human plasma following administration of the recommended clinical dosages; therefore, maternal use of plecanatide is not expected to result in fetal exposure.

Overall, the limited cases reported of plecanatide use in pregnant women during clinical developed have sparse information and are insufficient to inform a drug associated risk for major birth defects and miscarriage.

8.2 Lactation

It is not known if plecanatide is present in animal milk. No animal lactation studies have been conducted.

No clinical lactation studies have been conducted. It is not known whether plecanatide is present in breast milk or on the effects on the breastfeeding infant or on lactation.

Given the low systemic availability of plecanatide, fetal exposure and infant exposure through human milk is expected to be limited. Therefore, lactation should not be discouraged with maternal use of plecanatide. However, this section will also reiterate that exposure to plecanatide in breastfed infants has the potential for (b) (4) adverse effects.

8.4 Pediatric Use

Because the proposed indication will not include pediatric patients, this subsection will state that safety and effectiveness have not been established in pediatric patients. Additionally, given the results from the juvenile animal toxicity studies that raise potential safety concerns in young pediatric patients, the nonclinical safety findings will be summarized:

Juvenile Animal Toxicity Data

Single oral doses of plecanatide at 0.5 mg/kg and 10 mg/kg caused mortality in young juvenile mice on postnatal days 7 and 14, respectively (human age equivalent of approximately 1 month to less than 2 years).

Treatment-related increases in the weight of intestinal contents were observed in juvenile mice following single doses of plecanatide on postnatal day 14 (human age equivalent of approximately less than 2 years), consistent with increased fluid in the intestinal lumen. Although the recommended human dose is approximately 0.05 mg/kg/day, based on a 60-kg body weight, plecanatide and its active metabolite are not measurable in adult human plasma whereas systemic absorption was demonstrated in the juvenile animal toxicity studies. Animal and human doses should not be compared directly for evaluating relative exposure.

8.5 Geriatric Use

There were insufficient numbers of patients aged 65 and older in the clinical trials to make an assessment of any efficacy differences between younger and older patients.

11 DESCRIPTION

The sponsor wanted to include a statement (b) (4) which is not appropriate for this section. See discussion in Section 12.2 below.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Plecanatide is structurally similar to human endogenous uroguanylin, differs by only one amino acid, and also guanylin. The sponsor states there is no evidence that guanylin is important to the physiology of human intestinal water and electrolyte balance and it is not necessary to note the similarity between plecanatide and guanylin. They also believe that it is important for prescribers to know that plecanatide, by virtue of its GC-C receptor binding affinity, is also under the same degree of pH control as uroguanylin. Therefore, plecanatide is not only structurally, but also functionally, related to uroguanylin and the following sentence was included:

Plecanatide is structurally related to human uroguanylin, and similar to guanylin, plecanatide functions as a guanylate cyclase-C (GC-C) agonist.

The mechanism by which activation of GC-C results in increased fluid secretion and accelerated transit in the GI tract is described, as are the results of a validated animal model of intestinal pain:

In an animal model of visceral pain, plecanatide reduced abdominal muscle contraction, a measure of intestinal pain. The mechanism has not been studied.

12.2 Pharmacodynamics

A description of the PK/PD food effect study and results are included here (see discussion under DOSAGE AND ADMINISTRATION, above).

12.3 Pharmacokinetics

Plecanatide is minimally absorbed with negligible systemic availability following oral administration; consequently concentrations of plecanatide and its active metabolite in plasma are below the limit of quantitation after an oral plecanatide dose of 3 mg. Therefore, standard

pharmacokinetic parameters such as AUC, maximum concentration (C_{max}), and half-life ($t_{1/2}$) cannot be calculated.

As described [REDACTED] (b) (4), plecanatide is metabolized locally in the GI tract and *in vitro* it is neither an inhibitor of CYP2C9 or 3A4 nor an inducer of 3A4. Plecanatide is also not a substrate or inhibitor of P-gp or BCRP *in vitro*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Plecanatide is not carcinogenic, mutagenic and does not impair fertility or reproductive function in animals.

