

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202811Orig1s000

OTHER REVIEW(S)

Attachment B: Sample 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.

PMR/PMC Description: 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

PMR/PMC Schedule Milestones: Final protocol Submission Date: _____
Study/Clinical trial Completion Date: _____
Final Report Submission Date: September 2014
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

Because LINZESS has very limited systemic absorption and is a very small 14 amino acid peptide, the applicant argued the product was unlikely to cause an immunogenic reaction. While the applicant's rationale is understandable, the immunogenicity consult has concluded that the development of anti-LINZESS antibodies in patients should be assessed. Although LINZESS is a small peptide, it contains three disulfide bonds that result in a more rigid tertiary structure than is typical for a 14 amino acid peptide. The extensive disulfide bridging in LINZESS renders the product more immunogenic than other 14 amino acid peptides. The agency has determined an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess known serious risks of immune-mediated reactions or to identify unknown serious risks of the development of anti-drug antibodies that may cross react with endogenous guanylin peptide family members and lead to deficiency syndromes. The risk that patients will develop clinically important levels of anti-drug antibodies that cross-react with endogenous guanylin peptide family members is theoretical. Therefore the immunogenicity consult has agreed that it is appropriate for immunogenic trials to be carried out post-marketing. This PMR will be for development of the assay for detection of anti-Linaclotide antibodies in patients in a separate clinical trial.

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, because of the limited systemic absorption of LINZESS, the applicant did not perform immunogenicity studies prior to approval. The develop of antibodies is theoretical and may be conducted post-approval. The goal of this PMR is to develop an appropriate and validated assay that will detect anti-LINZESS antibodies, including IgM, IgG, and IgA.

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-LINZESS antibodies.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- 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
- 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
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.
-

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?

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)

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

/s/

ERICA WYNN
08/29/2012

ROBERT FIORENTINO
08/29/2012

Attachment B: Sample 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.

PMR/PMC Description: 1915-6 To conduct a clinical trial in adults to assess development of anti-drug antibody (ADA) response 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, will be used. Sampling will occur at 0, 2-weeks, 1, 3, 6 and 12 months. Immunogenicity rates and individual patient titers will be evaluated. Adverse events will be collected.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>November 2013</u>
	Study/Clinical trial Completion Date:	<u>March 2018</u>
	Final Report Submission Date:	<u>December 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

Because LINZESS has very limited systemic absorption and is a very small 14 amino acid peptide, the applicant argued the product was unlikely to cause an immunogenic reaction. While the applicant's rationale is understandable, the immunogenicity consult has concluded that the development of anti-LINZESS antibodies in patients should be assessed. Although LINZESS is a small peptide, it contains three disulfide bonds that result in a more rigid tertiary structure than is typical for a 14 amino acid peptide. The extensive disulfide bridging in LINZESS renders the product more immunogenic than other 14 amino acid peptides. The agency has determined an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess known serious risks of immune-mediated reactions or to identify unknown serious risks of the development of anti-drug antibodies that may cross react with endogenous guanylin peptide family members and lead to deficiency syndromes. The risk that patients will develop clinically important levels of anti-drug antibodies that cross-react with endogenous guanylin peptide family members is theoretical. Therefore the immunogenicity consult has agreed that it is appropriate for immunogenic trials to be carried out post-marketing after the development of an appropriate assay.

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, because of the limited systemic absorption of LINZESS, the applicant did not perform immunogenicity studies prior to approval. The develop of antibodies is theoretical and may be conducted post-approval. The goal is to definitely determine if patients will develop antibodies with LINZESS treatment and if, so what are the clinical manifestations of antibody development.

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 clinical trial in adults to assess development of anti-drug antibody (ADA) response 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, will be used. Sampling will occur at 0, 2-weeks, 1, 3, 6 and 12 months. Immunogenicity rates and individual patient titers will be evaluated. Adverse events will be collected.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
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- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
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- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- 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
A clinical trial in adults to assess development of anti-drug antibody (ADA) response in patient samples. Validated assays capable of sensitively detecting ADA responses that may be present at the time of patient sampling, will be used. Sampling will occur at 0, 2-weeks, 1, 3, 6 and 12 months. Immunogenicity rates and individual patient titers will be evaluated. Adverse events will be collected.
-

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?

