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RESEARCH**

APPLICATION NUMBER:

208745Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA# 208745
Product Name: Plecanatide

PMR/PMC Description: 3117-1: Determine the appropriate 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	12/31/2015 (completed)
	Study Completion:	12/31/2018
	Final Report Submission:	2/28/2019
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Adult studies of plecanatide are completed and ready for approval in chronic idiopathic constipation. However, there exists an unmet need for therapies for pediatric patients with chronic idiopathic constipation.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Through the evaluation of the safety, efficacy, and pharmacokinetics, the goal of this dose ranging study is to assess the appropriate dose of plecanatide in pediatric patients with chronic idiopathic constipation who are 12 years to less than 18 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This study is a (b)(4) 8 week treatment study, with sparse PK sampling, to evaluate the safety and efficacy of once daily oral plecanatide for the treatment of pediatric patients with chronic idiopathic constipation who are 12 years to less than 18 years of age.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA# 208745

Product Name: Plecanatide

PMR/PMC Description: 3117-2: Determine the appropriate 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>12/31/2018</u>
	Study Completion:	<u>12/31/2020</u>
	Final Report Submission:	<u>2/28/2021</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Adult studies of plecanatide are completed and ready for approval in chronic idiopathic constipation. However, there exists an unmet need for therapies for pediatric patients with chronic idiopathic constipation.

This study will follow the completion of planned dose-ranging, sparse PK sampling, efficacy and safety study in chronic idiopathic constipation pediatric patients 12 to years to less than 18 years of age.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Through the evaluation of the safety, efficacy, and pharmacokinetics, the goal of this dose ranging study is to assess the appropriate dose of plecanatide in pediatric patients with chronic idiopathic constipation who are 6 years to less than 12 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This study is a (b)(4) 8 week treatment study, with sparse PK sampling, to evaluate the safety and efficacy of once daily oral plecanatide for the treatment of pediatric patients with chronic idiopathic constipation who are 6 years to less than 12 years of age.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA# 208745

Product Name: Plecanatide

PMR/PMC Description: 3117-3: Confirm the efficacy and safety of plecanatide treatment 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>12/31/2018</u>
	Trial Completion:	<u>12/31/2021</u>
	Final Report Submission:	<u>2/28/2022</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Adult studies of plecanatide are completed and ready for approval in chronic idiopathic constipation. However, there exists an unmet need for therapies for pediatric patients with chronic idiopathic constipation.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this phase 3 study is to determine the effect (efficacy and safety) of plecanatide in the treatment of pediatric patients with chronic idiopathic constipation who are 6 to less than 18 years of age.

This study will follow the completion of planned dose-ranging, sparse PK sampling, proof-of-concept studies of pediatric patients with chronic idiopathic constipation ages 6 to 18 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A confirmatory randomized, double-blind, placebo-controlled, parallel group study will be required to evaluate the safety and efficacy of once daily oral plecanatide for 12 weeks for the treatment of pediatric patients with chronic idiopathic constipation who are 6 years to less than 18 years.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA# 208745
Product Name: Plecanatide

PMR/PMC Description: 3117-4: Determine the appropriate 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>12/31/2020</u>
	Study Completion:	<u>12/31/2022</u>
	Final Report Submission:	<u>2/28/2023</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Adult studies of plecanatide are completed and ready for approval in chronic idiopathic constipation. However, there exists an unmet need for therapies for pediatric patients with chronic idiopathic constipation.

Initiation of the trial is contingent on the determination that it is safe to proceed in patients 2 years to less than 6 years of age. This will be determined on completion and evaluation of the results from a biopsy GC-C receptor expression study to assess the ontogeny of the GC-C receptor in pediatric patients, which will be required under 505(o) and dose finding clinical studies in patients greater than 6 years to less than 18 years .

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Through the evaluation of the safety, efficacy, and pharmacokinetics, the goal of this dose ranging study is to assess the appropriate dose of plecanatide in pediatric patients with chronic idiopathic constipation who are 2 years to less than 6 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This study is a (b)(4) 8 week treatment study, with sparse PK sampling, to evaluate the safety and efficacy of once daily oral plecanatide for the treatment of pediatric patients with chronic idiopathic constipation who are 2 years to less than 6 years of age.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA# 208745

Product Name: Plecanatide

PMR/PMC Description: 3117-5: Confirm the efficacy and safety of 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>12/31/2022</u>
	Trial Completion:	<u>12/31/2025</u>
	Final Report Submission:	<u>2/28/2026</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Adult studies of plecanatide are completed and ready for approval in chronic idiopathic constipation. However, there exists an unmet need for therapies for pediatric patients with chronic idiopathic constipation.

The study will not be initiated until it has been determined that it is safe to proceed in patients 2 years to less than 6 years of age. This will be determined on completion and evaluation of the results from the biopsy GC-C receptor expression study which will be required under 505(o) to assess the ontogeny of the GC-C receptor in pediatric patients and the planned dose finding clinical studies in patients greater than 6 years to less than 18 years.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this phase 3 study is to determine the efficacy and safety of plecanatide in the treatment of pediatric patients with chronic idiopathic constipation who are 2 years to less than 6 years of age. This study would follow the completion of a planned dose-ranging, sparse PK sampling, proof-of-concept study in pediatric patient with chronic idiopathic constipation ages 2 to less than years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A confirmatory, randomized, double-blind, placebo-controlled, parallel group to evaluate the safety and efficacy of once daily oral plecanatide for 12 weeks as treatment for the relief of symptoms associated with chronic idiopathic constipation in patients 2 years to less than 6 years.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA# 208745
Product Name: Plecanatide

PMR/PMC Description: 3117-6: Assess the long-term safety of plecanatide treatment 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>2/28/2017</u>
	Study Completion:	<u>6/30/2026</u>
	Final Report Submission:	<u>8/31/2026</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Adult studies of plecanatide are completed and ready for approval in chronic idiopathic constipation. However, there exists an unmet need for therapies for pediatric patients with chronic idiopathic constipation. This study will include pediatric patients who have completed a confirmatory efficacy and safety study with plecanatide and thus cannot begin until after initiation of these studies. Initiation of enrollment of patients 2 years to less than 6 years of age will also be contingent on completion and evaluation of the results from the biopsy GC-C receptor expression study to assess the ontogeny of the GC-C receptor in pediatric patients, which will be required under 505(o) and the planned dose finding clinical studies in patients greater than 6 years to less than 18 years.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this phase 3 study is to evaluate the long-term safety of plecanatide in the treatment of pediatric patients with chronic idiopathic constipation who are 2 years to less than 18 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A long-term, (b)(4) to include any pediatric patient who successfully completes the confirmatory efficacy and safety study treatment for the relief of symptoms associated with chronic idiopathic constipation for their age group in pediatric patients 2 years to less than 18 years.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA# 208745
Product Name: Plecanatide
PMR/PMC Description: 3117-7: 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. .

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 04/30/2018
Other: MM/DD/YYYY

Note: only the final reports are requested; The final reports should include screening, confirmation and titer assay validation reports and assay standard operating procedures (SOPs).

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Plecanatide is a 16 amino acid peptide with very limited systemic absorption. Due to the structure similarity between plecanatide and endogenous guanylin peptide family (guanylin and uroguanylin), there is a theoretical immunogenicity risk for depletion syndrome if patients develop anti-plecanatide antibody which cross react with the endogenous proteins. The sponsor developed an anti-drug antibody (ADA) screening assay (without confirmation or titering) for detecting anti-plecanatide antibody in patient serum. However, the assay is deemed not adequate. Testing of patient samples was stopped until the assay is deemed adequate. In addition, the sponsor has not developed assays to evaluate the cross reactivity of the potential ADAs to endogenous guanylin and uroguanylin, nor have they developed an assay to evaluate the neutralizing capacity of the potential ADAs. 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 can be conducted post-marketing. This PMR is for developing an adequate assay to detect anti-plecanatide antibodies (ADA), including IgM, IgG, and IgA, that may be present in the serum at the time of patient sampling.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

1. The sponsor made multiple revisions to the assay after the assay validation work was conducted; therefore, the validation work conducted on the original version of the assay is no longer applicable to the revised assay.
2. The screening cut point in the current ADA assay was inappropriately defined.
3. The sponsor did not develop a confirmation assay to exclude false positive results from the screening assay. Therefore, using the current ADA assay would lead to inaccurate results in testing patient samples.
4. The sponsor did not develop a titer assay to evaluate and monitor titer change in ADA positive patients. The sponsor should develop and validate a sensitive and accurate assay for the detection of anti-drug antibodies, including IgM, IgG, and IgA, that may be present in the serum at the time of patient sampling.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Assay development for the detection of anti-plecanatide antibodies in serum

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
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.
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA# 208745
Product Name: Plecanatide

PMR/PMC Description: 3117-8: Develop and validate assays to evaluate the cross reactivity of anti-plecanatide antibodies to guanylin and uroguanylin.

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 04/30/2020
Other: _____ MM/DD/YYYY

Note: only the final reports are requested; the final study reports should include the assay validation report and the assay SOPs

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Plecanatide is a 16 amino acid peptide with very limited systemic absorption. Due to the structure similarity between plecanatide and endogenous guanylin peptide family (guanylin and uroguanylin), there is a theoretical immunogenicity risk for depletion syndrome if patients develop anti-plecanatide antibody which cross react with the endogenous proteins. The sponsor developed an anti-drug antibody (ADA) screening assay for detecting anti-plecanatide antibody in patient serum. However, the assay is deemed not adequate. Testing of patient samples was stopped until the assay is deemed adequate. In addition, the sponsor has not developed assays to evaluate the cross reactivity of the potential ADAs to endogenous guanylin and uroguanylin, nor have they developed an assay to evaluate the neutralizing capacity of the potential ADAs. 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 can be conducted post-marketing. This PMR is for developing assays to evaluate the cross reactivity of anti-plecanatide antibody to guanylin and uroguanylin.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Please see the response to #1 above. ADA cross reactivity to endogenous protein(s) is normally assessed in ADA positive samples from patients in the clinical development program. However, the sponsor has not developed any assay to evaluate the cross reactivity of the anti-plecanatide antibody to endogenous guanylin and uroguanylin. Depending on the ADA results and the clinical impact reported under PMR 3117-11, the sponsor should develop and validate assays to evaluate the such cross reactivity.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Assay development for evaluate the cross reactivity of anti-plecanatide antibodies detected in patient samples to guanylin and uroguanylin.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Depending on the anti-plecanatide antibody results and the clinical impact reported under PMR 3117-11, develop and validate assays to evaluate the cross reactivity of anti-plecanatide antibodies to guanylin and uroguanylin. Submit assay validation report and assay SOP to the FDA.
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation

- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 - The trial will emphasize risk minimization for participants as the protocol is developed
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA# 208745
Product Name: Plecanatide

PMR/PMC Description: 3117-9: Develop and validate an assay to evaluate the neutralizing capacity of ADA detected in the patient samples.

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 08/30/2020
Other: _____ MM/DD/YYYY

Note: only the final report(s) is requested; the final report submission should include the assay validation report and the assay SOP.

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Plecanatide is a 16 amino acid peptide with very limited systemic absorption. Due to the structure similarity between plecanatide and endogenous guanylin peptide family (guanylin and uroguanylin), there is a theoretical immunogenicity risk for depletion syndrome if patients develop anti-plecanatide antibody which cross react with the endogenous proteins. The sponsor developed an anti-drug antibody (ADA) screening assay for detecting anti-plecanatide antibody in patient serum. However, the assay is deemed not adequate. Testing of patient samples was stopped until the assay is deemed adequate. In addition, the sponsor has not developed assays to evaluate the cross reactivity of the potential ADAs to endogenous guanylin and uroguanylin, nor have they developed an assay to evaluate the neutralizing capacity of the potential ADAs. 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 can be conducted post-marketing. This PMR is for developing an assay to evaluate the neutralizing capacity of ADAs detected in the patient samples.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Please see the response to #1 above. The neutralizing capacity of the ADAs is normally assessed on ADA positive samples from patients in the clinical development program. However, the sponsor has not developed an assay to evaluate the neutralizing capacity of the ADAs. Depending on the ADA results and the clinical impact reported under PMR 3117-11, the sponsor should develop and validate an assay to evaluate the neutralizing capacity of ADAs detected in the patient samples.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Develop assay for evaluating the neutralizing capacity of ADA detected in patient samples.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Depending on the anti-plecanatide antibody results and the clinical impact reported under PMR 3117-11, develop and validate an assay to evaluate the neutralizing capacity of ADA detected in patient samples. Submit assay validation report and assay SOP to the FDA.
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA# 208745

Product Name: Plecanatide

PMR Description: 3117-10: 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 GI endoscopies as part of their medical care.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>12/15/2017</u>
	Study Completion:	<u>04/01/2019</u>
	Final Report Submission:	<u>07/15/2019</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Adult trials of plecanatide are completed and ready for approval in chronic idiopathic constipation (CIC), and there exists an unmet need for therapies for pediatric patients with CIC.