[REDACTED] (b) (4)

This subsection is not included. The relevant juvenile toxicology data is summarized for the prescriber in the Pediatric Use subsection of Section 8.4 [REDACTED] (b) (4)

14 CLINICAL STUDIES

As described above in ADVERSE REACTIONS, efficacy data from two questionable clinical sites were removed from the discussion of the two placebo-controlled clinical studies.

The design of the studies is described, along with key inclusion/exclusion criteria and demographic results. The primary efficacy endpoint was a responder analysis based upon complete spontaneous bowel movements (CSBMs). The sponsor wished to describe the endpoint [REDACTED] (b) (4) to differentiate their endpoint from endpoints used in studies of other approved products (i.e., Linzess). The FDA does not encourage use of descriptive terms [REDACTED] (b) (4), since there are no standardized definitions. As future endpoints are developed, additional terminology to differentiate endpoints becomes necessary; therefore, the review team encouraged the sponsor to define the endpoint objectively, as follows:

A responder was defined as a patient who had a least 3 CSBMs in a given week and an increase of at least 1 CSBM from baseline in the same week for at least 9 weeks out of the 12 week treatment period and at least 3 of the last 4 weeks of the study.

Results of pre-specified, Type 1 error-controlled secondary endpoints were also included:

Over the 12 week treatment period, improvements were observed in stool frequency (number of CSBMs/week and SBMs/week) and/or stool consistency (as measured by the BSFS), and/or in the amount of straining with bowel movements (amount of time pushing or physical effort to pass stool) in the TRULANCE group as compared to placebo.

Although the sponsor did not provide an evidence dossier to support the validity and reliability of the straining endpoint, the review team assessed the clinical meaningfulness of the difference between the plecanatide and placebo groups for this secondary efficacy endpoint using CDF plots. The CDF plots showed a reduction in straining scores averaged over 12 weeks, as anchored by the cross-validated, Patient Global Assessment constipation severity scores from the two Phase 3 studies.

The sponsor requested that this section also include mention of the [REDACTED] (b) (4) 6 mg dosage, so the following was added to Section 14:

In Studies 1 and 2, a third randomized treatment arm of TRULANCE 6 mg once daily did not demonstrate additional treatment benefit and had a greater incidence of adverse reactions than TRULANCE 3 mg once daily. Therefore, TRULANCE 6 mg once daily is not recommended [*see Dosage and Administration (2.1)*].

16 HOW SUPPLIED/STORAGE AND HANDLING

Plecanatide is supplied as a bottle of 30 tablets and in unit-dose blister packs of 30 in a child-resistant pack.

The child-resistant packing is important, given the contraindication in children less than 6 years of age.

Plecanatide is subject to moisture degradation, so statements to protect from moisture, store in the original bottle and not to remove the desiccant from the bottle are included.

17 PATIENT COUNSELING INFORMATION

This section summarizes the important risk information to inform patient counseling. In addition to discussing the risk of diarrhea from the Warnings and Precautions section, a subsection was added on accidental ingestion in children to instruct patients to store the drug securely out of reach of children.

Administration and handling instructions are discussed (i.e., take with food, the tablets can be crushed and administered orally in applesauce or with water, and to protect from moisture), with reference to additional instructions in the Medication Guide

Medication Guide

At the time of filing, the sponsor did not include a MG in their submission. In the filing review communication, the review team requested the sponsor submit a MG for plecanatide using linaclotide as the template.

The sponsor provided updated labeling including a MG, which was reviewed by DMPP and comments were provided to the sponsor on December 9, 2016. A response was provided by the sponsor on December 22, 2016. Final changes were provided to the sponsor on January 9, 2017 and discussed during a teleconference on January 10, 2017, where verbal agreement was reached on the MG.

Carton and Container Labeling

Comments on the carton/container were provided to the sponsor on December 9, 2016 and a response was provided on December 22, 2016. The carton/container labeling submitted by the sponsor on January 3, 2017 was found to be acceptable by OPQ and DMEPA and is considered final.

Postmarketing Requirements/Postmarketing Commitments

The following postmarketing requirements (PMRs) were agreed to by the sponsor in communications dated October 13, 2016 and November 29, 2016.

FDAAA Required Safety Study/Clinical Trial

- 3117-1. Develop and validate a sensitive and precise assay for the detection of anti-plecanatide antibodies (ADA), including IgM, IgG, and IgA, that may be present in the serum at the time of patient sampling.

