# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208745Orig1s000

# <u>OFFICE DIRECTOR MEMO</u>

Office Director Decisional Memorandum

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| **Date** | January 19, 2017 |
| **From** | Julie Beitz, MD |
| **Subject** | Office Director Decisional Memo |
| **NDA #** | 208745 |
| **Applicant Name** | Synergy Pharmaceuticals, Inc. |
| **Date of Submission** | January 29, 2016 |
| **PDUFA Goal Date** | January 29, 2017 |
| **Proprietary Name / Established (USAN) Name** | Trulance (plecanatide) |
| **Dosage Forms / Strengths** | Tablets 3 mg |
| **Proposed Indication** | Indicated in adults for the treatment of chronic idiopathic constipation (CIC) |
| **Recommended Action:** | Approval |

| **Materials Reviewed/Consulted**<br>Action Package, including reviews from: | **Discipline Reviewers** |
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| DGIEP / Medical Officer | Lesley Hanes, MD, MSc |
| DGIEP / Medical Team Leader | Laurie Muldowney, MD |
| DGIEP / Pharmacology / Toxicology | Eddie Ng PhD / David Joseph, PhD |
| DGIEP / Division Director | Donna Griebel, MD |
| OND / DPMH / Pediatric Team<br>OND / DPMH / Maternal Health Team | Carolyn Yancey, MD / Mona Khurana, MD<br>Christos Mastroyannis, MD / Tamara Johnson, MD, MS |
| OND / Clinical Outcomes Assessment Staff | Sarrit Kovacs PhD / Elektra Papadopoulos, MD MPH |
| OB / Division of Biometrics III | Shahla Farr, MS / Yeh-Fong Chen, PhD<br>Scott Komo, DrPH |
| OCP / Division of Clinical Pharmacology III | Dilara Jappar, PhD / Sue Chih Lee, PhD |
| Office of Biotechnology Products | Haoheng Yan, PhD / Michele Dougherty, PhD / Fred Mills, PhD / Joslyn Brunelle PhD |
| OSE / Division of Risk Management | Jacqueline Sheppard, PharmD |
| Office of Scientific Investigations | Susan Liebenhaut |

DGIEP = Division of Gastroenterology and Inborn Errors Products
DPMH = Division of Pediatrics and Maternal Health
OB = Office of Biostatistics
OCP = Office of Clinical Pharmacology
OND = Office of New Drugs
OSE = Office of Surveillance and Epidemiology



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## 1. Benefit-Risk Summary and Assessment

Trulance (plecanatide) is structurally related to human uroguanylin, functions as a guanylate cyclase-C (GC-C) agonist, and has been evaluated in adults for the treatment of chronic idiopathic constipation (CIC). Uroguanylin, a member of the guanylin peptide family that is secreted by enterochromaffin cells in the duodenum and proximal small intestine, regulates the secretion of intestinal fluid. Idiopathic constipation is a common gastrointestinal disorder, affecting up to approximately 15% of the U.S. population. Although many treatments for CIC are commercially available, additional treatment options are needed, particularly for patients who do not respond to, or tolerate, existing treatments.

Trulance (plecanatide) has been shown to be an efficacious, well-tolerated treatment option for adults with CIC and would be the second FDA-approved GC-C agonist for this condition. I concur with the recommendation of the Division of Gastroenterology and Inborn Errors Products to approve Trulance (plecanatide) for the treatment of CIC in adults. The recommended dose is 3 mg taken orally once daily. Although a 6 mg daily dose was also studied, the applicant will not market this dose.[1] The safety and effectiveness of Trulance (plecanatide) in patients less than 18 years of age have not been established.

An FDA Advisory Committee Meeting was not held to discuss this application because the application did not raise significant safety or efficacy issues that were unexpected for a drug in this class.