There exists a theoretical risk for severe dehydration in young pediatric patients based on nonclinical data identified during the plecanatide clinical development program. Specifically, plecanatide is a GC-C agonist which binds to GC-C locally on the intestinal epithelium. A primary safety concern identified during the plecanatide clinical development program resulted from a finding of lethality due to dehydration in neonatal/juvenile mice receiving plecanatide in a nonclinical study. 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 is 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 plecanatide will be contraindicated in patients less than 6 years of age. A research study characterizing guanylate cyclase-C mRNA expression in duodenal and colonic mucosal biopsies in pediatric patients 0 to 6 years may provide important information on the ontogeny of the GC-C receptor to help determine if pediatric studies may be safe in children 2 years to less than 6 years age.

Until the results of this 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.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Plecanatide is a GC-C agonist, similar to linaclotide, which binds to GC-C receptors locally on the luminal surface of the intestinal epithelium. Activation of GC-C receptors results in increased concentrations of cGMP and ultimately results in increased intestinal fluid and intestinal transit. In non-clinical studies, deaths occurred within 24 hours in young juvenile mice (1 to 2 week-old mice) following administration of one or two once daily oral doses of plecanatide. The mechanism of death was due to dehydration caused by fluid shift in the intestine. 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 is needed to determine if pediatric studies in children 2 years to less than 6 years may be safe.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A study to characterize guanylate cyclase-C mRNA expression in duodenal and colonic mucosal biopsies in pediatric patients undergoing diagnostic GI endoscopies as part of their medical care.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety

- Other (provide explanation)
This will be a study to characterize and quantitate GC-C mRNA expression in duodenal and colonic mucosal biopsies in pediatric patients 0 to 6 years of age . This study will be conducted in pediatric patients who are undergoing a diagnostic upper or lower GI tract endoscopy, or both, as part of their medical care and aims to assess the relationship between the GC-C mRNA levels and age.
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)
-

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 Are the objectives clear from the description of the PMR/PMC?
 Has the applicant adequately justified the choice of schedule milestone dates?
 Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
 There is not enough existing information to assess these risks
 Information cannot be gained through a different kind of investigation
 The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 The trial will emphasize risk minimization for participants as the protocol is developed
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*
-

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA# 208745
Product Name: Plecanatide

PMR/PMC Description: 3117-11: Assess development of anti-drug antibody (ADA) responses in patient samples using the immunogenicity serum samples collected in the plecanatide studies (SP304203-00 and SP304203-03 and SP304203-01). Validated assays capable of sensitively and accurately detecting ADA responses, developed under PMR 3117-7, will be used. Evaluate the anti-drug antibody (ADA) rates, individual patient titers and the relationships between ADA status and the drug safety and efficacy.

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 4/30/2019
Other: _____ MM/DD/YYYY

Note: only the final reports are requested

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Plecanatide is a 16 amino acid peptide with very limited systemic absorption. Due to the structure similarity between plecanatide and endogenous guanylin peptide family (guanylin and uroguanylin), there is a theoretical immunogenicity risk for depletion syndrome if patients develop anti-plecanatide antibody which cross react with the endogenous proteins. The sponsor developed an anti-drug antibody (ADA) screening assay for detecting anti-plecanatide antibody in patient serum. However, the assay is deemed not adequate. Testing of patient samples was stopped until the assay is deemed adequate. In addition, the sponsor has not developed assays to evaluate the cross reactivity of the potential ADAs to endogenous guanylin and uroguanylin, nor have they developed an assay to evaluate the neutralizing capacity of the potential ADAs. 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 can be conducted post-marketing. Developing an adequate ADA assay is required under PMR 3117-7. This PMR requires using this adequate ADA assay to test the immunogenicity samples collected during the plecanatide development program.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Please see the response to #1 above. Immunogenicity is normally assessed in the pre-market setting on a subset of samples taken from patients during the clinical development program. However, the current ADA assay is deemed inadequate to detect anti-plecanatide antibody in patient serum. The sponsor agreed to stop testing patient sample until the ADA assay is deemed adequate by the FDA. Once the sponsor validates an adequate ADA assay, they should test the immunogenicity samples that had been collected during the clinical trials to determine the ADA rate, titer, as well as to evaluate the relationships between ADA status and the drug safety and efficacy. Upon completion of this PMR, the sponsor should discuss with the FDA if PMR 3117-8, 3117-9, 3117-12 and 3117-13 can be waived.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Testing patient serum samples collected in plecanatide studies (SP304203-00, SP304203-03 and SP304203-1) to detect anti-plecanatide antibodies, assess titers and evaluate the relationships between ADA status and the drug safety and efficacy.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Use the validated assay developed under PMR 3117-7 to test the immunogenicity serum samples collected in the plecanatide trials (SP304203-00, SP304203-03 and SP304203-1). Evaluate the ADA rates, individual patient titers and the relationships between ADA status and the drug safety and efficacy. Provide the study report to the FDA.

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks

- Information cannot be gained through a different kind of investigation
 - The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 - The trial will emphasize risk minimization for participants as the protocol is developed
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA# 208745
Product Name: Plecanatide

PMR/PMC Description: 3117-12: Use the validated cross reactivity assays developed under PMR 3117-8 to test the ADA positive samples detected under PMR 3117-11. Evaluate the relationships between cross reactivity status and the drug safety and efficacy.

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 06/30/2020
Other: _____ MM/DD/YYYY

Note: only the final report(s) are requested

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Plecanatide is a 16 amino acid peptide with very limited systemic absorption. Due to the structure similarity between plecanatide and endogenous guanylin peptide family (guanylin and uroguanylin), there is a theoretical immunogenicity risk for depletion syndrome if patients develop anti-plecanatide antibody which cross react with the endogenous proteins. The sponsor developed an anti-drug antibody (ADA) screening assay for detecting anti-plecanatide antibody in patient serum. However, the assay is deemed not adequate. Testing of patient samples was stopped until the assay is deemed adequate. In addition, the sponsor has not developed assays to evaluate the cross reactivity of the potential ADAs to endogenous guanylin and uroguanylin, nor have they developed an assay to evaluate the neutralizing capacity of the potential ADAs. 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 can be conducted post-marketing.

Depending on the results reported for PMR 3117-11, the sponsor is required to develop an assay to evaluate the cross reactivity of ADA detected in patient samples to guanylin and uroguanylin in PMR 3117-8. This PMR requires using the validated assay to test the cross reactivity of ADAs in the ADA positive samples detected under PMR 3117-11.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Please see the response to #1 above. Cross reactivity to endogenous protein is normally assess in the pre-marketing setting on ADA positive samples detected from patients in the clinical development program. However, the sponsor has not developed an assay to evaluate the cross reactivity of the potential ADA detected in patients to endogenous guanylin peptide family. Depending on the ADA results and the clinical impact reported under PMR 3117-11, the sponsor should develop and validate assays to evaluate the cross reactivity of ADAs to guanylin and uroguanylin. The goal is to use the cross reactivity assay to test the cross reactivity of ADA positive samples detected under PMR 3117-11 and evaluate the relationships between cross reactivity status and the drug safety and efficacy.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Testing cross reactivity of ADA positive serum samples collected in plecanatide trials (SP304203-00, SP304203-03 and SP304203-1) and evaluation of the relationships between the cross reactivity status and the drug safety and efficacy.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Use the validated cross reactivity assays developed under PMR 3117-8 to test the ADA positive samples detected under PMR 3117-11. Evaluate the relationships between cross reactivity status and the drug safety and efficacy. Provide the study report to the FDA.
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation

- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 - The trial will emphasize risk minimization for participants as the protocol is developed
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA# 208745
Product Name: Plecanatide

PMR/PMC Description: 3117-13: Use the validated neutralizing antibody assay developed under PMR 3117-9 to test the anti-plecanatide antibody positive samples detected under PMR 3117-11. Evaluate the relationships between neutralizing antibody status and the drug safety and efficacy.

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 08/30/2021
Other: _____ MM/DD/YYYY

Note: only the final report(s) are requested

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Plecanatide is a 16 amino acid peptide with very limited systemic absorption. Due to the structure similarity between plecanatide and endogenous guanylin peptide family (guanylin and uroguanylin), there is a theoretical immunogenicity risk for depletion syndrome if patients develop anti-plecanatide antibody which cross react with the endogenous proteins. The sponsor developed an anti-drug antibody (ADA) screening assay for detecting anti-plecanatide antibody in patient serum. However, the assay is deemed not adequate. Testing of patient samples was stopped until the assay is deemed adequate. In addition, the sponsor has not developed assays to evaluate the cross reactivity of the potential ADAs to endogenous guanylin and uroguanylin, nor have they developed an assay to evaluate the neutralizing capacity of the potential ADAs. 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 can be conducted post-marketing.

Depending on the results reported for PMR 3117-11, the sponsor is required to develop an assay to evaluate the neutralizing capacity of ADAs detected in the patient samples. This PMR is for using the validated neutralizing antibody assay to test the neutralizing capacity of ADAs in the ADA positive samples detected under PMR 3117-11.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Please see the response to #1 above. Neutralizing antibody is normally assessed in the pre-marketing setting on ADA positive samples. However, the sponsor has not developed an assay to evaluate the neutralizing capacity of the potential ADAs detected in patient samples. Depending on the ADA results and the clinical impact reported under PMR 3117-11, the sponsor should develop and validate an assay to detect neutralizing antibodies in ADA positive samples. The goal is to use the neutralizing antibody assay to test the ADA positive samples detected under PMR 3117-11 and evaluate the relationships between the neutralizing antibody status and the drug safety and efficacy.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Sample testing: to test the neutralizing capacity of ADA positive samples collected in plecanatide trials (SP304203-00, SP304203-03 and SP304203-1) and evaluate the relationships between the neutralizing antibody status and the drug safety and efficacy.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Use the validated neutralizing antibody assay developed under PMR 3117-9 to test the anti-plecanatide antibody positive samples detected under PMR 3117-11. Evaluate the relationships between neutralizing antibody status and the drug safety and efficacy. Provide the study report to the FDA.
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation

- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 - The trial will emphasize risk minimization for participants as the protocol is developed
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA# 208745
Product Name: Plecanatide

PMR/PMC Description: 3117-14: Perform a milk-only lactation trial in lactating women who have received multiple, once daily, doses of plecanatide therapeutically to assess concentrations of plecanatide and its active metabolite in breast milk using a validated assay.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>12/31/2017</u>
	Trial Completion:	<u>06/30/2018</u>
	Final Report Submission:	<u>12/31/2018</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Given the anticipated use of the drug product in females of reproductive potential, the lack of data on safe use in lactating women, and animal data demonstrating serious findings (mortality) in juvenile and neonatal mice associated with decreasing age and decreasing dose for a similar drug in the class, this trial needs to be done in order to properly inform labeling. The likelihood of this product appearing in the breast milk is low due to the fact that there is a very low absorption of the product. This drug will be approved only in adults because it was determined, through clinical trials, that it is safe and effective in this population.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

See above.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A milk-only lactation trial in lactating women who have received multiple, once daily, doses of plecanatide therapeutically to assess concentrations of plecanatide and its active metabolite in breast milk using a validated assay in order to appropriately inform the Lactation subsection of the labeling.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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/s/

MAUREEN D DEWEY
01/19/2017

JOETTE M MEYER
01/19/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 18, 2017
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 208745
Product Name and Strength:	Trulance (plecanatide) Oral Tablets, 3 mg
Submission Date:	January 3, 2017
Applicant/Sponsor Name:	Synergy Pharmaceuticals
OSE RCM #:	2016-283-1
DMEPA Primary Reviewer:	Sherly Abraham, RPh
DMEPA Associate Director(Acting):	Mishale Mistry, PharmD, MPH

1 PURPOSE OF MEMO

The Division of Gastroenterology and Inborn Error Products (DGIEP) requested that we review the revised label and labeling for Trulance (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container label and carton labeling is acceptable from a medication error perspective. We have no further recommendations at this time.

^aAbraham.S. Label and Labeling Review for Trulance (NDA 208745). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 12 01. 32 p. OSE RCM No.:2016-283.