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/

ERICA WYNN
08/29/2012

ROBERT FIORENTINO
08/29/2012

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: No Format Deficiencies

Product Title	LINZESS (linaclotide) capsules, for oral use
Applicant	Forest Laboratories, Inc.
Application/Supplement Number	NDA 202811
Type of Application	Original Submission
Indication(s)	Indicated in adults for treatment of irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC)
Established Pharmacologic Class ¹	guanylate cyclase-C agonist
Office/Division	ODE III/DGIEP
Division Project Manager	Brian Strongin
Receipt Date	August 9, 2011
PDUFA Goal Date	September 9, 2012
SEALD Review Date	August 24, 2012
SEALD Labeling Reviewer	Jeanne M. Delasko
SEALD Division Director	Laurie B. Burke

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, final agreed-upon prescribing information (PI) for critical format elements reveals **NO outstanding labeling format issues** and the SEALD Director has **NO OBJECTION** to the approval of this PI at this time.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements for Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information (SRPI)

Highlights (HL)

GENERAL FORMAT

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

Comment:

- N/A** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

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

Selected Requirements of Prescribing Information (SRPI)

• 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 the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

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

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

YES

12. All text must be **bolded**.

Comment:

YES

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

Selected Requirements of Prescribing Information (SRPI)

- YES** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(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, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Selected Requirements of Prescribing Information (SRPI)

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

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

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has 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:

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

- YES** 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

- YES** 33. All subsection headings must be indented, not bolded, and in title case.

Selected Requirements of Prescribing Information (SRPI)

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

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 Labor and Delivery
8.3 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)

Selected Requirements of Prescribing Information (SRPI)

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** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- YES** 42. All text is **bolded**.

Comment:

- YES** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- YES** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“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 clinical practice.”

Selected Requirements of Prescribing Information (SRPI)

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), 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:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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

/s/

JEANNE M DELASKO
08/24/2012

LAURIE B BURKE
08/27/2012

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/BLA # NDA 202,811
Product Name: LINZESS (linaclotide) Capsules

PMR/PMC Description: 1915-1: A nonclinical study in neonatal and juvenile mice to determine the mechanism of death in neonatal and juvenile mice treated with linaclotide.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>01/30/2013</u>
	Study/Trial Completion:	<u>10/30/2013</u>
	Final Report Submission:	<u>04/30/2014</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

Linaclotide is a synthetic 14-amino acid peptide that binds to guanylate cyclase-C (GC-C) and stimulates the production of cGMP (cyclic guanosine 3', 5'-monophosphate) in the intestinal epithelium, which in turn stimulates secretion of chloride, bicarbonate, and fluid. The proposed indications for linaclotide are for treatment of irritable bowel syndrome with constipation, and treatment of chronic constipation in adults. In neonatal/juvenile mice, oral toxicity studies revealed that young mice are particularly sensitive to linaclotide toxicity, and lethality was found to be highly age-dependent. Results from the PMR are crucial for evaluating the potential risk of linaclotide and informing the design of future clinical studies in the pediatric 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."

In neonatal/juvenile mice, oral toxicity studies revealed that young mice are particularly sensitive to linaclotide toxicity, and lethality was found to be highly age-dependent. The minimum lethal dose (10 mcg/kg) in neonatal mice age 7 days is approximately 2 times the maximum recommended human dose, based on a mcg/kg comparison. Lethality occurred at higher doses in juvenile mice age 14 and 21 days (100 and 600 mcg/kg/day, respectively). The Sponsor has proposed a reasonable hypothesis to explain the potent lethality in neonatal mice, based on information in the literature. However, the nonclinical studies submitted by the Sponsor have not provided direct evidence to support the hypothesis. The requested study will investigate the mechanism of lethality in neonatal and juvenile mice treated with linaclotide. Results from this study will be crucial in informing the potential risk of linaclotide as well as the design of future clinical studies in the pediatric population.