Data submitted in the NDA supported the efficacy and safety of Trulance (plecanatide). The efficacy of Trulance (plecanatide) was established in two randomized placebo-controlled clinical trials involving adults with CIC. The assumption that GC-C agonism leads to movement of chloride and bicarbonate anions and water into the intestinal lumen and increased intestinal transit has been borne out by the submitted clinical trials of Trulance (plecanatide). I concur that the observed improvements in stool frequency, stool consistency, and straining on plecanatide treatment were both statistically superior to placebo and clinically meaningful to patients with CIC.

The safety profile of Trulance (plecanatide) is similar to that of the approved GC-C agonist, Linzess (linaclotide), including the risk of serious dehydration in pediatric patients. In nonclinical studies of young juvenile mice, administration of a single oral dose of plecanatide caused

[1] In clinical trials of Trulance (plecanatide), the 3 mg and 6 mg daily dose regimens were similarly effective. However, patients treated with the higher dose reported a slightly higher incidence of severe diarrhea and discontinuations due to diarrhea. At the July 14, 2016 Mid-Cycle Communication meeting, the applicant indicated that it will not market the higher dose regimen.



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deaths, likely due to dehydration. In adult patients with CIC, treatment with Trulance (plecanatide) was generally well tolerated. The treatment-emergent adverse event most commonly reported in clinical trials was diarrhea which was severe in some patients.

The prescribers of Trulance (plecanatide) will likely be general practitioners and gastroenterologists familiar with the attendant risks of available treatments for CIC, including those associated with Linzess (linaclotide), another GC-C agonist. The safety concerns identified in nonclinical studies and with use of Trulance (plecanatide) in clinical trials can be adequately communicated in professional labeling that will include a boxed warning about the risk of serious dehydration in pediatric patients, and contraindicate use in patients less than 6 years of age. A Medication Guide will be required as part of approved labeling to provide important safety information to patients.

A Risk Evaluation and Mitigation Strategy (REMS) will not be required for Trulance (plecanatide) to ensure that the benefits of the drug outweigh the risks. Routine pharmacovigilance will be conducted in the postmarketing setting. The results of required postmarketing studies will further inform product labeling regarding safe and effective use of Trulance (plecanatide) in pediatric patients, presence of the product in human breast milk, and its immunogenic potential.

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| **Analysis of Condition** | Chronic idiopathic constipation (CIC) is a common functional gastrointestinal motility disorder, with approximately 63 million adults in North America meeting Rome II criteria. To meet these criteria, symptoms should occur in the absence of a structural or biochemical explanation, should last for at least 12 weeks, which need not be consecutive, in the preceding 12 months, and include two or more of the following:<br><br>1. Straining during at least 25% of defecations;<br>2. Lumpy or hard stools in at least 25% of defecations;<br>3. Sensation of incomplete evacuation for at least 25% of defecations;<br>4. Sensation of anorectal obstruction/blockage for at least 25% of defecations;<br>5. Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor); and/or<br>6. < 3 defecations per week.<br><br>Rome criteria, however, do not identify all the symptoms that patients define as constipation. It is estimated that an additional 50 million in North America report that they have constipation but do not meet Rome II criteria. That is, they consider |