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/s/

SHERLY ABRAHAM
01/18/2017

MISHALE P MISTRY
01/18/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: December 1, 2016

Requesting Office or Division: Division of Gastroenterology and Inborn Error Products (DGIEP)

Application Type and Number: NDA 208745

Product Name and Strength: Trulance (plecanatide) Oral Tablets, 3 mg

Product Type: Single ingredient

Rx or OTC: Rx

Applicant/Sponsor Name: Synergy Pharmaceuticals

Submission Dates: January 29, 2016 (Prescribing Information)
September 9, 2016 (Container labels and Carton Labeling)

OSE RCM #: 2016-283

DMEPA Primary Reviewer: Sherly Abraham, RPh

DMEPA Team Leader: Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

This review evaluates the labels and labeling for Trulance (NDA 208745), a new molecular entity (NME) NDA, submitted on January 29, 2016. The Division of Gastroenterology and Inborn Error Products (DGIEP) requested that DMEPA review the proposed Prescribing Information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C- N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E- N/A
Other	F- N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Synergy Pharmaceuticals submitted a new molecular entity (NME) NDA for Trulance (plecanatide), indicated for the (b)(4) treatment of chronic idiopathic constipation (CIC). On June 8, 2016, the Applicant proposed alternative administration instructions for adult patients with swallowing difficulties in the Medication Guide. 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. In October 2016, DGIEP incorporated these proposed instructions to Section 2 Dosage and Administration of the Prescribing Information. 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. We recommend presenting strength statement as “3 mg” vs. (b)(4) as this information is repetitive and replacing “TRADENAME” placeholder with proprietary name, Trulance. We provide letter-ready recommendations for the Division in Section 4.1 and for the Applicant in Section 4.2 to address these concerns.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed prescribing information, carton labeling, and container labels can be improved to increase the clarity of information to promote the safe use of the product. Please see recommendations to the Division in Section 4.1 and for the Applicant in Section 4.2 below:

4.1 RECOMMENDATIONS TO THE DIVISION

A. Section 2 Dosage and Administration of the Full Prescribing Information

- B. We recommend revising the directions regarding oral administration in applesauce, oral administration in water, and administration with water via nasogastric or gastric feeding tube in order to increase the clarity of instructions. Additionally, we note that the time required to dissolve the tablet in water varies in the instructions for “Oral Administration in Water” (states at least 10 seconds) and “Administration with Water via Nasogastric or Gastric Feeding Tube” (states at least 15 seconds). We recommend that the Applicant provide clarification to the Agency as to the inconsistency in the time for the two procedures:

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

Preparation and Administration Instructions

- Take TRULANCE with or without food [see *Clinical Pharmacology* ([Error! Reference source not found.](#))]. APPEARS THIS WAY ON ORIGINAL
- If a dose is missed, skip the missed dose and take the next dose at the regular time. Do not take two doses at the same time.
- Swallow a tablet whole for each dose.
- For adult patients with swallowing difficulties, TRULANCE tablets can be crushed and administered orally either in applesauce or with water or administered with water via a nasogastric or gastric feeding tube. Mixing TRULANCE crushed tablets in other soft foods or in other liquids has not been tested.

Oral Administration in Applesauce:

1. In a clean container, crush the TRULANCE tablet to a powder and mix with 1 teaspoonful of room temperature applesauce.
2. Consume the entire tablet-applesauce mixture immediately. Do not store the mixture for later use.

Oral Administration in Water:

1. Place the TRULANCE tablet in a clean cup.
2. Pour approximately 30 mL of room temperature water into the cup.
3. Mix by gently swirling the tablet and water mixture for at least 10 seconds. The TRULANCE tablet will fall apart in the water.
4. Swallow the entire contents of the tablet water mixture immediately.
5. If any portion of the tablet is left in the cup, add another 30 mL of water to the cup, swirl for at least 10 seconds, and swallow immediately.

6. Do not store the tablet-water mixture for later use.

Administration with Water via a Nasogastric or Gastric Feeding Tube:

1. Place the TRULANCE tablet in a clean cup with 30 mL of room temperature water.
2. Mix by gently swirling the tablet and water mixture for at least 15 seconds. The TRULANCE tablet will fall apart in the water.
3. Flush the nasogastric or gastric feeding tube with 30 mL of water using an appropriate syringe.
4. Draw up the mixture using the syringe and immediately administer via the nasogastric or gastric feeding tube. Do not reserve for future use.
5. If any portion of the tablet is left in the cup, add another 30 mL of bottled water to the cup, swirl for at least 15 seconds, and using the same syringe, administer via the nasogastric or gastric feeding tube.
6. Using the same or a fresh syringe, flush the nasogastric or gastric feeding tube with at least 10 mL of water.

4.2 RECOMMENDATIONS TO THE APPLICANT

A. All Container Labels and Carton Labeling

1. Present the strength statement as “3 mg” vs. (b) (4) as this information is repetitive.
2. Replace “TRADENAME” Placeholder with proprietary name, Trulance.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Trulance submitted by Synergy Pharmaceuticals on January 29, 2016.

Table 2. Relevant Product Information for Trulance	
Initial Approval Date	N/A
Active Ingredient	plecanatide
Indication	Treatment of Chronic idiopathic constipation (CIC)
Route of Administration	oral
Dosage Form	tablets
Strength	3 mg
Dose and Frequency	One tablet (3 mg) once daily
How Supplied	Bottle of 30 and aluminum foil unit dose blister pack of 30 in a child resistant pack
Storage	Store at room temperature, 20 to 25°C (68 to 77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].
Container Closure	HDPE bottle with Child Resistant Closure and child resistant blister pack

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SHERLY ABRAHAM
12/01/2016

MISHALE P MISTRY
12/02/2016

REGULATORY PROJECT MANAGER PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208745

Application Type: New NDA

Drug Name/Dosage Form: Trulance (plecanatide) tablets

Applicant: Synergy Pharmaceuticals, Inc.

Receipt Date: 01/29/2016

Goal Date: 01/27/2017

1. Regulatory History and Applicant's Main Proposals

NDA 208745 Trulance (plecanatide) was submitted on January 29, 2016 as a 505(b)(1) application. Plecanatide (SP-304) is a new molecular entity (NME) that is not approved or marketed in the United States. It is an immediate-release solid formulation tablet that is intended for chronic oral administration for the treatment of CIC in adults. The development of plecanatide for the treatment of CIC was conducted under IND 074883 activated on May 3, 2008.

Pre-submission regulatory activities related to this application included formal face-to-face end of phase 2 (EOP2) and Pre-NDA meetings between the FDA and the sponsor. The primary efficacy endpoint, dose selection for the phase 3 trials, an agreed iPSP, and the development of antidrug-antibody (ADA) assays were discussed with the FDA.

NDA 208745 has a standard review designation with a PDUFA goal date of January 27, 2017.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

The sponsor should draft a Medication Guide using Linzess as a template.

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

Selected Requirements of Prescribing Information

All SRPI format deficiencies of the PI and other labeling issues identified above were conveyed to the applicant in the 74-day letter. The applicant was asked to correct these deficiencies and resubmit the PI in Word format by May 5, 2016. The resubmitted PI was to be used for further labeling review.

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. **Instructions to complete this item:** If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required

Selected Requirements of Prescribing Information

• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the

Selected Requirements of Prescribing Information

BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at**

Selected Requirements of Prescribing Information

(insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.”

Comment:

Patient Counseling Information Statement in Highlights

NO 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION** and **FDA-approved patient labeling**
- See 17 for **PATIENT COUNSELING INFORMATION** and **Medication Guide**

Comment:

Sponsor should draft a Medication Guide.

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS.”** This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading **“FULL PRESCRIBING INFORMATION: CONTENTS*”** must be followed by an asterisk and the following statement must appear at the end of the TOC: **“*Sections or subsections omitted from the full prescribing information are not listed.”**
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*].”

Comment:

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- NO** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
 - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

We recommend the sponsor refer to the Patient Counseling Information labeling guidance.
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368602.pdf>

Note the following:

These instructions are directed to the healthcare provider for discussion with the patient.
Do not include instructions related to storage and handling, unless there is atypical storage or handling information.
Do not include information unless it already appears in other sections of labeling.
Do not include general advice on the use of drugs during pregnancy or lactation, if there is no specific risk.

- NO** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

The sponsor should draft a Medication Guide for FDA review using Linzess as the template.

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
11/22/2016

KEVIN B BUGIN
11/22/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208745 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Trulance (SP-304) Established/Proper Name: plecanatide Dosage Form: tablets Strengths: 3 mg (b)(4)		
Applicant: Synergy Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: 01/28/2016 Date of Receipt: 01/29/2016 Date clock started after UN:		
PDUFA/BsUFA Goal Date: 01/27/2017		Action Goal Date (if different): 01/19/2017
Filing Date: March 29, 2016		Date of Filing Meeting: March 18, 2016
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): Chronic Idiopathic Constipation		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <hr/> <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
The application will be a priority review if:	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted 	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): IND 74883

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes, answer the bulleted	<input type="checkbox"/>	<input type="checkbox"/>	X	

questions below:				
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 	<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)]. 	<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p>	<input type="checkbox"/>	<input type="checkbox"/>		
If yes, please list below:				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>				
Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>				
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, # years requested: 5 years				
<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				

NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no , explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes , BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Not submitted with the original application. Submitted on 5/27/2016
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p><u>BPCA:</u></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
<p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
<p>Check all types of labeling submitted.</p>	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU)			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Medication Guide (MedGuide)			
	<input checked="" type="checkbox"/> Carton labels			
	<input checked="" type="checkbox"/> Immediate container labels			
	<input type="checkbox"/> Diluent			
	<input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has a review of the available pregnancy and lactation data been included?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label			
	<input type="checkbox"/> Immediate container label			

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

	<input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consults and dates sent:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	COA: 3/6/2016 OBP: 3/6/2016 OSI:3/17/2016 DPMH: 3/6/2016 PLT:3/6/2016 OSE:3/6/2016 OPDP:3/6/2016
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meetings? Date: June 5, 2013 and July 31, 2013 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meetings? Dates: July 28, 2015 and August 5, 2015 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Dates: January 31, 2013, April 12, 2013 <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input checked="" type="checkbox"/>			

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 18, 2016

BACKGROUND:

The sponsor submitted a NDA for plecanatide tablets (a NME) for the treatment of chronic idiopathic constipation (CIC) via 505(b)(1) regulatory pathway. PLECANATIDE (SP-304) is an analog of the endogenous human uroguanylin peptide is a guanylate cyclase-C (GC-C) agonists. The proposed formulation is immediate release tablet 3 mg (b)(4) for oral administration and the proposed dosing regimen is 3 mg (b)(4) once daily with or without meal. The applications contains 2 phase 1 studies in healthy subjects, 3 phase 2 studies in patient population, 2 dose-ranging phase 3 studies in the patient population, and one ongoing phase 3 long term safety study.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	James Carr	Y
	CPMS/TL:	Brian Strongin	N
Cross-Discipline Team Leader (CDTL)	Joette Meyer		Y
Division Director/Deputy	Donna Griebel		Y
Office Director/Deputy	Julie Beitz		Y
Clinical	Reviewer:	Lesley Hanes	Y
	TL:	Laurie Muldowney	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
OTC Labeling Review (for OTC products)	Reviewer:		
	TL:		
Clinical Microbiology (for antimicrobial products)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Dilara Jappar	Y

	TL:	Sue Chih Lee	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Andrejus Parfionovas	Y
	TL:	Yeh-Fong Chen	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Yuk-Chow Ng	Y
	TL:	David Joseph	Y
Statistics (carcinogenicity)	Reviewer:	Heipei Chen	N
	TL:		
Product Quality (CMC) Review Team:	ATL:	Danuta Gromek-Woods	Y
	RBPM:	Truong Quach	Y
• Drug Substance	Reviewer:	Martin Haber/Donna Christner	N
• Drug Product	Reviewer:	Zhengfang Ge	N
• Process	Reviewer:		
• Microbiology	Reviewer:	Bo Jiang/Yubing Tang	N
• Facility	Reviewer:	Juandria Williams/Grace McNally	N
• Biopharmaceutics	Reviewer:	Kalpana Paudel/Tien Mien Chen	N
• Immunogenicity	Reviewer:	Haoheng Yan	Y
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Karen Dowdy	Y
	TL:	Marcia Britt Williams	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Meeta Patel	Y
	TL:	Mishale Mistry	Y
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Matt Barlow/ Sherly Abram	Y
	TL:	Mishale Mistry	Y
OSE/DRISK (REMS)	Reviewer:	Jacqueline Sheppard	Y
	TL:	Jamie Wilkins-Parker	N

DPMH (PEDS)	Reviewer/ TL:	Carolyn Yancey/Hari Sachs	Y
	Reviewer/TL:	Christos Mayostrannis/Tamara Johnson	Y
Bioresearch Monitoring (OSI)	Reviewer:	Susan Leibenhaut	Y
	TL:	Susan Thompson	Y
Other reviewers/disciplines			
<ul style="list-style-type: none"> COA <p>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</p>	Reviewer:	Sarrit Kovacs	Y
	TL:	Elektra Papadopoulos	Y
Other attendees	DPV: Lisa M Harinstein/Ling Y(Eileen) Wu		Y
	DEPI: Sukhminder Sandhu		
	OSE/SRPM: Aleks Winiarski/Marcus Cato		Y
*For additional lines, right click here and select "insert rows below"			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505 b)(2) filing issues: <ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p> 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments 	<input type="checkbox"/> Not Applicable

List comments:	<input checked="" type="checkbox"/> No comments
CLINICAL Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? If no, explain: 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: This drug/biologic is not the first in its class
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments: 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
CONTROLLED SUBSTANCE STAFF <ul style="list-style-type: none">Abuse Liability/Potential Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>New Molecular Entity (NDAs only)</u></p> <ul style="list-style-type: none"> Is the product an NME? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO July 28, 2015 CMC Pre-NDA Meeting: FDA permitted sponsor to submit 3 months of Drug Substance and Drug Product stability data 30 days after receipt of the original application. <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Julie Beitz, ODE III Director

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):
June 29, 2016

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

PeRC Meeting: September 28, 2016
Late Cycle Meeting: October 25, 2016

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review

ACTION ITEMS

<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)

<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MAUREEN D DEWEY
11/21/2016

JAMES B CARR
11/21/2016

KEVIN B BUGIN
11/21/2016

- May 5, 2016, Applicant's proposed labeling

Consult Question: Assist with Pregnancy and Lactation Labeling

INTRODUCTION

The applicant, Synergy Pharmaceuticals Inc, submitted a 505(b)(1) New Drug Application (NDA) for Trulance (plecanatide) Oral Tablets, NDA 208-745, on January 29, 2016. The proposed indication is for the treatment of Chronic Idiopathic Constipation (CIC) in adult patients. The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Division of Pediatric and Maternal Health (DPMH) on March 6, 2016, to assist with reviewing the Pregnancy and Lactation subsections of labeling.