Final Report Submission: 04/18

- 3117-2. Develop and validate assays to evaluate the cross reactivity of anti-plecanatide antibodies to guanylin and uroguanylin.

Final Report Submission: 04/20

- 3117-3. Develop and validate an assay to evaluate the neutralizing capacity of ADAs detected in the patient samples taking Trulance (plecanatide).

Final Report Submission: 08/20

- 3117-4. A study to characterize guanylate cyclase-C (G-CC) mRNA expression in duodenal and colonic mucosal biopsies in pediatric patients ages 0 to 6 years undergoing diagnostic gastrointestinal endoscopies as part of their medical care.

Final Protocol Submission: 12/17

Study Completion: 04/19

Final Report Submission 07/19

Pediatric Research Equity Act (PREA) Postmarketing Requirements

- 3117-5. Determine the appropriate Trulance (plecanatide) treatment dose for pediatric patients with chronic idiopathic constipation (CIC) who are 12 years to less than 18 years of age by assessing the safety and efficacy of once daily oral plecanatide in an eight (8) week, proof-of-concept, dose-ranging with sparse pharmacokinetic (PK) sampling study.

Final Protocol Submission: 12/31/15 (completed)
Study Completion: 12/18
Final Report Submission: 02/19

- 3117-6. Determine the appropriate Trulance (plecanatide) treatment dose for pediatric patients with chronic idiopathic constipation (CIC) who are 6 years to less than 12 years of age by assessing the safety and efficacy of once daily oral plecanatide in an eight (8) week, proof-of-concept, dose-ranging with sparse pharmacokinetic (PK) sampling study.

Final Protocol Submission: 12/18
Study Completion: 12/20
Final Report Submission: 02/21

- 3117-7. Confirm the efficacy and safety of Trulance (plecanatide) in pediatric patients with chronic idiopathic constipation (CIC) who are 6 years to less than 18 years of age by performing a randomized, double-blind, placebo-controlled, parallel group, 12 week treatment study.

Final Protocol Submission: 12/18
Study Completion: 12/21
Final Report Submission: 02/22

- 3117-8. Determine the appropriate Trulance (plecanatide) treatment dose for pediatric patients with chronic idiopathic constipation (CIC) who are 2 years to less than 6 years of age by assessing the safety and efficacy of once daily oral plecanatide in an eight (8) week, proof-of-concept, dose-ranging with sparse pharmacokinetic (PK) sampling study.

Final Protocol Submission: 12/20
Study Completion: 12/22
Final Report Submission: 02/23

- 3117-9. Confirm the efficacy and safety of Trulance (plecanatide) treatment in pediatric patients with chronic idiopathic constipation (CIC) who are 2 years to less than 6 years of age by performing a randomized, double-blind, placebo-controlled, parallel group, 12 week treatment study.

Final Protocol Submission: 12/22
Study Completion: 12/25

Final Report Submission: 02/26

- 3117-10. Assess the long-term safety of Trulance (plecanatide) in pediatric patients with chronic idiopathic constipation (CIC) who are 2 years to less than 18 years of age and have completed a confirmatory efficacy and safety study with plecanatide.

Final Protocol Submission: 02/17

Study Completion: 06/26

Final Report Submission: 08/26

Attachment: Benefit-Risk Framework

Benefit-Risk Summary and Assessment

The currently available treatment armamentarium does not completely meet the needs of patients with chronic idiopathic constipation (CIC). The available treatments are not effective in all patients and may have limited by tolerability; therefore, additional treatment options are needed.

Plecanatide is a synthetic hexadecapeptide that is designed to mimic the action of uroguanylin, an endogenous peptide agonist for the guanylate cyclase C (GC-C) receptor, which is secreted in the GI tract and up-regulates intracellular production of cGMP (cyclic guanosine 3', 5'-monophosphate) in the intestinal epithelium. Elevated cGMP activates the cystic fibrosis transmembrane conductance regulator (CFTR), which leads to trans-epithelial efflux of chloride and bicarbonate from enterocytes lining the GI tract into the lumen of the gut, and secretion of water into the intestinal lumen. Increased secretion of water into the GI tract can loosen stools, stimulate bowel movements, and thus relieve constipation.