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 nonclinical study to determine the mechanism of death in neonatal and juvenile mice treated with linaclotide.

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)

Continuation of Question 4

- 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
 - 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?

PMR/PMC Development Coordinator:

X 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.

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/s/

DAVID B JOSEPH
08/16/2012

JOYCE A KORVICK
08/20/2012

Date: August 16, 2012

From: Susan Kirshner, Ph.D.

To: NDA 202811

Product: Linzess (Linaclotide)

Purpose: Original NDA Immunogenicity Consult

Proposed Use: Chronic constipation and irritable bowel syndrome with chronic constipation

Applicant: Ironwood Pharmaceuticals

Recommendation: The development of anti-linzess antibodies in patients should be assessed as part of a planned post-marketing clinical trial. Since loss of Linzess efficacy was not noted in the clinical trial the risk that patients will develop clinically important levels of anti-drug-antibodies that cross-react to endogenous guanylin peptide family members is theoretical. Therefore, it is appropriate that these studies be carried out as part of proposed post-market clinical trials.

Background:

Ironwood Pharmaceuticals is seeking approval of Linzess (linaclotide) for the treatment of chronic constipation and irritable bowel syndrome with chronic constipation. Linzess is an agonist of the GC-C receptor. GC-C receptor activation leads to increased secretion of chloride and bicarbonate into the intestinal lumen. This in turn leads to increased luminal fluids and decreased transit time. This consult will discuss the need for immunogenicity data for Linzess. The Applicant did not assess product immunogenicity during development.

Although Linzess is a small peptide, it contains multiple attributes that make it potentially immunogenic. Linzess is a 14 amino acid peptide (aa) that contains three disulphide bonds, which is unusual for a peptide that short. As a result Linzess likely has more rigid tertiary structure than is typical for a 14 aa peptide. While antibodies do develop against linear structures such as peptides, conformational epitopes are usually better antibody epitopes. Therefore the extensive disulfide bridging in Linzess may render it more immunogenic than many 14 amino acid peptides.

T cells are generally required for maintained adaptive immune responses such as class switched (from IgM to IgG, A or E), affinity matured (selection for mutations that increase antibody affinity for the antigen) memory B cell responses. The ideal T cell epitopes for activation via the HLA class 2 pathway are around 12 – 18 amino acids in length. T cell epitopes for activation via the HLA class 1 pathway are at least 9 amino

acids in length and generally no longer than 12 amino acids. Therefore Linzess is long enough to be a T cell epitope, which contributes to the immunogenic potential of the molecule.

Oral administration of proteins and peptides has been found to generate immune tolerance to the administered antigen in animal models. It is not clear to what extent this is true for humans as most oral tolerance clinical trials have failed (there has been some success for treating allergy) and at least one trial for treatment of multiple sclerosis exacerbated the disease. Therefore induction of anti-drug antibody responses remains a risk.

Linzess has structural homology to endogenous guanylin peptide family members. The most likely risk if anti-linzess antibodies develop is loss of product efficacy. However, anti-drug antibodies could cross react with endogenous peptides potentially leading to deficiency syndromes. Because of these risks it is recommended that assays be developed and samples be obtained to assess for the development of anti-linzess antibodies in future clinical trials. Since mucosal routes of exposure favor isotype switching to from IgM to IgA rather than IgG, assays should be developed that screen for anti-drug antibodies of the IgM, A and G isotypes.

During a discussion in April 2012, the clinical reviewer, Lara Dimick, related that loss of efficacy was not observed during the clinical trial. Therefore the risk that patients develop clinically important levels of anti-drug-antibodies that cross-react to endogenous guanylin peptide family members is theoretical. Therefore, it is appropriate that these studies be carried out as part of proposed post-market clinical trials.