This 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.

REGULATORY HISTORY

The applicant, Synergy Pharmaceuticals Inc., submitted the 505(b)(1) NDA 208-745 for Trulance (plecanatide) Oral Tablets, on January 29, 2016 for the treatment of chronic idiopathic constipation (CIC). Prescription options for the treatment of CIC include:

- Lubiprostone (Amitiza), NDA 021-908, approved on January 31, 2006
- Linaclotide (Linzess), NDA 202-811, approved on August 30, 2012

BACKGROUND

Drug

Characteristics

Plecanatide is a hexadecapeptide synthetic analogue of the human endogenous peptide uroguanylin and has a molecular weight of 1682^{(b)(4)} Daltons.¹ Plecanatide is a guanylate cyclase-C (G-CC) receptor agonist, as is linaclotide. Guanylate cyclase-C receptors, found in the GI tract, are known to be involved in the regulation of fluid and electrolyte transport and in the maintenance of GI acidity.^{2,3,4} Endogenous mammalian peptides, such as guanylin, uroguanylin, and lymphoguanylin, have been demonstrated to bind to and activate G-CC. Binding of an agonist to the G-CC stimulates cyclic guanosine monophosphate (cGMP) synthesis and activates cystic fibrosis transmembrane conductance regulator (CFTR), a major chloride channel in the GI tract¹ which result is chloride and sodium/potassium ion efflux and secretion of fluid into the intestinal lumen.

Plecanatide or its metabolite SP-338 following clinically relevant oral doses are not measurable

¹ Applicant's submission, January 29, 2016

² Forte LR Jr. Uroguanylin and guanylin peptides: pharmacology and experimental therapeutics. *Pharmacol Ther.* 2004;104:137-62

³ Sindic A and Schlatter E. Cellular Effects of Guanylin and Uroguanylin. *J Am Soc Nephrol.* 2006; 17: 607-16

⁴ Shailubhai K. Therapeutic applications of guanylate cyclase-C receptor agonists. *Curr Opin Drug Discov Devel.* 2002;5:261-68.

in plasma. Plecanatide is minimally distributed in tissues. Oral plecanatide is localized to the gastrointestinal tract. Both plecanatide and the metabolite are proteolytically degraded within the intestinal lumen to smaller peptides and naturally occurring amino acids.¹

Disease Background¹

Chronic idiopathic constipation (CIC), also known as functional constipation, is a common disorder, affecting between 12% and 19% of North Americans. Chronic idiopathic constipation has a higher prevalence in women than in men, and the prevalence increases with age. Similar prevalences are observed in most areas worldwide.^{5,6} Prevalence rates vary depending on demographic factors and the definitions of the condition used. Actual prevalence may be greater than these estimates as not all patients seek medical attention for the condition.^{7,8} Constipation is a symptom of many diseases and is defined as infrequent stools, incomplete bowel movements (BMs), straining, bloating, and hard, lumpy stool.^{9,10}

Treatments for CIC

First-line treatments for constipation currently include increased dietary fiber consumption and supplementation with bulking agents, increased exercise, increased water consumption, and bowel habit training. Often, only partial relief of symptoms is obtained with these treatments. Prescription options for the treatment of CIC include:

- **Lubiprostone (Amitiza):** It activates a type-2 chloride channel in the gastrointestinal (GI) tract to increase secretion of fluid in the intestine, making it easier for a patient to have a BM.¹¹
- **Linaclotide (Linzess):** A once daily (QD) guanylate cyclase-C (G-CC) agonist that acts locally in the gut to reduce colonic pain and promote BMs. Linaclotide is approved and marketed in the U.S. and Canada for the treatment of CIC as well as irritable bowel syndrome with constipation (IBS-C) in adults, and it is approved and marketed as Constella in some European countries for the treatment of IBS-C.

In Europe, an additional drug has been approved by the European Medicines Agency (EMA), Prucalopride (Resolor or Resotran), which is a 5-hydroxytryptamine₄ receptor agonist that works as a prokinetic to target the impaired motility associated with CIC.

⁵ Higgins, PD & Johanson, JF. Epidemiology of constipation in North America: a systematic review. *Am J Gastroenterol.* 2004;99:750-759.

⁶ Lembo A, Camilleri M. Chronic constipation. *N Engl J Med.* 2003;349:1360-1368.

⁷ Pare P, Ferrazzi S, Thompson WG, Irvine EJ, Rance L. An epidemiological survey of constipation in Canada: definitions, rates, demographics, and predictors of health care seeking. *Am J Gastroenterol.* 2001;96:3130-3137

⁸ Stewart WF, Liberman, JN, Sandler RS, et al. Epidemiology of constipation (EPOC) study in the United States: relation of clinical subtypes to sociodemographic features. *Am J Gastroenterol.* 1999;94:3530-3540.

⁹ Cash BD, Chang L, Sabesin SM, Vitat P. Update on the management of adults with chronic idiopathic constipation. *J Fam Practice.* 2007;96:513-519

¹⁰ Lembo A, Camilleri M. Chronic constipation. *N Engl J Med.* 2003;349:1360-1368

¹¹ Lembo A, Johanson JF, Parkman HP, Rao SS, Miner PB Jr, Ueno R. Long-term safety and effectiveness of lubiprostone, a chloride channel (CIC-2) activator, in patients with chronic idiopathic constipation. *Dig Dis Sci.* 2011;56:2639-2645

Pregnancy and Lactation Labeling Rule (PLLR)

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”¹² also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule¹³ format to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW

Pregnancy

Nonclinical experience

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

In animal developmental studies, there were neither teratogenic nor embryo-fetal effects observed with oral administration of plecanatide in mice and rabbits during organogenesis through lactation at doses much higher than the maximum recommended human dosage (8,000 and 2,500 times, respectively, the MRHD) (up to 800 mg/kg/day in mice and 250 mg/kg/day in rabbits). A pre- and postnatal development study was conducted in pregnant mice where plecanatide doses up to 600 mg/kg/day (up to 6,000 times the MRHD) were administered during organogenesis through lactation. No developmental abnormalities or effects on growth, learning and memory, or fertility and reproductive function were observed in the offspring, from delivery through maturation.

A series of studies have been performed in mice and cynomolgus monkeys to evaluate the PK parameters of plecanatide in vivo. Bioavailability in these animals was very low (<0.1% in mice and monkeys). Exposure levels across animal species were also fairly comparable, as evidenced by C_{max} and AUC values calculated for mice, rats, and cynomolgus monkeys in 13-week (rats), 26-week (mouse) or 39-week (monkeys) studies.¹⁴ Plecanatide was well tolerated in adult mice, rats and monkeys at doses up to 1500, 1000 and 1000-times respectively, the MRHD (0.1 mg/kg, based on mg/kg comparison). Plecanatide achieved limited systemic exposure following oral administration of 250 mg/kg/day (~2,500 times the MRHD) in rabbits. Plecanatide and its active metabolite are minimally absorbed in animals at high doses and not measurable in human plasma following administration at the recommended clinical dosages.

The reader is referred to the Pharmacology/Toxicology review by Yuk-Chow Ng, Ph.D. for further details on animal studies with plecanatide.

¹² Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

¹³ Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, published in the Federal Register (71 FR 3922; January 24, 2006).

¹⁴ Applicants submission, 2.6.4 Pharmacokinetics Summary

Review of Literature

No literature with plecanatide use in pregnancy exists outside of the clinical trials performed. DPMH searched PubMed, Embase, ReproTox and TERIS databases for information regarding plecanatide and use during pregnancy. No published information was identified. As per the applicant, no studies of plecanatide have been conducted in pregnant women.

Review of Clinical Trials

Because the drug has not yet been approved, no pharmacovigilance database has been established. Across the plecanatide clinical program, 6 pregnancies (in the primary safety pool- includes subjects from the two controlled phase 3 trials who received placebo vs plecanatide 3mg or 6 mg) following maternal plecanatide or placebo exposure have been reported across all plecanatide clinical studies. Of those, 3 pregnancies were reported in the 3 mg plecanatide group, 1 in the 6 mg plecanatide group and 2 in the placebo group. One of the placebo patients with pregnancy experienced a spontaneous abortion. In the secondary safety pool which includes subjects from the long-term, open label extension, phase 3 trial and two phase 2 trials), 13 pregnancies were reported, 2 in the placebo group, 4 in the 3 mg plecanatide group, and 7 in the 6 mg plecanatide group. One patient each in the placebo, 3 mg plecanatide group, and 6 mg plecanatide group experienced a spontaneous abortion. An additional patient in the 6 mg plecanatide group discontinued the study because of the pregnancy. The rest of the subjects had a delivery of a normal infant. During the dose selection phase 2a and 2b trials, doses of 0.3mg, and 1mg in addition to 3mg and 6 mg were explored. Table 1 shows pregnancy outcomes observed during the development program of plecanatide. One subject in the 3mg and 3 subjects in the 6 mg dose were lost to follow up, so the is known outcome of their pregnancy. These limited clinical data are insufficient to draw meaningful safety conclusions about the effects of plecanatide during pregnancy and lactation.

Table 1: Pregnancy Outcomes from Clinical Trials

	Screening/Placebo	Plecanatide 1 mg	Plecanatide 3 mg	Plecanatide 6 mg
Normal Pregnancy* outcome	4	1	3	4
Pregnancy with unknown outcome (lost to follow up)	0	0	1	3
Spontaneous Abortion	2	0	1	1
Total	6	1	5	8

*Subject carried pregnancy to term and delivered a healthy baby

From applicant's response to IR regarding pregnancy outcomes, June 29, 2016

Summary

There is no evidence that administration of plecanatide to mice and rabbits during organogenesis causes adverse developmental effects. Plecanatide and its active metabolite are not measurable in animal and human plasma following administration of the recommended clinical dosages.

Overall, the limited cases reported of plecanatide use in pregnant women have sparse information and are insufficient to inform a drug associated risk. As such, these cases should not be included under the Section 8.1 Pregnancy, Human Data heading of the proposed labeling.

DPMH recommends the following language be included in Section 8.1 Pregnancy, Risk Summary of the Trulance labeling to summarize the data:

Plecanatide is negligibly absorbed systemically following oral administration [*see Clinical Pharmacology (12.3)*], and is not expected to result in fetal exposure to the drug. The available data on Trulance use in pregnant women are not sufficient to inform any drug-associated risk for major birth defects and miscarriage. 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 maximum recommended human dosage.

Lactation

Nonclinical Experience

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

The toxicokinetics of plecanatide was evaluated in pregnant female Dutch Belted rabbit plasma following daily oral gavage administration for 13 days from GD 7 to GD 19. Plecanatide achieved limited systemic exposure following oral administration of 250 mg/kg/day in rabbits. Plasma concentrations of plecanatide were all below the lower limit of quantitation (10.0 ng/mL) in control group samples. In treated animals, no plecanatide was quantifiable in samples collected at 4 or 8 hours post dose or in samples collected prior to dose on GD 19, at all dose levels. Plecanatide is negligibly absorbed systemically following oral administration in humans. Therefore, animal and human doses should not be compared directly for evaluating relative

systemic exposure. Drug presence in breast milk is species-specific; therefore, no direct relationship can be made about drug levels in human milk.

A juvenile animal toxicity study was conducted in mice and demonstrated lethality associated with decreasing age and decreasing plecanatide dose. Similar findings were seen in the other drug in the class (linaclotide). DGIEP Nonclinical considers that the mechanism of lethality is related to higher G-CC expression in newborn mice. Binding of an agonist to the G-CC stimulates cyclic guanosine monophosphate (cGMP) synthesis and activates CFTR which result is chloride and sodium/potassium ion efflux and secretion of fluid into the intestinal lumen. This led to dehydration and death in the youngest mice. See Table 2 below for Non-clinical comparison of lethal dose between plecanatide and linaclotide.

