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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 # Supplement#	NDA 208745
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 ***not*** made a final overall "Approval" recommendation for the facilities involved in this application as of this review. The label/labeling issues have ***not*** been

	completely resolved as of this review. The ATL review includes the following other reviews: 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. 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. Process/Microbiology (Bo Jiang): The application is recommended for approval from manufacturing process aspect. Environmental Analysis (Raanan Bloom), 10/3/16: The claim for the categorical exclusion for the Environmental Assessment is granted. 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. 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. *Addenda:* Labeling (Moo-Jhong Ree), October 18, 2016: The outstanding labeling deficiencies were noted to be adequately addressed by the sponsor.

	Facilities (Juandria Williams), 11/22/16: The inspection of [redacted] (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. 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. *CDTL Comment: An addendum from the ATL is pending at the time of this review.*
OBP	Haoheng Yan/Fred Mills, 10/11/16: 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. 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. 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. [redacted] (b) (4) [redacted] (b) (4) Overall, the ADA assay needs more development work before it can be appropriately validated for detection of ADA response. *CDTL Comment:* *Six PMRs related to assay development will be issued. See Postmarketing Requirements section.*
Pharmacology Toxicology	Eddie Ng/David Joseph, 10/18/16: 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.

	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. The Executive CAC Committee concluded the 2-year mouse and rat carcinogenicity studies were adequate and there were no treatment-related neoplasms. From a nonclinical standpoint, there are no approvability issues. The findings in juvenile mice and clinical relevance to pediatric patients are described in labeling. 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. Abigail Jacobs (Tertiary Review), 10/13/16: I concur that there are no pharm-tox related approval issues.
Clinical	Lesley Hanes / Laurie Muldowney, 10/12/16: 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). 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. Additionally, three main secondary endpoint results of weekly CSBMs and spontaneous bowel movements (SBMs) frequency and stool consistency were clinically meaningful and statistically significant. 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. (b) (4) (b) (4) . Hence, (b) (4) the 3 mg dose is recommended for approval.

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