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/s/

BRIAN K STRONGIN

08/17/2012

EMANUELA LACANA on behalf of SUSAN L KIRSHNER

08/17/2012

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# 202-811
Product Name Linzess (linaclotide) Capsules

PMR/PMC Description: 1915-4: A multiple-dose milk-only lactation study in healthy lactating but non-nursing female volunteers receiving Linzess (linaclotide) to assess concentrations of linaclotide and its active metabolite in breast milk, using a validated assay in order to appropriately inform the nursing mothers' subsection of the labeling.

PMR/PMC Schedule Milestones: Final Protocol Submission: 3/31/2013
Study/Trial Completion: 9/30/2014
Final Report Submission: 9/30/2015

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 animal data in juvenile and neonatal mice regarding deaths, a serious side effect, it was felt that in order to inform labeling this study needed to be done. 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 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."

Please 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 multiple-dose milk-only lactation trial in healthy lactating but non-nursing female volunteers receiving Linzess (linaclotide) to assess concentrations of linaclotide and its active metabolite in breast milk, using a validated assay in order to appropriately inform the nursing mothers' 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)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - X Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - 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?

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

PMR/PMC Development Coordinator:

- X *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.*

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/s/

SUE CHIH H LEE
08/16/2012

RUYI HE
08/16/2012

Attachment B: Sample 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.

PMR/PMC Description: 1915-3 A safety and efficacy study in pediatric patients with irritable bowel syndrome with constipation ages seven years to 17 years.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>04/30/2015</u>
	Study/Clinical trial Completion Date:	<u>12/31/2022</u>
	Final Report Submission Date:	<u>12/31/2023</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

This PMR is a PREA study. The safety profile of product was found to be acceptable and the drug is ready for approval in adults. The applicant requested a waiver to conduct PREA-required pediatric trials in patients less than 6 years of age. A waiver was granted because IBS-C study in children with IBS-C younger than 6 years of age would be highly impractical, if not impossible to conduct. The applicant also requested a deferral to conduct PREA-required trials in pediatric patients from 7 to 17 years of age. The results of the nonclinical review revealed lethality in juvenile mice equivalent to pediatric patients ages 0 to 23 months. Lethality in juvenile rabbits was not observed, however the deaths in the juvenile mice occurred at a dose that is only 2 fold greater than the highest dose proposed by the applicant for use in adults. The mechanism of action for the deaths is unknown. There are no nonclinical data in juvenile mice to provide any information that corresponds to pediatric patients ages 2 to 12 years. Before pediatric trials may commence, additional nonclinical data are required.

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.”

As stated above, there were deaths in juvenile mice during the nonclinical trials. The applicant asserts that the deaths seen in the neonatal mice were most likely explained by increase intestinal secretion in a markedly underdeveloped mouse intestinal tract. However, there are no definitive data to support this theory nor has the applicant provided the full characterization of the G-CC receptor over time in juvenile mice. IBS-C is a nonlethal condition. Based on the information provided, the vulnerability of the population and in consideration of the condition being treated, it does not seem prudent to use this product in any capacity in the pediatric patient until additional nonclinical data have been gathered and reviewed. The reason for these nonclinical deaths and the mechanism of action can not be determined based on the information that is currently available and should be studied further before clinical trials in pediatric patients starts.

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 safety, efficacy, and PK trial in pediatric patients with irritable bowel syndrome with constipation ages seven years to 17 years. Additional details related to the specific design of the trial will be discussed with the sponsor at the time of the protocol submission.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- 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
 - 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
A safety, efficacy, and PK trial in pediatric patients with irritable bowel syndrome with constipation ages seven years to 17 years
-

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?

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/

RUYI HE
08/15/2012

Attachment B: Sample 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.

