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APPLICATION NUMBER:

208745Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memorandum

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 Action Package, including reviews from:	**Discipline Reviewers**
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 OND / DPMH / Maternal Health Team	Carolyn Yancey, MD / Mona Khurana, MD 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 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

1. Benefit-Risk Summary and Assessment

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

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

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

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

e safety profile of Trulance (plecanatide) is similar to that of the approved GC-C agonist, Linzess (linaclotide), including the risk of serious hydration 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.

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

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

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

Dimension	Evidence, Uncertainties and Conclusions
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: 1. Straining during at least 25% of defecations; 2. Lumpy or hard stools in at least 25% of defecations; 3. Sensation of incomplete evacuation for at least 25% of defecations; 4. Sensation of anorectal obstruction/blockage for at least 25% of defecations; 5. Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor); and/or 6. < 3 defecations per week. 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

Dimension	Evidence, Uncertainties and Conclusions
	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] ***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. 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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