Plecanatide is the second in the GC-C agonist class of drugs. The first GC-C agonist was Linzess (linaclotide) which was approved on August 30, 2012 for CIC.

The efficacy and safety of plecanatide as a treatment for adults with CIC has been adequately assessed. The data from two adequate and well-controlled trials have demonstrated the efficacy of plecanatide over placebo, as measured by the proportion of patients with an increase in the number of complete spontaneous bowel movements (CSBMs) in at least 9 weeks out of the 12 weeks in the trial and at least 3 of the last 4 weeks. Other measures of efficacy included an increase in the number of bowel movements per week and an improvement in stool consistency and straining compared to placebo. Although the treatment difference between plecanatide and placebo were modest (approximately 10%), this drug may offer an alternative option for patients with CIC.

Plecanatide was shown to be safe and well-tolerated in adult patients with CIC. The most common adverse reaction was diarrhea. Severe diarrhea was reported and may lead to discontinuation, but can be managed by patient monitoring, withholding the medication and rehydration. In the clinical trials severe diarrhea did not lead to serious outcomes. Additionally, plecanatide may increase hepatic enzymes.

Due to the structure similarity between plecanatide and the endogenous peptides uroguanylin and guanylin, there is a theoretical immunogenicity risk for deficiency if patients develop cross-reacting anti-plecanatide antibodies. No signals of deficiency-related adverse events (e.g., hypertension, edema, pulmonary edema, hypernatremia, weight gain) were seen in the clinical trials database for plecanatide.

Serious adverse reactions, related to diarrhea, increases in liver biochemical tests, and guanylin/uroguanylin deficiency should be monitored using routine postmarketing surveillance.

Plecanatide and its active metabolite are negligibly absorbed systemically following oral administration. There are no clinically relevant drug interactions.

Use in pregnant women is not expected to result in fetal exposure. There is no information on the effects of maternal exposure to plecanatide in the breastfed infant. Exposure to plecanatide in breastfed infants has the potential for (b) (4) adverse effects. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for plecanatide.

Since the efficacy of (b) (4) the plecanatide 3 mg (b) (4)

Pediatric patients have not been studied clinically. The nonclinical findings of death in young juvenile mice (human age equivalent of less than 2 years of age) and risk of severe dehydration, preclude use of plecanatide in pediatric patients of all ages until more information is available. The sponsor will be required to conduct a postmarketing study in patients from birth to 6 years of age to assess the ontogeny of the GC-C receptor in the gastrointestinal tract to inform whether plecanatide can be safely dosed in pediatric patients 2 years to less than 6 years of age. They will also be required to conduct postmarketing trials to assess the safety, pharmacokinetics and efficacy of plecanatide in pediatric patients 2 years to less than 18 years of age. Results will be assessed in order to assure safety before progressively lower age cohorts are studied. Until the results of the biopsy study, pharmacokinetic and clinical data in pediatric patients 6 years to less than 18 years of age are available, pharmacokinetic dose-ranging and confirmatory clinical studies in pediatrics 2 years to less than 6 years of age are deferred. A lactation study is also required to assess the presence of plecanatide in breast milk to determine the safety of plecanatide for breast-fed infants whose mothers are receiving therapy. Finally, the sponsor will be required to develop anti-drug antibody assays in order to determine the immunogenic potential of plecanatide.