Table 2: Lethality Comparisons in Juvenile Mice between Plecanatide and Linaclotide.*

	Plecanatide		Linaclotide	
	Minimum Lethal Dose (mg/kg)	Multiples of Clinical Dose (6 mg/day) ^a	Minimum Lethal Dose (mg/kg)	Multiples of Clinical Dose (0.29 mg/day) ^b
PND 7	0.5	5X	0.01	2.1X
PND 14	10	100X	0.1	20.8X
PND 21	no deaths at up to 300	3000X	0.6	125X
PND 28	no deaths at up to 300	3000X	no deaths at up to 1	208X

a: 0.1 mg/kg;

b: 4.8 µg/kg

*Presented at the Mid-cycle meeting by DGIEP Nonclinical Reviewer, Yuk-Chow Ng, Ph.D.

Review of Literature

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. Plecanatide and its active metabolite are not measurable in plasma following administration of the recommended clinical dose.

DPMH conducted a search of Medications and Mother’s Milk¹⁵, the Drugs and Lactation Database (LactMed)¹⁶, Micromedex¹⁷, and of published literature in PubMed using the search terms “plecanatide and lactation,” “plecanatide and breastfeeding”. No reports of clinical lactation studies or case reports of plecanatide use in lactating women were found in published

¹⁵ Hale, Thomas (2012) Medications and Mothers’ Milk. Amarillo, Texas Hale Publishing

¹⁶ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

¹⁷ Truven Health Analytics information, <http://www.micromedexsolutions.com/>.

literature.

Reviewer comment

Trulance acts locally on the luminal surface of the intestinal epithelium. Clinical pharmacology studies demonstrated minimal absorption with low systemic availability following oral administration. Because of the low bioavailability of plecanatide and its active metabolite in both humans and animals, doses cannot be compared from animals for evaluating relative human exposure using systemic exposure comparisons of C_{max} or AUC. 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.

The applicant should conduct a post-marketing milk-only lactation study in patients, using a validated assay, in order to appropriately inform the lactation section of labeling. The reasoning lies in the anticipated use of the drug product in females of reproductive potential, the lack of data on safe use in lactating women, the mechanism of action, and the juvenile animal toxicity study which demonstrated mortality in juvenile mice associated with decreasing age and decreasing dose. As mentioned above, another drug in the class, linaclotide, has similar mortality findings in a juvenile animal toxicity study. A post-marketing milk-only lactation study was initiated and is ongoing for linaclotide, but the final data are not available yet. Although the likelihood of these drug products appearing in the breast milk is low, the hypothetical risk of exposure to a breastfed infant is serious and warrants additional investigation. Plecanatide is proposed for use only in adults because it was determined, through clinical trials, that it is safe and effective in this population. Warning has been placed in labeling to contraindicate the use of plecanatide in children less than 6 years old based on the finding of mortality in juvenile animals. Therefore, it is important to determine how much drug is present in breast milk and whether it accumulated in breast milk and could potentially impact a breastfed infant. DPMH has discussed with the Division a post-marketing milk-only lactation study for plecanatide.

Summary

Based on recent DPMH recommendations for linaclotide (Linzess) and given the lack of lactation information for plecanatide, DPMH recommends that the following statement appear in the “Risk Summary” section of Trulance labeling:

The effects of local gastrointestinal and limited systemic exposure to plecanatide on the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Trulance and any potential adverse effects on the breastfed infant from Trulance or from the underlying maternal condition.

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. The following PMR language is suggested:

PMR: Perform a milk-only lactation trial in lactating women who have received multiple, once daily, doses of plecanatide therapeutically to assess concentrations of plecanatide and its active metabolite in breast milk using a validated assay in order to appropriately inform the Lactation subsection of the labeling.

The following PMR schedule milestones are recommended:

Final Protocol Submission:	12/31/2017
Study/Trial Completion:	06/30/2018
Final Report Submission:	12/31/2018

This PMR is necessary to further refine the safety and optimal use of the drug in order to appropriately inform the Lactation subsection of the labeling.

Females and Males of Reproductive Potential

Nonclinical Experience

Plecanatide was evaluated for effects on reproduction and development in both mice and rabbits. In mice, doses up to 600 mg/kg/day (up to 6,000 times the MRHD), did not cause any adverse effects on reproductive parameters in a fertility study. Similar findings were observed in rabbits, at doses up to 250 mg/kg/day (~2,500 times the MRHD).

Review of Literature

DPMH performed a search of published literature in PubMed and Embase on plecanatide and infertility and did not identify any publications.

Summary

Because there are no human data available on the effect of plecanatide on fertility and no evidence of infertility in animal studies to inform a potential clinical risk, Section 8.3, Females and Males of Reproductive Potential, will not be included in Trulance labeling.

CONCLUSION

The Pregnancy and Lactation, sections of Trulance labeling were structured to be consistent with the PLLR as follows:

- **Pregnancy, Section 8.1**
 - The “Pregnancy” section of Trulance labeling was formatted in the PLLR format to include: “Risk Summary”, and “Data” sections.
- **Lactation, Section 8.2**
 - The “Lactation” section of Trulance labeling was formatted in the PLLR format to include the “Risk Summary” section.
- **Females and Males of Reproductive Potential, Section 8.3**
 - Females and Males of Reproductive Potential, Section 8.3 is omitted because there is nothing to be reported.
- **Patient Counseling Information, Section 17**
 - The “Patient Counseling Information” section of labeling was updated to correspond with sections 8.1 and, 8.2 of labeling. Nothing is being reported

RECOMMENDATIONS

DPMH revised sections 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see below). The below recommendation include discussion with the Nonclinical and discussion from the August 17, 2016 labeling meeting. DPMH refers to the final NDA action for final labeling.

DPMH PROPOSED PREGNANCY AND LACTATION LABELING EDITS FOR TRULANCE

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Plecanatide is negligibly absorbed systemically following oral administration [*see Clinical Pharmacology (12.3)*], and is not expected to result in fetal exposure to the drug.

The available data on TRULANCE use in pregnant women are not sufficient to inform any drug-associated risk for major birth defects and miscarriage. 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 maximum recommended human dose.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Pregnant mice and rabbits were administered plecanatide during the period of organogenesis.

There was no evidence of harm to embryo-fetal development at oral doses up to 800 mg/kg/day in mice and 250 mg/kg/day in rabbits. Oral administration of up to 600 mg/kg/day in mice during organogenesis through lactation produced no developmental abnormalities or effects on growth, learning and memory, or fertility in the offspring through maturation.

The maximum recommended human dose is approximately 0.05 mg/kg/day, based on a 60-kg body weight. Limited systemic exposure to plecanatide was achieved in animals ([AUC]_t = 449 ng•h/mL in rabbits given 250 mg/kg/day during organogenesis). Plecanatide and its active metabolite are not measurable in human plasma following administration of the recommended clinical dosages. Therefore, animal and human doses should not be compared directly for evaluating relative exposure.

8.2 Lactation

Risk Summary

There is no information regarding the presence of plecanatide in human milk, or on its effects on milk production or the breast-fed infant. No lactation studies in animals have been conducted. However, plecanatide is negligibly absorbed systemically following oral administration [*see Clinical Pharmacology (12.3)*].

The effects of local gastrointestinal and limited systemic exposure to plecanatide on the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRULANCE and any potential adverse effects on the breastfed infant from TRULANCE or from the underlying maternal condition.

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/s/

CHRISTOS MASTROYANNIS
11/10/2016

TAMARA N JOHNSON
11/10/2016

LYNNE P YAO
11/10/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200

MEMORANDUM: PEDIATRIC LABELING REVIEW

Date: October 20, 2016

From: Carolyn L. Yancey, MD, Medical Officer
Division of Pediatric and Maternal Health (DPMH)

Through: Mona Khurana, MD, Acting Pediatric Team Leader,
DPMH

John J. Alexander, MD, MPH, Deputy Director,
DPMH

To: Division of Gastroenterology and Inborn Errors Products
(DGIEP)

NDA: 208745

Drug: Plecanatide Tablets for Oral Use, 3 mg

Applicant: Synergy Pharmaceuticals, Inc.

Proposed Indication: Treatment of chronic idiopathic constipation (CIC) in
adults

Consult request: To assist the Division in the review of the labeling for this
505(b)(1) New Drug Application (NDA)

Materials Reviewed:
Trulance (plecanatide)

- January 29, 2016: Receipt of submission of original NDA 208745 for plecanatide as an immediate-release tablet that is intended for chronic oral administration for the treatment of CIC in adults

- January 29, 2016: Draft Labeling submitted in NDA 208745 Trulance (plecanatide)
- DPMH consult request from DGIEP dated March 1, 2016
- February 6, 2015: Applicant's Agreed upon initial Pediatric Study Plan based on a revised initial pediatric study plan (iPSP) for chronic idiopathic constipation under IND 74,883
- March 16, 2015: Agency's Advice letter to Synergy to submit a pediatric waiver request in CIC in the birth to 6 months age group

Linzess (linaclotide)

- February 14, 2014: DPMH consult review for Linzess (linaclotide) NDA 202811 written by Erica Wynn, M.D., DPMH
- August 31, 2016: NDA 202811 Linzess (linaclotide) Prescribing Information most recently revised labeling as of this review

I. Introduction

On January 29, 2016, Synergy Pharmaceuticals, Inc. (Synergy) submitted the original NDA 208745 for Trulance (plecanatide) Tablet for oral use (3 mg (b)(4) tablets). The plecanatide development program is conducted under investigational new drug (IND) applications 74,883 (b)(4). The proposed plecanatide indication is for the treatment of CIC in adults. The applicant's proposed dosage and administration is 3 mg (b)(4) taken orally once daily, with or without food. The sponsor proposes that the tablets be swallowed whole.

II. Background

A. Chronic Idiopathic Constipation

Chronic idiopathic constipation also known as functional constipation is a common disorder affecting between 12% and 19% of North Americans. The prevalence of CIC is higher in women than in men, and the prevalence increases with age.¹ Constipation is a symptom of many diseases and is a collective term used to imply infrequent stool, incomplete bowel movements (BMs), straining, bloating, and hard, lumpy stool.²

According to the applicant, first-line treatments for constipation currently include increased dietary fiber consumption and supplementation with bulking agents, increased exercise, increased water consumption, and bowel habit training. Often, only partial relief of symptoms is obtained with these treatments. As a result, many patients also use non-bulking laxatives on a regular basis such as osmotic laxatives, stool softeners, and

¹ Higgins PD and Johanson JF. Epidemiology of constipation in North America: a systematic review, Am J Gastroenterol. 2004;99:750-759.

² Cash BD, Chang L, Sabesin SM, Vitat P. Update on the management of adults with chronic idiopathic constipation. J Fam Practice. 2007;96:513-519.

stimulant laxatives. Chronic use of laxatives may lead to side effects such as dependency, progressive tolerance, electrolyte imbalance, and for the anthraquinones, melanosis coli. In addition, overuse of stimulant laxatives may damage the myenteric plexus, resulting in cathartic colon.³

B. Armamentarium of Therapy for Chronic Idiopathic Constipation

According to the applicant, at this time, prescription options for treatment of CIC are limited. Lubiprostone (Amitiza®) activates a type-2 chloride channel in the gastrointestinal (GI) tract to increase secretion of fluid in the intestine, making it easier for a patient to have a BM.⁴ Prucalopride, a 5-hydroxytryptamine 4 receptor agonist that works as a prokinetic to target the impaired motility associated with CIC, is approved for the treatment of chronic constipation in Europe (Resolor®), Canada (Resotran®), and Israel, and is in development in the United States (US) [Resolor 2014; Resotran 2014]. Linaclotide (Linzess) is a once daily (QD) guanylate cyclase-C (GC-C) agonist that acts locally in the gut to reduce colonic pain and promote BMs. Linaclotide is approved and marketed as Linzess® (NDA 202-811) in the U.S. and Canada for the treatment of CIC as well as irritable bowel syndrome with constipation (IBS-C) in adults, and it is approved and marketed as Constella® in some European countries for the treatment of IBS-C. Given the limited number of approved treatments for patients with CIC, additional treatment options are needed for patients who do not respond to first-line treatments.