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| | themselves constipated, perhaps because they do not have daily bowel movements, despite the absence of straining, hard stools, or feelings of incomplete evacuation. In either case, individuals who self-report constipation or meet Rome criteria will seek treatment either by use of over-the-counter products or by visiting their physician and requesting a prescription medication. Constipation is more common in women than men and increases with advancing age, particularly after age 70. Data on the incidence of constipation, the natural history of constipation, or quality of life in patients with constipation are limited.[2]<br><br>***Comment.*** The availability of Trulance (plecanatide) would offer an FDA-approved, safe and effective alternative oral treatment for adults with symptoms of CIC. Although not life-threatening, symptoms of CIC can be bothersome to many millions of individuals in the U.S. |
| **Current Treatment Options** | Treatment for patients with CIC is highly individualized and usually includes increased dietary fiber and supplementation with bulking agents, exercise, and bowel habit training. However, patients often obtain only partial relief, and the majority use non-bulking laxatives on a regular basis without medical supervision. Laxatives available over-the-counter are not intended for chronic use however. Chronic use of non-bulking laxatives may lead to dependency and progressive tolerance, electrolyte imbalance, and, for the anthraquinones, melanosis coli. Chronic use of stimulant laxatives may result in bloating, feelings of fullness, abdominal pain, and incomplete fecal evacuation.<br><br>Linzess (linaclotide) was the first GC-C agonist to be approved in 2012. Linaclotide, structurally related to the guanylin peptide family, binds to the GC-C receptor expressed on intestinal epithelial cells thereby stimulating the intracellular production of cyclic guanosine monophosphate (cGMP) and activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel. Activation of CFTR and the subsequent enhancement of transepithelial efflux of chloride and bicarbonate anions lead to movement of water into the intestinal lumen. The secretion of water into the lumen, in turn, is believed to facilitate bowel movements and accelerate intestinal transit. Linaclotide is indicated in adults for the treatment of CIC and for irritable bowel syndrome with constipation. Plecanatide is structurally related to human uroguanylin, a member of the guanylin peptide family. Like linaclotide, plecanatide acts as a GC-C agonist to increase intestinal fluid secretion and accelerate intestinal transit. If approved, Trulance (plecanatide) would be the second orally administered GC-C agonist for the treatment of CIC. |

[2] Higgins PD, Johanson JF. Epidemiology of constipation in North America: a systematic review. *Am J Gastroenterol* (2004)99:750-759.



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| | ***Comment.*** Although many treatments for CIC are commercially available in the U.S., additional therapeutic options are needed, particularly for patients who do not respond to, or tolerate, existing treatments. Trulance (plecanatide) would offer an FDA-approved, safe and effective alternative oral treatment for adults with symptoms of CIC. |
| **Benefit** | The efficacy of Trulance (plecanatide) was established in two identical randomized, double-blind, placebo-controlled clinical trials involving adults with CIC, Trials SPD-304203-00 and SPD-304203-03. Patients were randomized 1:1 to either placebo or plecanatide 3 mg, once daily for 12 weeks without respect to food intake. The mean age of participants was 45.4 years (range 18 to 80 years), 80% were female, 72% were white, and 24% were black.<br><br>Eligible patients were required to meet modified Rome III criteria for at least 3 months prior to the screening visit, that is, report less than 3 defecations per week, rarely have a loose stool without the use of laxatives, not use manual maneuvers to facilitate defecations, and not meet criteria for constipation-predominant irritable bowel syndrome. In addition, patients were required to report at least two of the following symptoms:<br>• Straining during at least 25% of defecations<br>• Lumpy or hard stool in at least 25% of defecations<br>• Sensation of incomplete evacuation for at least 25% of defecations<br>• Sensation of anorectal obstruction/blockage for at least 25% of defecations<br><br>Efficacy was assessed using information provided by patients on a daily basis in an electronic diary. The primary efficacy endpoint was the proportion of patients who were CSBM responders (i.e., having spontaneous bowel movements associated with a sense of complete evacuation) during the 12-week treatment period. 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 trial.<br><br>In Trial SPD-304203-00, 21% of plecanatide-treated patients vs. 10% of placebo-treated patients met the responder criteria, for a treatment difference of 11% (95% CI: 6.1%, 15.4%). In Trial SPD-304203-03, data from 30 patients were removed from analysis due to integrity issues identified at two clinical sites. The efficacy findings in this trial were similar; 21% of plecanatide- |