PMR/PMC Description: 1915-2 A safety and efficacy study in pediatric patients with chronic idiopathic constipation ages seven months to 17 years.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>04/30/2015</u>
	Study/Clinical trial Completion Date:	<u>12/31/2022</u>
	Final Report Submission Date:	<u>12/31/2023</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

This PMR is a PREA requirement. The safety profile of product was found to be acceptable and the drug is ready for approval in adults. The applicant requested a waiver to conduct PREA-required pediatric trials in patients less than 6 months of age. A waiver was granted because CIC does not exist in this age group. The applicant also requested a deferral to conduct PREA-required trials in pediatric patients from 7 months to 17 years of age. The results of the nonclinical review revealed lethality in juvenile mice equivalent to pediatric patients ages 0 to 23 months. Lethality in juvenile rabbits was not observed, however the deaths in the juvenile mice occurred at a dose that is only 2 fold greater than the highest dose proposed by the applicant for use in adults. The mechanism of action for the deaths is unknown. There are no nonclinical data in juvenile mice to provide any information that corresponds to pediatric patients ages 2 to 12 years. Before pediatric trials may commence, additional nonclinical data are required.

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.”

As stated above, there were deaths in juvenile mice during the nonclinical trials. The applicant asserts that the deaths seen in the neonatal mice were most likely explained by increase intestinal secretion in a markedly underdeveloped mouse intestinal tract. However, there are no definitive data to support this theory nor has the applicant provided the full characterization of the G-CC receptor over time in juvenile mice. Chronic idiopathic constipation is a nonlethal condition and there are a number of products available that are used off-label to treat the condition. Based on the information provided and in consideration of the condition being treated and the number of alternative products, it does not seem prudent to use this product in any capacity in the pediatric patient until additional nonclinical data have been gathered and reviewed. The reason for these nonclinical deaths and the mechanism of action cannot be determined based on the information that is currently available and should be studied further before clinical trials in pediatric patients (under PREA) starts.

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 safety, efficacy, and PK trial in pediatric patients with Chronic Idiopathic Constipation ages 7 months to 17 years will be conducted. Additional details related to the specific design of the trial will be discussed with the sponsor at the time of the protocol submission.

Required

- Observational pharmacoepidemiologic study
 Registry studies

Continuation of Question 4

- 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
 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

A safety, efficacy, and PK trial in pediatric patients with CIC ages 7 months to 17 years.

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?

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/

ERICA WYNN
08/15/2012

ROBERT FIORENTINO
08/15/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 16, 2012

TO: NDA 202-811; LINZESS (linaclotide) Capsules

FROM: Brian Strongin, R.Ph., MBA
Chief Project Management Staff
Division of Gastroenterology and Inborn Errors Products

SUBJECT: FDA Mark-Up of Sponsor's Proposed Package Insert

Sponsor Attendees:

Forest Laboratories Inc.

Marco Taglietti, MD	Senior Vice President, R & D
June Bray, RPh, MBA	Senior Vice President, FRI Regulatory Affairs
James DeMartino, PhD	Senior Director, Regulatory Affairs
Linda Kunka, MA	Senior Manager, Regulatory Affairs
Donato Forlenza, PharmD, MBA	Post-Doctoral Fellow, Regulatory Affairs
Gavin Corcoran, MD	Executive Vice President, R&D Clinical & Early Development
Harvey Schneier, MD	Executive Director, Clinical Development Internal Medicine & GI
Steven Shiff, MD	Director, Clinical Development
Charles Lindamood III, Ph.D., D.A.B.T.	Executive Director, Early Development
Stephan Ortiz, R.Ph., Ph.D.	Associate Director, Clinical Pharmacology and Drug Dynamics
Christina Carruthers	Principal Scientist, Toxicology
George Zhang	Senior Principal Scientist
Daniel Jia, Ph.D.	Senior Director, Biostatistics

Ironwood Pharmaceuticals

Mark Currie, PhD	Senior VP R&D, Chief Scientific Officer
Gwyn Reis	Vice President, Regulatory Affairs
Sarah Lieber, MS	Associate Director, Regulatory Affairs
Caroline Kurtz, PhD	Vice President, Program Management