C. Product Background

Plecanatide (SP-304), a new molecular entity, is a hexadecapeptide synthetic analogue of the human endogenous peptide uroguanylin, discovered and synthesized by Synergy Pharmaceuticals, Inc. Plecanatide is an agonist of the GC-C receptor, similar to linaclotide. The GC-C receptors, found in the GI tract, are known to be involved in the regulation of fluid and electrolyte transport and in the maintenance of GI acidity.⁵ Endogenous mammalian peptides, such as guanylin, uroguanylin, and lymphoguanylin, have been demonstrated to bind to and activate GC-C. Binding of an agonist to the GC-C stimulates cyclic guanosine monophosphate (cGMP) synthesis and activates cystic fibrosis transmembrane conductance regulator (CFTR), a major chloride channel in the GI tract. The result is chloride and sodium/potassium ion efflux and secretion of fluid into the intestinal lumen. According to the applicant, oral administration of plecanatide is expected to increase bowel movements and improve stool consistency for both CIC and irritable bowel syndrome (IBS) indications. The applicant explains that plecanatide is

³ NDA 208-745 Trulance (plecanatide), GS, Module 2.5 Clinical Overview, Subsection 1 Product Development Rationale, page 6 of 47.

⁴ Lembo A, Johanson JF, Parkman HP, Rao SS, Miner PB Jr, Ueno R. Long-term safety and effectiveness of lubiprostone, a chloride channel (CIC-2) activator, in patients with CIC. *Dig Dis Sci.* 2011;56:2639-2645.

⁵ Forte LR Jr. Uroguanylin and guanylin peptides: pharmacology and experimental therapeutics. *Pharmacol Ther.* 2004;104:137-162.

being developed as an alternative treatment option for adults with CIC.

III. Regulatory History of NDA 208745 Trulance (plecanatide)

Under the Pediatric Research Equity Act (PREA), any application submitted for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration must submit a pediatric assessment. Trulance (plecanatide) triggers PREA as a new active ingredient, new indication, new dosage form, new dosing regimen, and new route of administration. The application has a Prescription Drug User Fee Act (PDUFA) goal date of January 29, 2017.

The applicant submitted the following Agreed upon iPSP (dated February 6, 2015) in the NDA 208745 submission received on January 29, 2016 (see **Tables 1 - 4**). The applicant's proposed age ranges for deferral were revised by the DGIEP with feedback from the DPMH during the pre-approval review cycle for this NDA (see *italicized* language in **Tables 1 - 4**).



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IV. Clinical Program in NDA 208745 Submission

As cited in the Introduction and Background sections, in this review, the studies described in this NDA submission and this labeling review were only conducted in adults. There are no pediatric studies conducted at this time therefore, a pediatric assessment has not been submitted to the DGIEP. See Section III, Regulatory History, in this review for the Agreed upon iPSP, revisions to the applicant per DGIEP, and feedback from PeRC on the proposed request for a waiver and deferral of pediatric studies.

The applicant conducted the following studies in adults to support NDA 208745:

- Two adequate, well-controlled, Phase 3, efficacy and safety studies in CIC patients (SP304203-00 and SP304203-03);
- Two placebo-controlled (PBO-C), Phase 2 studies in CIC patients (SP304-20210 and SP304201-09)
- One supportive PBO-C Phase 2 study in IBS-C patients (SP304-20212);
- Two Phase 1 studies in healthy volunteers (SP304101-08 and SP304101-09); and
- One ongoing open-label (OL), long-term (LT), Phase 3 safety study in CIC patients (SP304203-01)

The proposed to-be-marketed formulation and dosage is only the 3 mg oral tablet. (b) (4)

(b) (4)

In the adult clinical program for plecanatide, one death occurred in a 47-year old male (Patient # 630-105) who had been receiving 6 mg once daily plecanatide treatment in the long-term safety Study SP304203-01. Per the NDA 208745 Clinical Reviewer, after two years of reported abstinence from substance abuse, the patient used crack cocaine, intravenous heroin, and alcohol soon after initiation of the study. Five months after starting plecanatide, the patient was hospitalized with acute renal insufficiency (creatinine 2 mg/dL) and myocardial infarction (MI). The MI was attributed to recent cocaine abuse in the setting of underlying coronary disease, and the event resolved at the time of discharge. The event of acute renal failure was considered resolved by the same day with sequelae (creatinine 1.1 mg/dL). Less than a month after discharge, the patient experienced a second MI at home, which was fatal. The investigator reported that the autopsy report was not available. Both MIs and the event of acute renal failure were not considered to be causally attributed to plecanatide.

Table 5 describes the common adverse events occurring in more than 1 % of adult

patients in the primary safety data from the adult CIC studies.

Table 5 - Common Adverse Events (>1% of adult patients) in Primary Safety

Adverse Event (Preferred Term)	Plecanatide 3 mg treatment group N=863 n (%)	Placebo N=870 n (%)
Diarrhea	43 (5.0%)	11 (1.8%)
Headache	16 (1.9%)	18 (2.1%)
Urinary tract infection	14 (1.6%)	16 (1.8%)
Sinusitis	12 (1.4%)	3 (0.3%)
Upper respiratory tract infection	12 (1.4%)	10 (1.1%)
Abdominal distension	10 (1.2%)	3 (0.3%)
Flatulence	9 (1.0%)	5 (0.6%)
Nasopharyngitis	9 (1.0%)	14 (1.6%)

Source: Late Cycle Meeting presentation on Clinical Review of Efficacy and Safety by Lesley Hanes, M.D., DGIEP. Note that DGIEP does not plan to include abdominal distension as an AE in labeling to be consistent with labeling for Linzess (linaclotide) that is silent on reporting abdominal distension for data on CIC.

DPMH Pediatric Reviewer Comments: There were no new significant safety issues reported in any of the adult studies. This reviewer agrees with the DGIEP on not including abdominal distension in this table to be consistent with labeling for linaclotide, common adverse events.

V. DPMH Review of Pediatric Use Information in Labeling

PEDIATRIC USE LABELING

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population.

When a pediatric indication is not supported by available data, the Pediatric Use subsection must contain a statement explaining that safety and effectiveness have not been established in the relevant pediatric population(s) (21 CFR 201.57(c)(9)(iv)(F)). If a specific risk has been identified for pediatric patients, this risk information must be described in the Pediatric Use subsection and, if appropriate, placed in the Contraindications section or Warnings and Precautions section. In such cases, the Pediatric Use subsection must refer to the risk information in the Contraindications or Warnings and Precautions section, as required by regulation (21 CFR 201.57(c)(9)(iv)(B), (E), and (F)).

See draft Guidance for Industry and Review Staff Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling (February, 2013).⁶

Our recommendations reflect labeling provided to the DGIEP on October 5, 2016. See the approval letter for the final version of labeling.

DPMH Discussion of Pediatric Use Information in Labeling

DPMH reviewed the applicant's draft labeling and participated in the internal meetings between September 7 through 12, 2016. DPMH provided labeling recommendations for the pediatric population per 21 CFR 201.57(c)(9)(iv) and 21 CFR 201.57(c)(9)(iv)(B), (E), and (F).

Because the proposed indication will not include pediatric patients, DPMH recommends that the Pediatric Use subsection 8.4 should 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, DPMH agreed with DGIEP that the non-clinical safety signal should be summarized in subsection 8.4, conveyed in the Box Warning, and added to the Contraindications (Section 4), and Warnings and Precautions subsection 5.1 of the proposed plecanatide labeling. The inclusion of this safety information is consistent with that included in the approved labeling for linaclotide.

DPMH Actions and Labeling Recommendations

DPMH provided comments in labeling meetings held on September 7, 9, and 12, 2016 to support revisions to pediatric labeling for TRULANCE (plecanatide). DPMH also participated in team meetings during the review of the NDA 208745 and assisted DGIEP in preparing paperwork for the PeRC meeting including revisions to the applicant's proposed partial waiver request and request for deferral of pediatric studies in CIC. The substantially complete proposed labeling with revisions (in track changes) including comments was sent to the applicant on September 23, 2016. The Division presented the necessary revisions to the applicant's proposed request for a pediatric waiver and deferral of pediatric studies in CIC to PeRC on September 28, 2016. Refer to the final PeRC meeting minutes for a record of the committee discussion. This memorandum and labeling review reflect DPMH Pediatric Team recommendations provided to DGIEP.

DPMH's review focused on edits to the Box Warning, Contraindications, Warnings and Precautions subsections 5.1, Pediatric Use subsection 8.4, and Animal Toxicology and/or Pharmacology subsection 13.2. The following recommendations were agreed upon between DPMH and DGIEP based on labeling discussions. DPMH's input will be reflected in the final labeling and the approval letter. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested in this DPMH labeling review.

6

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm341394.pdf>

General Recommendations:

- DPMH recommends revising the upper pediatric age to be less than 18 years of age rather than through 17 years of age throughout labeling.
- DPMH recommends summarizing relevant juvenile toxicology data, which would most likely be sought by a pediatric provider, in the Pediatric Use subsection 8.4 in lieu of including this information in subsection 13.2. With inclusion of clinically relevant juvenile toxicology information in subsection 8.4, DPMH recommends deleting subsection 13.2 and any cross-references to subsection 13.2 throughout labeling.

BOXED WARNING

Proposed DPMH language

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

- **TRULANCE is contraindicated in patients less than 6 years of age; in nonclinical studies in young juvenile mice, administration of a single, clinically relevant adult oral dose of plecanatide caused deaths due to dehydration [see *Contraindications (4), Use in Specific Populations (8.4)*].**
- **Avoid use of TRULANCE in patients 6 years to less than 18 years of age [see *Warnings and Precautions (5.1), Use in Specific Populations (8.4)*].**
- **The safety and effectiveness of TRULANCE has not been established in patients less than 18 years of age [see *Use in Specific Populations (8.4)*].**

4 CONTRAINDICATIONS

Proposed DPMH Language

- **Patients less than 6 years of age due to the risk of serious dehydration [see *Warnings and Precautions (5.1), Use in Specific Populations (8.4)*].**
- **Patients with known or suspected mechanical gastrointestinal obstruction.**

5 WARNINGS AND PRECAUTIONS

Proposed DPMH Language

5.1 Risk of Serious Dehydration in Pediatric Patients

TRULANCE is contraindicated in patients less than 6 years of age. The safety and effectiveness of TRULANCE in patients less than 18 years of age have not been established. In young juvenile mice (1- to 2-week-old mice), 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 significant diarrhea and its potentially serious consequences.

Avoid use of TRULANCE in patients 6 years to less than 18 years of age. [see *Contraindications (4), Warnings and Precautions (5.2), Use in Specific populations (8.4)*].

8 USE IN SPECIFIC POPULATIONS

Proposed DPMH Language

8.4 Pediatric Use

TRULANCE is contraindicated in patients less than 6 years of age. Avoid use of TRULANCE in patients 6 years to less than 18 years of age [see *Contraindications (4), Warnings and Precautions (5.1)*]. The safety and effectiveness of TRULANCE in patients less than 18 years of age have not been established.

In nonclinical studies, deaths occurred within 24 hours in young juvenile mice (human age equivalent of approximately 1 month to less than 2 years) following administration of one or two once daily oral doses of plecanatide as described below in Juvenile Animal Toxicity Data. Because of 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 diarrhea and its potentially serious consequences. TRULANCE is contraindicated in patients less than 6 years of age. There were no deaths attributed to plecanatide in older juvenile mice (human age equivalent of approximately 2 years), as described below in Juvenile Animal Toxicity Data. Given the deaths in young juvenile mice and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of TRULANCE in patients 6 years to less than 18 years of age.

Juvenile Animal Toxicity Data

Single doses of plecanatide at 0.5 mg/kg and 10 mg/kg caused mortality in young juvenile mice on postnatal days (PNDs) 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 PND 14 (human age equivalent of approximately less than 2 years), and to a lesser extent PND 21 (human age equivalent 2 years), consistent with increased fluid in the intestinal lumen. No deaths were attributed to plecanatide in older juvenile mice given plecanatide beginning on PND 21 (human age equivalent of approximately 2 years) at oral doses up to 300 mg/kg/day. The maximum 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 human plasma following administration of the recommended clinical doses, whereas systemic absorption was demonstrated in the juvenile animal toxicity studies. Therefore, animal and human doses should not be compared directly for evaluating relative exposure.

Conclusion:

DPMH provided comments in labeling meetings (cited above) to support revisions to pediatric labeling for TRULANCE (plecanatide). DPMH also participated in team meetings during the review of the NDA 208745 and assisted DGIEP in preparing paperwork for the PerC meeting including revisions to the applicant's proposed partial

waiver request and request for deferral of pediatric studies in CIC. The substantially complete proposed labeling with revisions (in track changes) including comments was sent to the applicant on September 23, 2016. The Division presented the necessary revisions to the applicant's proposed request for a pediatric waiver and deferral of pediatric studies in CIC to PeRC on September 28, 2016. Refer to the final PeRC meeting minutes for a record of the committee discussion. This memorandum and labeling review reflect DPMH Pediatric Team recommendations provided to DGIEP.

APPENDIX:

See the next page for the clinical studies for plecanatide in pediatric CIC.