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| | treated patients vs. 13% of placebo-treated patients met the responder criteria, for a treatment difference of 8% (95% CI: 2.6%, 12.4%). In both trials, the responder rate for plecanatide was statistically superior to the placebo responder rate.<br><br>In addition, patients who received plecanatide 3 mg in these trials had statistically significant improvements in the secondary efficacy endpoints of change from baseline over the 12-week treatment period in: CSBM frequency, SBM frequency (i.e., spontaneous bowel movements occurring in the absence of laxative use), stool consistency score (as measured by the Bristol Stool Form Scale) and straining score relative to placebo. The meaningfulness of these findings was evaluated using cumulative distribution function plots to assess the amount of separation between treatment groups at meaningful responder thresholds derived from Phase 2 data, if available. A modest but consistent separation between treatment groups was observed at the 1.8 CSBM, 2.8 SBM and 1.4 stool consistency thresholds. The meaningfulness of the improvement in straining score was also demonstrated, but to a lesser extent as the separation between treatment groups at the -1 point straining threshold was small.<br><br>Following completion of the drug treatment period, patients continued to record symptom data in the daily diary for 2 weeks post-treatment. During this time, plecanatide-treated patients generally returned to baseline levels of constipation.<br><br>***Comment.*** The efficacy of Trulance (plecanatide) has been established in two randomized placebo-controlled clinical trials in adults with CIC. The efficacy of plecanatide in pediatric patients less than 18 years of age has not been established. The assumption that GC-C agonism leads to movement of chloride and bicarbonate anions and water into the intestinal lumen and increased intestinal transit has been borne out by the submitted clinical trials of Trulance (plecanatide). I concur that the observed improvements in stool frequency, stool consistency and straining on plecanatide treatment were both statistically superior to placebo and clinically meaningful to adult patients with CIC. |
| **Risk** | A total of 863 and 870 adult patients with CIC administered plecanatide 3 mg or placebo, respectively, once daily for 12 weeks in two double-blind, placebo-controlled clinical trials are evaluable for safety. The safety of plecanatide in pediatric patients less than 18 years of age has not been established.<br><br>**General Considerations.** Plecanatide is negligibly absorbed systemically following oral administration. Plecanatide does not inhibit CYP2C9 or CYP3A4, and does not induce CYP3A4 *in vitro*. Plecanatide is neither a substrate or inhibitor of the transporters P-glycoprotein or breast cancer resistance protein *in vitro.* |

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| | Although there are no data on plecanatide use in pregnancy to inform any drug-associated risks, use by pregnant women is not expected to result in fetal exposure to the drug. No information is available regarding the presence of plecanatide in human milk, or its effects on milk production or the breastfed infant.<br><br>Plecanatide is not tumorigenic in 2-year carcinogenicity studies in mice and rats. Plecanatide is not genotoxic in *in vitro* assays or the *in vivo* mouse bone marrow micronucleus assay, and has no effect on fertility or reproductive function in male or female mice.<br><br>**Treatment-Emergent Adverse Events.** During the 12-week double-blind, placebo-controlled period of the two randomized clinical trials, the most frequent treatment-emergent adverse event was diarrhea. Diarrhea was reported in 5% and 1% of patients treated with plecanatide 3 mg and placebo, respectively. The majority of cases occurred within 4 weeks of treatment initiation. Severe diarrhea was reported in 0.6% and 0.3% of patients treated with plecanatide 3 mg and placebo, respectively, and occurred within 3 days of treatment. Diarrhea was the most common adverse reaction leading to treatment discontinuation: 2% of patients treated with plecanatide 3 mg and 0.5% of patients treated with placebo withdrew due to diarrhea. Treatment-emergent adverse events were similar across age, gender, race and BMI subgroups.<br><br>***Comment.*** In adults with CIC, treatment with plecanatide was generally well tolerated. Consistent with the known activity of the drug, the treatment-emergent adverse event most commonly reported in clinical trials of plecanatide was diarrhea which was severe in some cases. I concur with the recommendation to suspend treatment with plecanatide and rehydrate the patient if severe diarrhea develops. Plecanatide shares structural homology with uroguanylin, however, there was no evidence of uroguanylin peptide depletion syndrome in clinical trials (as evidenced by hypernatremia, pulmonary edema, peripheral edema, sudden weight gain, and/or hypertension).<br><br>**Risk of Serious Dehydration in Pediatric Patients.** In young (1- to 2-week-old) juvenile mice (human age equivalent of approximately 1 month to less than 2 years), single oral daily doses of plecanatide at 0.5 mg/kg and 10 mg/kg increased fluid secretion into the intestine as a consequence of stimulation of GC-C. Deaths occurred 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 older patients to develop severe diarrhea and its potentially serious complications. |