A REMS is not necessary for plecanatide to ensure the benefits outweigh the risks. The safety profile of plecanatide is similar to linaclotide, the other approved GC-C agonist. Therefore, the safety and risk mitigation approach of plecanatide will follow that of linaclotide, i.e., the risks will be communicated via labeling. A Medication Guide is required to inform patients of the risk of serious outcomes if plecanatide is administered to pediatric patients. A Boxed Warning in the Prescribing Information will convey that plecanatide is contraindicated in patients less than 6 years of age due to the risk of serious dehydration and to avoid use in pediatric patients 6 years to less than 18 years of age.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><u>Analysis of Condition</u></p>	<p>CIC affects an average of 15% of North Americans and is manifested by infrequent stools, incomplete bowel movements, straining, bloating, and hard, lumpy stool for at least six months. Moderate to severe symptoms of abdominal pain and/or straining with defecation can be debilitating for patients and if left untreated impact negatively on a patient’s general well-being. CIC has a higher prevalence in women, those with reduced caloric intake and the elderly. Population studies have shown that in patients with chronic constipation, poor quality of life (general well-being) was an important predictor of healthcare utilization and resultant healthcare costs.</p>	<p>CIC is a serious condition associated with morbidity and symptoms can be debilitating.</p>
<p><u>Current Treatment Options</u></p>	<p>Linzess (linaclotide) and Amitiza (lubiprostone) are indicated for use in adult patients with CIC. The efficacy of these therapies cannot be directly compared to plecanatide due to the fact that there are no randomized trials that compare these drugs in the same trial. Cross-study comparisons are less valid. The available randomized placebo-controlled trials also use varying definitions for the primary endpoint.</p> <p>Amitiza demonstrated efficacy in primary endpoint of the number of spontaneous bowel movements (SBMs) compared to placebo during the first of four weeks of treatment (a mean increased of about 2 SBMs). Symptom scores were significantly improved with lubiprostone compared to placebo for stool consistency, straining, and constipation severity. The safety profile of lubiprostone is notable for adverse reactions of nausea, diarrhea, headache, and acute symptoms of dyspnea (generally occurring with 30 to 60 minutes after the first dose).</p> <p>Linzess demonstrated a treatment difference of 10% to 17% over placebo in two trials in the primary efficacy endpoint of complete spontaneous bowel movements (CSBMs) where patients met the response criteria in at least 9 out of 12 weeks of the study. Linzess is in the same pharmacologic</p>	<p>The current treatment armamentarium does not completely meet the needs of the patients with CIC. The available approved drugs have a modest treatment benefit over placebo. OTC and nondrug therapies are of limited benefit in patients with CIC.</p> <p>Therefore, additional treatment options are needed for patients with CIC.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>class as plecanatide (G-CC agonist); therefore the safety profile is similar to plecanatide and is notable for the adverse reaction of diarrhea. In post-marketing experience, severe diarrhea associated with dizziness, syncope, hypotension and electrolyte abnormalities (hypokalemia and hyponatremia) requiring hospitalization or intravenous fluid administration have been reported. Other adverse reactions in clinical trials included abdominal pain. As with plecanatide, there is a risk of serious diarrhea due to dehydration in pediatric patients, especially those less than 6 years of age, based on mortality in young juvenile mice and a lack of clinical safety and efficacy data in pediatric patients.</p> <p>Zelnorm (tegaserod maleate) was marketed from 2004 to 2007 for patients less than 65 years of age with CIC, but was voluntarily withdrawn due to (b) (4) the risk of ischemic cardiovascular events. It continues to be available through expanded access to individual patients who have failed other therapies.</p> <p>There are a variety of over-the-counter (OTC) therapies, such as laxatives, and nondrug interventions available to prevent/treat constipation by increasing bowel motility, decreasing GI transit time, or facilitating the passage of stool without straining. OTC therapies are labeled for occasional, discreet episodes of constipation and not for chronic use. Patients with CIC who use OTC products off-label often fail to respond.</p>	