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/s/

CAROLYN L YANCEY
10/20/2016

MONA K KHURANA
10/20/2016

JOHN J ALEXANDER
10/20/2016



Immunogenicity Consult Review-Assay Validation

BB-NDA: 208745
SERIAL: 0000
DATE: 8/30/2016
FROM: Haoheng Yan, MD PhD
Product Quality Reviewer, OPQ/OBP/DBRR IV
Fred Mills, PhD
Staff Scientist, OPQ/OBP/DBRR IV
THROUGH: Michele Dougherty, PhD
Acting Review Chief, OPQ/OBP/DBRR IV
PRODUCT: Plecanatide (SP304), Peptide Tablet, Guanylate cyclase-C receptor agonist.
INDICATION: Chronic idiopathic Constipation
ROUTE OF ADMIN: Oral
DOSE REGIMEN: 30mg/day.
SPONSOR: Synergy Pharmaceuticals

CLINICAL DIVISION: CDER/ODEIII/DGIEP
CONSULT DATE: 3/6/2016
PDUFA Date: 1/20/2017

CONSULT QUESTION:

Plecanatide is an oral peptide product and a GC-C agonist, similar to linaclotide. OBP previously required the Sponsor of linaclotide to conduct immunogenicity assessments with linaclotide because it has multiple attributes that were believed to make it potentially immunogenic. Because linaclotide has structural homology to endogenous guanylin peptides, the OBP reviewers were concerned that the development of anti-drug antibodies could lead to deficiency syndromes related to cross reaction with endogenous guanylin peptides. As such, the Sponsor of linaclotide was issued PMRs to develop anti-drug antibody assays and to test patient samples for the presence of these antibodies. Given the similarities between linaclotide and plecanatide, OBP previously recommended the Sponsor of plecanatide monitor the immunogenicity potential of plecanatide in Phase 2/3 clinical trials. We request an OBP reviewer to assess the adequacy of the immunogenicity assessments in NDA 208745 and determine if there is a need for any postmarketing studies.

Summary

Plecanatide is an oral GC-C agonist proposed to treat chronic idiopathic constipation. There is no systemic absorption for plecanatide. Since the product is a 16 amino acid peptide, there is the possibility that patients will develop antibodies against the drug. Due to the structure similarity between plecanatide and two endogenous proteins: guanylin and uroguanylin, there is also a theoretical immunogenicity concern for depletion syndrome if patients develop anti-plecanatide antibody which cross react with guanylin and uroguanylin.

Linaclotide, a similar GC-C agonist, was approved in 2012 with no immunogenicity assay or clinical data (PMRs were issued for the assay and the clinical data). With this precedent, plecanatide NDA was filed with only ADA screening assay with no clinical immunogenicity data. It was agreed the clinical data will be submitted during the review cycle.

Several assay deficiencies were communicated with the sponsor during the review cycle. The sponsor reported high plate failure rate (44%) during initial clinical sample testing. Per FDA request, testing of the clinical samples were paused until the assay was found to be adequate by the FDA. The main issue is that the sponsor continues to rely on a fixed cut point to identify ADA positive samples, despite a statistical analysis that clearly shows the mean and variance were different between validation runs. Thus samples with similar antibody content and titer may give varying results depending on the assay run, making it difficult to assess patient antibody status. Overall, the ADA assay needs more development work before it can be appropriately validated for detection of ADA response.

Six PMRs will be issued:

- 3117-1. Develop and validate a sensitive and precise assay for the detection of antiplecanatide antibodies (ADA), including IgM, IgG, and IgA, that may be present in the serum at the time of patient sampling. Submit screening and confirmation assay validation reports and assay SOPs to the FDA.
- 3117-2. Assess development of anti-drug antibody (ADA) responses in patient samples using the immunogenicity serum samples collected in the plecanatide studies (SP304203-00 and SP304203-03 and SP304203-01). Validated assays capable of sensitively and accurately detecting ADA responses, developed under PMR 3117-1, will be used. Evaluate the anti-drug antibody (ADA) rates, individual patient titers and the relationships between ADA status and the drug safety and efficacy. Provide the study report to the FDA.
- 3117-3. Develop and validate assays to evaluate the cross reactivity of anti-plecanatide antibodies to guanylin and uroguanylin. Submit assay validation report and assay SOP to the FDA.
- 3117-4. Use the validated cross reactivity assays developed under PMR 3117-3 to test the ADA positive samples detected under PMR 3117-2. Evaluate the relationships between cross reactivity status and the drug safety and efficacy. Provide the study report to the FDA.
- 3117-5. Develop and validate an assay to evaluate the neutralizing capacity of ADA detected in the patient samples. Submit assay validation report and assay SOP to the FDA.
- 3117-6. Use the validated neutralizing antibody assay developed under PMR 3117-5 to test the anti-plecanatide antibody positive samples detected under PMR 3117-2. Evaluate the relationships between neutralizing antibody status and the drug safety and efficacy. Provide the study report to the FDA.

Reviewer's Comments:

The sponsor was informed of the above immunogenicity PMRs in the 9/23/2016 letter of labelling PMR/PMC comments, and that PMR 3 through 6 are conditional based upon PMR3117-2 (clinical results of ADA analysis).

Precedent

Linaclotide, also a GC-C agonist, was approved in Aug 2012. No immunogenicity assay or clinical immunogenicity data was provided in the original NDA. Two immunogenicity related PMRs were issued for Linaclotide at the time of approval:

PMR 1915-4: Develop and validate sensitive and precise assays for the detection of anti-linaclotide antibodies, including IgM, IgG, and IgA, that may be present in the serum at the time of patient sampling. A summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay SOP will be provided to FDA.

Interim Report Submission (**Screening and Confirmatory Assays**): November 2014

Final Report Submission (**Cross-Reactivity, Neutralization, and IgA Isotyping Assays**): February 2015

PMR 1915-6: A clinical trial in adults receiving Lincess (linaclotide) to assess development of anti-drug antibody (ADA) responses in patient samples. Validated assays capable of sensitively detecting ADA responses that may be present at the time of patient sampling, developed under PMR 1915-4 above, will be used. Sampling will occur at 0 and 2 weeks, and at 1, 3, 6 and 12 months. Immunogenicity rates and individual patient titers will be evaluated. Adverse events will be collected. The trial will be conducted according to the following schedule:

Final Protocol Submission: November 2013

Trial Completion: March 2018

Final Report Submission: December 2018

Regulatory Background

In the pre-NDA meeting (8/5/2015) and subsequent email correspondence on 8/21/2015, 9/1/2015 and 9/14/2015, the sponsor stated that they would submit an anti-plecanatide antibody screening assay in the NDA, but they had not developed a confirmation assay. The FDA commented that “FDA expressed concerns that there is no confirmation assay to eliminate false positive samples from the screening assay, which may confound the ability to establish relationships between anti-drug antibodies and safety and efficacy” (see pre-NDA meeting minutes). The sponsor agreed to provide anti-plecanatide antibody screening data obtained from patient serum samples in the Phase 3 studies SP304203-00, SP304203-03 and the open label long term safety study, SP304203-1 in part in the initial NDA submission with the remaining data be provided in the 120-day safety update report to the NDA.

After the pre-NDA meeting, the sponsor submitted the anti-drug antibody screening assay validation report on 1/18/2016. In the same submission, the sponsor stated that the screening immunogenicity data will not be available for the initial NDA submission due to technical issues at a contract lab, (b)(4). The sponsor planned to submit the data by the 120 NDA safety date.

The NDA package was submitted on 1/29/2016 with no immunogenicity data. Considering the precedent of linaclotide, which was approved without immunogenicity assays or data, and there was no apparent immunogenicity related safety issue during the trials, the lack of immunogenicity assays or clinical immunogenicity data for the plecanatide NDA was not considered a refuse-to-file issue.

During the 1st review team meeting on 4/4/2016, the clinical pharmacology reviewer stated that plecanatide has no detectable systemic absorption and the clinical reviewer stated that there was no sign of depletion syndrome in the data reviewed up to that point. Therefore, plecanatide was considered relatively low risk from the immunogenicity perspective and it was acceptable for the sponsor to submit the immunogenicity data by the 120 day safety update.

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/s/

HAOHENG N YAN
10/11/2016

FREDERICK C MILLS
10/11/2016

MICHELE K DOUGHERTY
10/11/2016

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: September 21, 2016

To: Heather Buck, MS, MBA, Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer,
Office of Prescription Drug Promotion (OPDP)

Subject: NDA # 208745 – TRULANCE (plecanatide) tablets, for oral use

Reference is made to DGIEP's consult request dated March 6, 2016, requesting review of the proposed Package Insert (PI), Medication Guide (MG), and Carton/Container labeling for TRULANCE (plecanatide) tablets, for oral use.

OPDP has reviewed the proposed PI entitled, "Plecanatide Draft Label_9-14-16.docx" that was sent via e-mail from DGIEP to OPDP on September 14, 2016. OPDP's comments on the proposed PI are provided directly on the attached copy of the labeling (see below).

Please note that comments on the proposed MG were provided on September 19, 2016, under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).

OPDP has also reviewed the proposed Carton/Container labeling entitled, "Revised Sept 7 plecanatide packaging.pdf" that was accessed via SharePoint on September 20, 2016, at 7:02pm. OPDP has no comments at this time on the proposed Carton/Container labeling.

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or adewale.adeleye@fda.hhs.gov

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/s/

ADEWALE A ADELEYE
09/21/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: September 19, 2016

To: Donna Griebel, MD
Director
**Division of Gastroenterology and Inborn Errors
Products (DGIEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Adewale Adeleye, Pharm.D., MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): TRULANCE (plecanatide)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 208745

Applicant: Synergy Pharmaceuticals Inc.

1 INTRODUCTION

On January 29, 2016, Synergy Pharmaceuticals Inc. submitted for the Agency's review an Original New Drug Application (NDA) 208745 for TRULANCE (plecanatide) tablets. TRULANCE is a New Molecular Entity (NME) with a proposed indication as a uroguanylin analog and guanylate cyclase-C (GC-C) agonist indicated in adults for the treatment of chronic idiopathic constipation (CIC).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Gastroenterology and Inborn Errors Products (DGIEP) on March 6, 2016 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TRULANCE (plecanatide) tablets.

2 MATERIAL REVIEWED

- Draft TRULANCE (plecanatide) tablets MG received on May 8, 2016 and received by DMPP and OPDP on September 14, 2016.
- Draft TRULANCE (plecanatide) tablets Prescribing Information (PI) received on January 29, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 14, 2016.
- Approved LINZESS (linaclotide) capsules comparator labeling dated August 31, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
09/19/2016

ADEWALE A ADELEYE
09/19/2016

MARCIA B WILLIAMS
09/19/2016

LASHAWN M GRIFFITHS
09/19/2016

Clinical Inspection Summary

Date	September 16, 2016
From	Susan Leibenhaut, M.D.
To	Lesley Hanes, M.D., Medical Officer, DGIEP
NDA/BLA #	NDA #208745
Applicant	Synergy Pharmaceuticals Inc.
Drug	Plecanatide
NME (Yes/No)	Yes
Therapeutic Classification	Cathartics and Laxatives
Proposed Indication	Chronic idiopathic constipation (CIC)
Consultation Request Date	March 17, 2016
Summary Goal Date	September 22, 2016
Action Goal Date	January 29, 2017
PDUFA Date	January 29, 2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

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.

(b)(4)

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.

II. BACKGROUND

The sponsor submitted this NDA for plecanatide (SP-304) for the indication of chronic oral administration for the treatment of chronic idiopathic constipation in adults.

Drug: Plecanatide

Studies – Protocol number and title for all studies that were inspected:
Protocol SP304203-00 and Protocol SP304203-03 are identical protocols entitled “A Randomized, 12-Week, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Plecanatide (3 mg (b)(4)) in Patients with Chronic Idiopathic Constipation (CIC).”

1. Protocol SP304203-00

Number of subjects: 1394 subjects randomized

Number of sites: 183

Number of countries where subjects were enrolled: 2 (U.S. and Canada)

Dates that study was conducted: December 3, 2013 to April 23, 2015

Primary efficacy endpoint: the proportion of patients who were “complete spontaneous bowel movement” (CSBM) overall responders over the 12-week Treatment Period.

A SBM was defined as a BM that occurred in the absence of laxative use within 24 hours of the BM. A CSBM was defined as an SBM with the sense of complete evacuation. A CSBM weekly responder was defined as a subject who had ≥ 3 CSBMs for a given week and an increase from baseline of ≥ 1 CSBM for that same week. An overall CSBM responder was defined as a patient who was a weekly responder for at least 9 of the 12 treatment weeks, and a durable overall CSBM responder was also a weekly responder in at least 3 of the last 4 weeks.

2. Protocol SP304203-03

Number of subjects: 1410 subjects

Number of sites: 162 sites

Number of countries where subjects were enrolled: 1 (all United States)

Dates that study was conducted: May 16, 2014 to May 13, 2014

Primary efficacy endpoint: the proportion of patients who were “complete spontaneous bowel movement” (CSBM) overall responders over the 12-week Treatment Period.