Jeff Johnston, MD	Vice President, Clinical Development, and Chief Medical Officer
Joseph Lavins, MD	Senior Director, Clinical Research
James MacDougall, Ph.D.	Vice President, Biometrics
Karel Van Loon, MD	Senior Director, Drug Safety and Pharmacovigilance
Alex Bryant, PhD	Vice President, Drug Metabolism and Pharmacokinetics
Adeline Smith PhD	Director, Toxicology

FDA Attendees:

Vickie Kusiak, M.D.	Deputy Director, Office of Drug Evaluation III
Donna Griebel, M.D.	Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Joyce Korvick, M.D.	Deputy Director for Safety, DGIEP
Ruyi He, M.D.	Medical Team Leader, DGIEP
Rob Fiorentino, M.D.	Medical Team Leader, DGIEP
Erica Wynn, M.D.	Medical Reviewer, DGIEP
Lara Dimick M.D.	Medical Reviewer, DGIEP
David Joseph, Ph.D.	Pharmacology Team Leader
Yuk-Chow Ng, Ph.D.	Pharmacology Reviewer
Sharon R. Mills	Senior Patient Labeling Reviewer
Eunice Chung-Davies, PharmD.,	Division of Medical Policy Programs (DMPP)
Kathleen Klemm, Pharm.D.	Regulatory Review Officer, Office of Prescription Drug Promotion (OPDP)
Brian Strongin, R Ph, M.B.A.	Regulatory Review Officer, OPDP
	Chief, Project Management Staff, DGIEP

Background

NDA 202-811, sponsor Forest Laboratories, for LINZESS (linaclotide) Capsules, submitted and received August 9, 2011 provides for the treatment of constipation-predominant irritable bowel syndrome (IBS-C) and chronic idiopathic constipation (CIC). Sponsorship changed from Ironwood Pharmaceuticals to Forest Laboratories after the NDA was submitted. Linaclotide is an NME.

On July 13, 2012 the Division sent the sponsor the Agency's mark-up of the sponsor's proposed package insert. At today's teleconference, we discussed the Agency's inclusion of: information and figures regarding the results from secondary endpoints in Section 14, Clinical Studies; a Boxed Warning regarding deaths in juvenile mice studies.

Teleconference Discussion

Section 14: Clinical Studies

The sponsor began by asking why the results of secondary endpoints used in the IBS-C and CIC clinical studies were removed in the FDA mark-up. They contended that the FDA stated, at the end-of-phase 2 meeting, that clinically meaningful secondary endpoint results could stay in the label. They added that the results from these endpoints convey important information about the time-course of LINZESS's effects and should remain in the label.

The Division responded that, although the results from these endpoints may be statistically significant, we need data demonstrating that they are clinically meaningful. The sponsor responded that evidence submitted with the Patient-Reported Outcome dossier demonstrated that these results were clinically meaningful. They also explained that even after adjustments for multiplicity were made, the results were statistically significant. In response to the Division's request, the sponsor stated that they would submit a justification for inclusion of the results of secondary endpoints, including their clinical meaningfulness.

In addition, the sponsor stated their intention of providing a rationale for the inclusion of Figures 1 and 2, regarding the results of secondary endpoints, in Section 14. These figures were removed in the FDA mark-up sent to the sponsor July 13, 2012.

Boxed Warning

A Boxed Warning regarding lethality seen in juvenile mouse studies and the risk of pediatric use of LINZESS was added by the Division in its mark-up sent to the sponsor July 13, 2012. In response to the sponsor's question, the Division explained that a Boxed Warning was a conservative approach for delivering risk information in a prominent way. The sponsor contended that a limitation restricting use to adults could be added to the Indications and Use section. The Division responded that a Boxed Warning is stronger and more appropriate in this unusual situation. The sponsor explained that they were not surprised by the deaths in pre-clinical studie (b) (4)

The call then concluded.

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/s/

BRIAN K STRONGIN
07/27/2012

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

PATIENT LABELING REVIEW

Date: June 28, 2012

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

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

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

Drug Name (established name): LINZESS (linaclotide)

Dosage Form and Route: capsules

Application Type/Number: NDA 202-811

Applicant: Forest Laboratories, Inc.