<p><u>Benefit</u></p>	<p>The efficacy of plecanatide for the management of symptoms of CIC was evaluated in two 12-week, double-blind, placebo-controlled, randomized, multicenter clinical studies in adult patients with CIC, as defined by the modified Rome III criteria. Patients were randomized to plecanatide 6 mg, plecanatide 3 mg, or placebo once daily. Only the results for the 3 mg dose will be described here. In the Intention-to-Treat (ITT) population, a</p>	<p>The efficacy of plecanatide in increasing the number of bowel movements in adult patients with CIC was demonstrated throughout 12-weeks in two adequate and well-controlled trials. In addition, patients began to respond to treatment within the</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>total of 891 patients (Study 1) and 854 patients (Study 2) were included.</p> <p>The primary efficacy endpoint was the proportion of patients who were responders over the 12-week treatment period. The study population was patients with less than 3 complete spontaneous bowel movements (CSBMs) per week at baseline. A CSBM is a spontaneous bowel movement that is associated with a sense of complete evacuation. A responder was defined as a patient who had a least 3 (CSBMs) in a given week and an increase of at least 1 CSBM from baseline in the same week for at least 9 weeks out of the 12 week treatment period and at least 3 of the last 4 weeks of the study.</p> <p>This endpoint was recommended to the sponsor by FDA during drug development and is felt to encompass both magnitude of effect and durability of response. In patients with CIC and less than 3 CSBMs per week at baseline, an increase in at least 1 CSBM is considered to be clinically meaningful. Based upon assessments of CSBMs, patients were assessed for both weekly and overall response. Weekly responders demonstrated a response in at least 75% of the weeks (i.e., at least 9 out of 12 weeks), including the last month of the study (i.e., at least 3 of the last 4 weeks).</p> <p>In one study the responder rates were 21% for plecanatide and 10% for placebo, for an 11% treatment difference. In the second study the responder rates were 21% for plecanatide and 13% for placebo, for an 8% treatment difference. In both studies the treatment difference was statistically significant.</p> <p>In addition, in both studies improvements in the frequency of CSBMs/week were seen as early as week 1 with improvement maintained</p>	<p>first week and maintained improvement for 12 weeks.</p> <p>Although the treatment difference between plecanatide and placebo is modest (approximately 10%), plecanatide may offer an alternative treatment option to patients with CIC.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>through week 12. The difference between plecanatide and placebo in the mean change of CSBMs/week frequency from baseline to week 12 was approximately 1.1 CSBMs/week.</p> <p>In both studies, patients in the plecanatide group had improvements in the number of spontaneous bowel movements (SBM) and in stool consistency compared to patients in the placebo group.</p> <p>In both studies, patients in the plecanatide group also had improvements in the amount of straining with bowel movements, as further defined by the amount of time pushing or physical effort to pass stool, in comparison to patients in the placebo group.</p> <p>There were insufficient numbers of patients to make meaningful conclusions about the efficacy in subgroups of age (less than 65 years vs. 65 years and older).</p> <p>Plecanatide was generally significantly more effective than placebo for female patients, both over the course of the entire treatment period and for each weekly assessment. For male patients, less consistent results were observed for both doses; the small population size for male patients likely impacted these results.</p> <p>Plecanatide was generally more effective in white patients compared to nonwhite patients, but nonwhite patients also generally saw consistent improvements relative to placebo.</p>	
<u>Risk</u>	<p>In both placebo-controlled trials, the overall incidence of adverse events and serious adverse events was similar between plecanatide and placebo. There were a total of 1745 patients who received the 3 mg plecanatide or placebo in the safety population.</p>	<p>Overall, plecanatide is well-tolerated with few serious adverse reactions in adult patients. The adverse event profile is similar to the other approved GC-C agonist,</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>The most common adverse reactions (defined as adverse events occurring at a higher rate in the plecanatide group compared to placebo) in the two trials was diarrhea: 5% in the plecanatide 3 mg group and 1% in the placebo group.</p> <p>The majority of cases of diarrhea occurred within 4 weeks of treatment initiation. Severe diarrhea was reported in 0.6% of patients treated with 3 mg plecanatide compared to 0.3% of placebo-treated patients. Severe diarrhea occurred within the first 3 days of treatment.</p> <p>Of note, the incidence of severe diarrhea was higher in the 6 mg plecanatide group in comparison to the 3 mg plecanatide group and placebo (1.3% versus 0.3% for 3 mg and placebo, respectively).</p> <p>Discontinuations due to adverse reactions occurred in 4% of plecanatide-treated patients and 2% of placebo-treated patients. The most common adverse reaction leading to discontinuation was diarrhea: 2% of plecanatide-treated patients and 0.5% of placebo-treated patients withdrew due to diarrhea.</p> <p>Increases in liver biochemical tests were seen in 5 patients treated with plecanatide 3 mg: 2 patients with alanine aminotransferase (ALT) greater than 5 to 15 times the upper limit of normal and 3 patients with aspartate aminotransferase (AST) greater than 5 times the upper limit of normal. These laboratory abnormalities were not associated with clinical symptoms and did not meet the criteria for Hy’s law.