A SBM was defined as a BM that occurred in the absence of laxative use within 24 hours of the BM. A CSBM was defined as an SBM with the sense of complete evacuation. A CSBM weekly responder was defined as a subject who had ≥ 3 CSBMs for a given week and an increase from baseline of ≥ 1 CSBM for that same week. An overall CSBM responder was defined as a patient who was a weekly responder for at least 9 of the 12 treatment weeks, and a durable overall CSBM responder was also a weekly responder in at least 3 of the last 4 weeks.

III. RESULTS (by site):

Name and type of inspected entity/Address	Protocol # /Site # # of Subjects	Inspection Date	Classification
CI: Elena Valor, M.D. 9240 Sunset Drive, Suite 116 Miami, FL 33173	SP304203-00/ Site 149/ 41 Subjects	April 26 to 28, 2016	VAI
CI: William Koltun, M.D. 9040 Friars Road, Suite 540 San Diego, CA 92108	SP304203-00/ Site 224/ 35 Subjects	May 25 to June 2, 2016	VAI
CI: John Lentz, M.D. 2121 Fountain Drive, Suite A. Snellville, GA 30078	SP304203-03/ Site 291/ 38 Subjects	April 11 to 25, 2016	NAI
CI: Felix Penate, M.D. 8260 West Flagler Street, Suite 2N Miami, FL 33144	SP304203-03/ Site 415/ 43 Subjects	April 25 to 29, 2016	NAI
CI: Sady Alpizar, M.D. 3434 W. Columbus Drive, Suite 106 Tampa, FL 33607	SP304203-03/ Site 495/ 33 Subjects	May 9 to 13, 2016	NAI
CI: Rosa Suarez, M.D. 434 SW 12th Ave., Suite 302 Miami, FL 33130	SP304203-00/ Site 631/ 26 Subjects	May 31 to June 10, 2016	NAI
CRO: eResearch Technology, Inc. 225 West Station Square Drive, Suite 220 Pittsburgh, PA 15219-1174	SP304203-00 SP304203-03	July 6 to 7, 2016	NAI
Sponsor: Synergy Pharmaceuticals Inc. 420 Lexington Ave, Suite 2012 New York, New York 10170	SP304203-00 SP304203-03	August 1 to 4, 2016	NAI

Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Elena Valor, M.D., Miami, FL 33173

At this site for SP304203-00, 47 subjects were screened and 41 subjects were enrolled into the study. A total of 28 subjects completed the study. Subject 149-132 withdrew because of an adverse event, elevated liver function tests at baseline, but after screening, so the subject had been enrolled and randomized but had not received study drug.

According to the study report, three subjects, one from each treatment arm, withdrew consent prior to study completion, and three subjects withdrew because of non-compliance and six subjects withdrew for other reasons.

The records for 21 subjects were reviewed in depth and compared to line listings from the NDA provided for adverse events, and eligibility criteria. There was no evidence of under-reporting of adverse events. For the primary eDiary data, the endpoints were checked against the CD available at the site, using the key provided in the CD. There were no discrepancies between the data in the line listings and the source documents. A Form FDA 483 was issued for failure to conduct the investigation in accordance with the investigational plan. Specifically:

1. Eligibility violations were noted for 9 of 21 subjects whose records were reviewed. One subject took prohibited medication during the pre-treatment assessment, three subjects did not meet electronic diary eligibility for bowel movements and rescue medication, and five subjects that took rescue medication within 72 hours of the first dose of investigational product. Specifically,
 - a. Subject 149-119 took Orlistat, a prohibited medication, for weight loss during the pretreatment period.
 - b. Three subjects were randomized even though the electronic diary eligibility report for the pre-treatment assessment indicated that the subjects did not meet eligibility criteria.
 - i. Subject 149-122 did not meet the inclusion criterion of less than three complete spontaneous bowel movements each week.
 - ii. Subjects 149-134 and 149-135 reported the use of rescue medication for more than two days in either of two weeks in the pre-treatment assessment period.
 - c. The electronic diary for five subjects, Subjects 149-110, 149-124, 149-125, 149-127, and 149-131 indicate that these subjects took rescue medication within 72 hours prior to the first dose of investigational product without extension of the pretreatment period.

Reviewer note: The sponsor allowed the ineligible subjects to remain in the study once deviations were known. These deviations are documented in the protocol deviations line listings.

2. Assessments for seven subjects did not have the post dose electrocardiogram as required and lacked patient assessment questionnaires at various study visits.

The clinical investigator responded to the Form FDA 483 stating that clinical staff has been re-educated on regulations and institutional procedures. While the study was ongoing, the sponsor monitored the site and placed the site on screen hold after the monitoring visits. The violations noted above are documented in the clinical study report and do not have a significant impact on subject safety or data integrity.

Verbal observations included one subject that received the incorrect investigational product kit (noted by the monitor and included in the protocol deviations listing in the

NDA), one subject that was documented to have a screening physical examination and chronic idiopathic constipation questionnaire completed prior to signing the informed consent form, inconsistent maintenance of the IWRS confirmation sheets and patient questionnaires conducted the day after study visits (subjects were called back by the site to complete the questionnaires). This site enrolled a high number of duplicate subjects. The site denied knowledge of the enrollment of duplicate subjects and worked with the sponsor to mitigate this issue.

The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

2. William Koltun, M.D., San Diego, CA 92108

At this site for Protocol SP304203-00, 56 subjects were screened, 35 subjects were enrolled, and 27 subjects completed the study. Five subjects withdrew consent and three subjects were lost to follow-up. The records for all subjects that completed the trial were reviewed in depth and compared to line listings from the NDA. There was no evidence of under-reporting of adverse events. There were no discrepancies between the data in the line listings and the source documents. A Form FDA 483 was issued for inadequate drug accountability records. Specifically, the quantity of tablets per kit returned to the sponsor was not recorded by the site.

Reviewer note: The number of tablets returned by the subjects to the site was captured in the subject source documents, so subject compliance could be established. In addition, the number of kits returned to the sponsor was recorded. However, the number of tablets returned by the site to the sponsor was not recorded by the site in the Investigational Product Return form. Dr. Koltun proposed adequate corrective action in his response of June 10, 2016.

The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

3. John Lentz, M.D., Snellville, GA 30078

At this site for Protocol SP304203-03, 55 subjects were screened, 38 subjects were randomized, and 35 subjects completed the study. One subject each in the placebo (b)(4) dose arms of the study withdrew consent, and a subject in the 3 mg dose group was discontinued because it was determined after randomization that this subject had not completed the required colonoscopy. The records for 12 subjects were reviewed in depth and compared to line listings from the NDA provided for adverse events and eligibility criteria. There was no evidence of under-reporting of adverse events. For the primary eDiary data, the endpoints were checked against the CD available at the site, using the key provided in the CD. There were no discrepancies between the data in the line listings and the source documents. A Form FDA 483 was issued for failure to conduct the investigation in accordance with the investigational plan. Specifically:

1. The determination of subject eligibility for 9 of the 12 subjects reviewed included post dose EKGs during some of the office visits which were between 3 and 14 minutes late.

Reviewer note: As the CI stated in his response, there was a 30 minute window allowed for the performance of the EKG, so this is not considered a violation.

2. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the observations. Specifically:
 - a. Subject 291-221 (randomized to 6 mg plecanatide) returned one less pill at the Week 8 visit and three less pills at the Week 12 visit than would have been anticipated for the number of days, indicating the possibility that the subject took up to three more pills than expected for a once daily dosing. The violation cited on the Form FDA 483 is that this should have been reported as a protocol deviation.

Reviewer note: According to Section 8.6 of the protocol "Treatment Compliance", compliance is defined as taking 80% of the drug dosage prescribed. The possibility that the subject might have taken three extra pills over the course of four weeks is not considered significant and is not a requirement to file a deviation report.

- b. Subject 291-231 (randomized to placebo) returned four tablets at the Week 4 visit, indicating one missed dose of medication. On the drug accountability record, the number 29 was changed to 28 by over writing the number instead of using the correct procedure of initials, date, and justification for change.

Reviewer note: This observation is a mixed bag of issues, none of them significant. The first item is a minor subject compliance issue (not a violation as noted in "a." above), the second is a mathematical error that was not corrected according to GCP guidelines (technically a violation, but an isolated instance and not, in itself, a justification for a VAI classification), and the third is a an apparent transcription error (minor violation, see previous comment)

- c. Subject 291-223 (randomized to 3 mg plecanatide) returned nine tablets at the Week 4 visit, indicating five missed doses of medication. At Week 12, five pills were returned, indicating 96% compliance.

Reviewer note: As noted above, this is not a violation.

The clinical investigator responded adequately to the Form FDA 483. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

4. Felix Penate, M.D., Miami, FL 33144

At this site for SP304203-03, a total of 45 subjects were screened, 43 subjects were enrolled, and 42 completed the study. Subject 415-212 was withdrawn after the chemistry values were noted to be elevated at the Week 1 visit. This was originally captured as an adverse event, but the elevated values occurred prior to dosing. It was then captured as a protocol deviation although there are no clear guidelines for elevated laboratory values and the screening values were normal. The records for 18 subjects

were reviewed in depth and compared to line listings from the NDA provided for primary endpoints, adverse events, and eligibility criteria. There were no limitations to the inspection. There was no evidence of under-reporting of adverse events. There were no discrepancies between the data in the line listings and the source documents.

The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

5. Sady Alpizar, M.D. Tampa, FL 33607

At this site for SP304203-03 a total of 43 subjects were screened, 33 subjects were enrolled into and completed the study. The records for 12 enrolled subjects were reviewed in depth and compared to line listings from the NDA provided for primary endpoints, adverse events, and eligibility criteria. There were no limitations to the inspection. There was no evidence of under-reporting of adverse events. There were no discrepancies between the data in the line listings and the source documents.

The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

6. Rosa Suarez, M.D., Miami, FL

At this site for SP304203-00, a total of 31 subjects were screened, 26 subjects were enrolled into and completed the study. The records for 19 enrolled subjects were reviewed in depth and compared to line listings from the NDA provided for primary endpoints, adverse events, and eligibility criteria. There were no limitations to the inspection. There was no evidence of under-reporting of adverse events. There were no discrepancies between the data in the line listings and the source documents.

The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

7. eResearch Technology, Inc., Pittsburgh, PA 15219-1174

The purpose of the inspection, which was conducted in accordance with the Sponsor/Monitor/Contract Research Organization (CRO) compliance program to inspect the conduct of the CRO in fulfilling their responsibilities of designing and maintaining the electronic hand held device (EHD) used for Protocols SP304203-00 and SP304203-03. For each clinical trial, subjects entered daily values in response to questions concerning number and quality of bowel movements and rescue medication usage into the password protected EHD. These data were used to determine eligibility and captured the primary endpoint “complete spontaneous bowel movement” (CSBM).

The inspection audited Protocols SP304203-00 and SP304203-03 and focused on the following clinical investigators for Protocol SP304203-00: Valor, Site 149; Koltun, Site 224; Suarez, Site 631 and for Protocol SP304203-03: Lentz, Site 291; Penate, Site 415; and Alpizar, Site 495. The inspection reviewed the following: quality assurance and clinical operations, Master Service agreements and associated work orders, data management quality plans, clinical design specifications, software validation reports, qualification of clinical sites for use of DIARYpro, SITEpro and EPX website and receipt records of archival CDs sent to clinical sites. In addition, records associated with defects found in 2014 in the EPX eligibility reports and changes requested by the sponsor were inspected. The inspector also compared selected subject CRFs with the firm's data listings. No violations were noted and no Form FDA 483 was issued. Concerning the problems with determining eligibility, it was explained that, in November 2014, the change in daylight savings time resulted in incorrect time calculations in the EPX portal. This error was corrected and the sponsor conducted the eligibility determination manually. The CRO corrected the programming error according to their procedures.

The studies appear to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.

8. Synergy Pharmaceuticals Inc., New York, New York 10170

This inspection evaluated compliance with sponsor responsibilities concerning the conduct of Protocols SP304203-00 and SP304203-03, including selection and oversight of contract research organizations, monitoring, financial disclosure, FDA Form 1572s, quality assurance (QA), and handling of data. The inspection included review of general correspondence and study master files, site monitoring for the clinical sites, and handling of adverse events and other sponsor/monitor related activities. The inspection focused on the following clinical investigators for Protocol SP304203-00: Valor, Site 149; Koltun, Site 224; Suarez, Site 631, and for Protocol SP304203-03: Lentz, Site 291; Penate, Site 415; and Alpizar, Site 495; (b)(4)

Review of the sponsor documents did not note any significant deficiencies. As noted above for the inspection of eResearch Technology, there were issues with the eDiary that were addressed while the studies were ongoing. In addition, the clinical study report for Protocol SP304203-00 noted issues with the data management system under one CRO and this was migrated to a data system managed by another CRO. Clinical sites were educated on the new system and source data verification was conducted to ensure accurate data migration.

The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

{See appended electronic signature page}

Susan Leibenhaut, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
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/s/

SUSAN LEIBENHAUT
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