CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208745Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA#	208745
Applicant	Synergy Pharmaceuticals, Inc.
Date of Submission	1/29/2016
PDUFA Goal Date	1/29/2017
Proprietary Name / Non-Proprietary Name	Trulance/plecanatide
Dosage Form(s) / Strength(s)	Tablet; 3 mg
Applicant Proposed Indication(s)/Population(s)	Treatment of chronic idiopathic constipation
Recommended Action:	*Approval*
Approved/Recommended Indication/Population(s) (if applicable)	Treatment of chronic idiopathic constipation

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Lesley Hanes, MD/Laurie Muldowney, MD
Statistical Review	Shahla Farr, MS/ Yeh-Fong Chen, PhD
Pharmacology Toxicology Review	Yuk-Chow Ng, PhD/David Joseph, PhD
DB-VI Carcinogenicity Study Review	Hepei Chen/Karl Lin, PhD
OPQ Review	See table below
COA	Sarrit Kovacs, PhD/Elektra Papadopoulos, MD, MPH
Clinical Pharmacology Review	Dilara Jappar, PhD/ Sue Chih Lee, PhD/ Hae Young Ahn, PhD
DPMH	Christos Mastroyannis, MD/Tamar Johnson, MD/Carolyn Yancey, MD/Mona Khurana, MD/Lynne Yao, MD
OPDP	Adewale Adeleye, PharmD, MBA
CDTL Review	Joette Meyer, PharmD
OMPT/DMPP	Karen Dowdy/Marcia Britt Williams
OSE/DMEPA	Matt Barlow, PharmD/ Sherly Abraham, RPh/Mishale Mistry, PharmD, MPH
OSE/DRISK	Jacqueline Sheppard, PharmD/Robert Pratt, PharmD/Jamie Wilkins Parker, PharmD
OSI	Susan Leibenhaut, MD/Susan Thompson, MD/Kassa Ayalew, MD, MPH

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
COA= Clinical Outcome Assessment Team
OMPT=Office of Medical Policy Initiatives
OSE= Office of Surveillance and Epidemiology
OSI=Office of Scientific Investigations
DB-VI=Division of Biometrics - VI
DMPP=Division of Medical Policy Programs
DMEPA=Division of Medication Error Prevention and Analysis
DPMH=Division of Pediatric and Maternal Health
DRISK=Division of Risk Management

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Martin Haber	CDER/OPQ/ONDP/ DNDAPI/NDBII
Drug Product	Zhengfang Ge	CDER/OPQ/ONDP/ DNDPII/NDPBV
Process	Bo Jiang	CDER/OPQ/OPF/ DPAI/PABI
Microbiology	Bo Jiang	CDER/OPQ/OPF/ DPAI/PABI
Facility	Juandria Williams	CDER/OPQ/OPF/DIA/IABIII
Biopharmaceutics	Kalpana Paudel	CDER/OPQ/ONDP/ DB/BBII
Regulatory Business Process Manager	Truong Quach	CDER/OPQ/OPRO/DRBPMI/ RBPMBI
Application Technical Lead	Hitesh Shroff	CDER/OPQ/ONDP/ DNDPII/NDPBV
Laboratory (OTR)	N/A	N/A
ORA Lead	Paul Perdue Jr.	ORA/OO/OMPTO/ DMPTPO/MDTP
Environmental Analysis (EA)	Raanan Bloom	CDER/OPQ/ONDP
Immunogenicity	Haoheng Yan, MD, PhD/Fred Mills PhD	OPQ/OBP/DPRR IV

1. Benefit-Risk Assessment

I concur with the CDTL's risk benefit assessment. The following Risk-Benefit Summary and Assessment table was presented in the CDTL review. I have reproduced it within my review, with some limited modifications, as I concur. My modifications are marked with double underlining. I have deleted a few sentences, which are not tracked.

Benefit-Risk Summary and Assessment

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

Plecanatide is a synthetic hexadecapeptide designed to mimic the action of uroguanylin, an endogenous peptide agon
cyclase C (GC-C) receptor, which is secreted in the GI tract and up-regulates intracellular production of cGMP (cycl
monophosphate) in the intestinal epithelium. Elevated cGMP activates the cystic fibrosis transmembrane conductanc
which leads to trans-epithelial efflux of chloride and bicarbonate from enterocytes lining the GI tract into the lumen
of water into the intestinal lumen. Increased secretion of water into the GI tract can loosen stools, stimulate bowel m
relieve constipation.

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

The efficacy and safety of plecanatide as a treatment for adults with CIC has been adequately assessed. The data fro
controlled trials have demonstrated the efficacy of plecanatide over placebo, as measured by the proportion of patien
number of complete spontaneous bowel movements (CSBMs) in at least 9 weeks out of the 12 weeks in the trial and
weeks. Other measures of efficacy included an increase in the number of bowel movements per week and an improv
consistency and straining compared to placebo. Although the treatment difference between plecanatide and placebo
(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
diarrhea was reported and may lead to discontinuation, but can be managed by patient monitoring, withholding the n
rehydration. In the clinical trials, severe diarrhea did not lead to serious outcomes. Additionally, plecanatide may in

Due to structural similarity between plecanatide and the endogenous peptides uroguanylin and guanylin, there is a th
risk for deficiency if patients develop cross-reacting anti-plecanatide antibodies. No signals of deficiency-related adv
hypertension, edema, pulmonary edema, hypernatremia, weight gain) were seen in the clinical trials database for ple

Serious adverse reactions, related to diarrhea, increases in liver biochemical tests, and guanylin/uroguanylin deficien

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