</p> <p>There are no clinically relevant drug interactions. Plecanatide is metabolized in the GI tract to an active metabolite by loss of the terminal</p>	<p>linaclotide.</p> <p>The most common adverse reaction in the plecanatide clinical trials was diarrhea. Severe diarrhea was reported and may lead to discontinuation, but can be managed by patient monitoring, withholding the medication and rehydration. In the clinical trials severe diarrhea did not lead to serious outcomes.</p> <p>Serious adverse reactions, related to diarrhea, increases in liver biochemical tests, and UPD should be monitored using routine postmarketing surveillance.</p> <p>Plecanatide and its active metabolite are negligibly absorbed systemically following oral administration. There are no clinically relevant drug interactions.</p> <p>Due to the structure similarity between plecanatide and endogenous peptides, there is a theoretical immunogenicity risk for uroguanylin/guanylin deficiency if patients develop cross reacting anti-plecanatide antibodies. No safety signals of uroguanylin/guanylin deficiency were seen in the clinical trials database for plecanatide</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>leucine moiety and there is negligible systemic absorption of either plecanatide or its active metabolite.</p> <p>Due to the structure similarity between plecanatide and endogenous peptides, there is a theoretical immunogenicity risk for deficiency of uroguanylin and guanylin if patients develop anti-plecanatide antibodies which cross react with the endogenous proteins. Potential adverse events associated with uroguanylin/guanylin deficiency include hypernatremia, pulmonary edema, peripheral edema, sudden weight gain, and hypertension. No safety signals were seen in the clinical trials database for plecanatide for these adverse reactions.</p> <p>There were no clinically meaningful differences in the safety profile with respect to age (less than 65 years vs. 65 years and older), race or sex.</p> <p>Plecanatide has not been studied in pediatric patients less than 18 years of age. In young juvenile mice (1- to 2-week-old mice corresponding to human age equivalent of 1 month to less than 2 years), plecanatide increased fluid-secretion into the intestines as a consequence of stimulation of guanylate cyclase-C (GC-C), resulting in mortality in some mice within the first 24 hours, apparently due to dehydration. Due to increased intestinal expression of GC-C, patients less than 6 years of age may be more likely than patients 6 years of age and older to develop severe diarrhea and its potentially serious consequences.</p> <p>The available data on plecanatide use in pregnant women are not sufficient to inform any drug-associated risks for major birth defects and miscarriage.</p> <p>In animal developmental studies, no effects on embryo-fetal development were observed with oral administration of plecanatide in mice and rabbits during organogenesis at doses much higher than the recommended human</p>	<p>Deaths were observed in young juvenile mice (human age equivalent of less than 2 years. There were no deaths in older juvenile mice. These data, and other published findings, suggest an age-dependency of the pharmacodynamic response and indicate that plecanatide would not be safe to administer to children under the age of 2 years; however, more data are needed to determine whether plecanatide can be administered safely to children 2 years to less than 6 years. Plecanatide has not been studied in any pediatric patients less than 18 years of age.</p> <p>Therefore, plecanatide will be contraindicated in patients less than 6 years of age and should be avoided in patients 6 years to less than 18 years of age until more information is known.</p> <p>Use of plecanatide in pregnant women is not expected to result in fetal exposure. However, it is unknown whether the negligible systemic absorption of plecanatide in adults will result in a clinically relevant exposure to breastfed infants. Exposure to plecanatide in breastfed infants has the potential for (b) (4) adverse</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>dosage.</p> <p>There is no information regarding the presence of plecanatide in human breast milk, or its effects on milk production or the breastfed infant. No lactation studies in animals have been conducted.</p> <p>There are no unresolved issues with product quality. Overall, the chemistry, manufacturing and controls information provided were found satisfactory.</p>	<p>effects. Therefore, the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for plecanatide.</p>