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| | ***Comment.*** Given the deaths observed in young juvenile mice in nonclinical studies and the lack of clinical safety and efficacy data in pediatric patients less than 18 years of age, I concur with the recommendation to contraindicate use of Trulance (plecanatide) in pediatric patients less than 6 years of age. |
| **Risk Management** | **Labeling.** The prescribers of Trulance (plecanatide) will likely be general practitioners and gastroenterologists familiar with treatments for CIC, including Linzess (linaclotide). Product labeling will address the serious safety concerns identified in nonclinical studies in young juvenile mice and with use in clinical trials, namely:<br><br>• Risk of serious dehydration in pediatric patients<br>• Severe diarrhea<br><br>In addition, a Medication Guide will be required as part of approved labeling to provide important safety information to patients; routine pharmacovigilance will be conducted in the postmarket setting.<br><br>**Risk Mitigation.** A Risk Evaluation and Mitigation Strategy (REMS) will not be required for Trulance (plecanatide). It is likely that practitioners who will prescribe Trulance (plecanatide) for CIC will be aware of the attendant risks of treatment with GC-C agonists, given the previous marketing experience with the FDA-approved Linzess (linaclotide) product.<br><br>**Postmarketing Required Studies.**<br><br>***Pediatric Research Equity Act (PREA)***<br><br>The Agency is waiving the pediatric study requirement for ages birth to less than 2 years because there is evidence strongly suggesting that Trulance (plecanatide) would be unsafe in this pediatric group. The applicant will be required to 1) assess the pharmacokinetic profile of Trulance (plecanatide) in pediatric patients with CIC ages 12 to less than 18 years, then in patients ages 6 to less than 12 years, and finally, in ages 2 to less than 6 years; 2) confirm the product's efficacy and safety in pediatric patients with CIC ages 6 to less than 18 years, then in patients ages 2 to less than 6 years; and 3) assess long-term safety in |



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| | pediatric patients with CIC ages 2 to less than 18 years.<br><br>***Food and Drug Administration Amendments Act (FDAAA)***<br><br>The applicant will be required to:<br>• Characterize GC-C mRNA expression in duodenal and colonic mucosal biopsies in pediatric patients undergoing diagnostic gastrointestinal endoscopies as part of their medical care. An analogous requirement was imposed on Forest Laboratories, Inc., the applicant for the Linzess (linaclotide) NDA (202811). The Trulance applicant is encouraged to collaborate with Forest Laboratories to complete this study.<br>• Perform a milk-only lactation trial in lactating women receiving plecanatide therapeutically to assess concentrations of plecanatide and its active metabolite in breast milk to inform product labeling. Because young juvenile mice demonstrated increased sensitivity to plecanatide, it is important to determine how much drug is present in human breast milk.<br>• Develop and validate a sensitive assay for the detection of anti-plecanatide antibodies, including IgM, IgG, and IgA that may be present in patient serum samples, and evaluate individual patient titers and the relationship between antibody status and drug efficacy and safety;<br>• Develop and validate assays to evaluate the cross-reactivity of anti-plecanatide antibodies to guanylin and uroguanylin, and evaluate the relationship between cross-reactivity status and drug efficacy and safety; and<br>• Develop and validate an assay to evaluate the neutralizing capacity of anti-plecanatide antibodies detected in patient samples, and evaluate the relationship between neutralizing antibody status and drug efficacy and safety.<br><br>***Comment.*** The safety concerns identified in nonclinical studies and with use of Trulance (plecanatide) in clinical trials can be adequately managed by professional labeling, a Medication Guide, that will be required as part of approved labeling to communicate important safety information to patients, and routine pharmacovigilance in the postmarketing setting. The results of required postmarketing studies will further inform product labeling regarding the safe and effective use of Trulance (plecanatide) in pediatric patients, presence of the product in human breast milk, and its immunogenic potential. |



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JULIE G BEITZ
01/19/2017