<p><u>Risk Management</u></p>	<p>Pediatric patients have not been studied in the plecanatide developmental program and due to deaths in young juvenile mice (human age equivalent of approximately 1 month to less than 2 years) in nonclinical studies, which occurred within 24 hours following oral administration of plecanatide and are thought to be due to the increased expression of intestinal GC-C in this age group.</p> <p>These data along with data from a review of the literature regarding GC-C ontogeny suggest an age-dependency of the pharmacodynamic response and indicate that plecanatide would not be safe to administer to children under the age of 2 years; however, more data are needed to determine whether plecanatide can be administered safely to children 2 years to less than 6 years. As a result, plecanatide will have a Boxed Warning that there is a risk of serious dehydration in pediatric patients, and a Contraindication in patients less than 6 years of age. A study characterizing GC-C mRNA expression in duodenal and colonic mucosal biopsies in pediatric patients will be required as a postmarketing study to assess the ontogeny of the GC-C receptor in order to determine if pediatric studies may be safe in children 2 years to less than 6 years age.</p> <p>Under the Pediatric Research Equity Act (PREA), clinical trials of the safety, pharmacokinetics and efficacy of plecanatide will be required to be</p>	<p>A REMS is not necessary for plecanatide to ensure the benefits outweigh the risks. The safety profile is similar to linaclotide, the other approved GC-C agonist. Therefore, the safety and risk mitigation approach is similar to linaclotide; the risks will be communicated via labeling including the use of a Medication Guide and Boxed Warning in the Prescribing Information.</p> <p>The Indications and Usage section of the Prescribing Information states that plecanatide is indicated in adults. There is a Boxed Warning, Contraindication, and Warning and Precaution stating that plecanatide is contraindicated in patients less than 6 years of age due to the risk of serious dehydration and to avoid use in pediatric patients 6 years to less than 18 years of age.</p> <p>A Medication Guide is needed to inform</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>conducted as there is an unmet need for treatment of pediatric patients with CIC. The sponsor has been granted a waiver from studying pediatric patients less than 2 years of age, as plecanatide may be unsafe in this age group. Clinical trials will be required in pediatric patients 2 years to less than 18 years of age. These trials will be conducted in sequential order in pediatric patients from oldest to youngest: 12 years to less than 18 years; 6 years to less than 12 years, and 2 years to less than 6 years. All data will be reviewed before studies in the next age cohort can be initiated. Until the results of the GC-C biopsy study are reviewed, pharmacokinetic and clinical data in pediatric patients 6 years to less than 18 years of age are available, the pharmacokinetic dose-ranging trials and confirmatory clinical trial in pediatrics 2 years to less than 6 years of age will not be conducted.</p> <p>There is no information regarding the presence of plecanatide in human breast milk, or its effects on milk production or the breastfed infant. The likelihood of plecanatide or its metabolite being measureable in breast milk is low due to the fact that there is negligible systemic absorption. However, given the anticipated use of plecanatide in females of reproductive potential, the lack of data on safe use in lactating women, and animal data demonstrating serious findings (mortality) in juvenile mice, a milk-only lactation study is required postmarketing to assess concentrations of plecanatide and its active metabolite in breast-milk in order to inform labeling.</p> <p>Due to the structure similarity between plecanatide and endogenous peptides, there is a theoretical immunogenicity risk for uroguanylin/guanylin deficiency if patients develop anti-plecanatide antibodies which cross react with the endogenous proteins. The sponsor developed an anti-drug antibody screening assay during clinical</p>	<p>patients of the risk of serious outcomes if plecanatide is administered to pediatric patients.</p> <p>The sponsor will be required to conduct a postmarketing study in patients from birth to 6 years of age to assess the ontogeny of the GC-C receptor in the gastrointestinal tract to inform whether plecanatide can be safely dosed in pediatric patients 2 years to less than 6 years of age.</p> <p>Clinical trials in pediatric patients to obtain information of the safety, pharmacokinetics and efficacy of plecanatide will be required to be conducted sequentially, such that younger age groups will not be initiated until safety has been demonstrated in older age groups and results from the GC-C biopsy study have been reviewed. The sponsor is not required to conduct studies in pediatric patients less than 2 years, as the drug may be unsafe.</p> <p>A milk-only lactation study will be required to assess the presence of plecanatide and metabolite in breast-milk.</p> <p>The sponsor will also be required to develop immunogenicity assays to assess for the</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	development but it was not adequate. Since the immunogenicity risk is theoretical, the lack of adequate immunogenicity assays and clinical immunogenicity data does not preclude approval. The development of immunogenicity assays and sample testing will be required to be conducted post-marketing.	development of anti-plecanatide drug antibodies, assays to evaluate the cross-reactivity of the potential anti-drug antibodies to endogenous guanylin/uroguanylin, and an assay to evaluate the neutralizing capacity of the potential anti-drug antibodies.

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/s/

JOETTE M MEYER
01/12/2017