1 INTRODUCTION

On August 9, 2011, Ironwood Pharmaceuticals, Inc. submitted for the Agency's review an Original New Drug Application (NDA) 202-811 for LINZESS (linaclotide) capsules. The two proposed indications for LINZESS (linaclotide) capsules are as follows:

- for the treatment of irritable bowel syndrome with constipation (IBS-C) in adults
- for the treatment of chronic idiopathic constipation (CIC) in adults

On October 3, 2011, the Division of Gastroenterology and Inborn Error Products (DGIEP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for LINZESS (linaclotide) capsules. On June 27, 2012, DGIEP requested that DMPP convert the Applicant's proposed PPI to a Medication Guide (MG). This review is written in response to the request by DGIEP for DMPP to review the Applicant's proposed Patient Package Insert (PPI) for LINZESS (linaclotide) capsules, and convert the proposed PPI to a MG.

The Agency was notified on November 7, 2011 of an Administrative Change of Applicant to Forest Laboratories, Inc.

2 MATERIAL REVIEWED

- Draft LINZESS (linaclotide) capsules Patient Package Insert (PPI) received on August 9, 2011.
- Draft LINZESS (linaclotide) capsules Prescribing Information (PI) received on August 9, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on June 11, 2012 and June 27, 2012.

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 have converted and reformatted the PPI document into a Medication Guide (MG), using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible

- ensured that the MG is consistent with the Prescribing Information (PI)
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- 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)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- There are inconsistencies in the wording of the pediatric risk information throughout the PI, such as in the Boxed Warning in Highlights and Full Prescribing Information, and Contraindications sections, thus making it difficult to clearly word the MG. We recommend that DGIEP address these inconsistencies in the PI so that the information is clear.
- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the MG is appended to this memorandum. Consult DMPP 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/

SHARON R MILLS
06/28/2012

BARBARA A FULLER
06/28/2012

LASHAWN M GRIFFITHS
06/28/2012

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

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

Memorandum

Date: June 28, 2012

To: Brian Strongin, Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
(DGIEP)

From: Kathleen Klemm, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

CC: Lisa Hubbard, Group Leader, DPDP, OPDP

Eunice Chung-Davies, Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP), OPDP

Subject: NDA 202811
OPDP labeling comments for LINZESS (linaclotide) capsules for oral use
(Linzess)

OPDP has reviewed the proposed Package Insert (PI) for LINZESS (linaclotide) capsules for oral use (Linzess) submitted for consult on January 18, 2012, and offers the following comments.

OPDP's comments on the PI are based on the proposed draft marked-up labeling titled, "Linaclotide Sponsor's Proposed PI 8-9-11.doc" sent via email from Stacy Barley on June 27, 2012.

OPDP's comments on the PI are provided directly in the marked-up document attached below. (Please note that we hid previous track changes in order for our comments to be more easily viewed.) We also note that some sections of the draft PI are not complete (i.e., sections 5 and 14); therefore, we are unable to comment on those sections.

OPDP's comments on the proposed patient labeling will follow under separate cover at a later date.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions regarding the PI, please contact Katie Klemm at (301) 796-3946 or kathleen.klemm@fda.hhs.gov.

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/s/

KATHLEEN KLEMM
06/28/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff Labeling Review

Date: June 12, 2012

From: Jeanine Best, MSN, RN, PNP, Senior Clinical Analyst
Elizabeth L. Durmowicz, MD, Medical Officer

Through: Hari Cheryl Sachs, MD, Team Leader
Melissa Tassinari, PhD, DABT, Acting Team Leader
Lisa Mathis, MD, OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

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

Subject: Pregnancy, Nursing Mothers, and Pediatric Use Labeling

Drug: linaclotide (Linzess)

NDA: 202-811

Sponsor: Ironwood Pharmaceuticals, Inc.

Indication (proposed): irritable bowel syndrome with constipation and chronic constipation

Dosage form: oral

Consult Question:

DGIEP requests PMHS review of the proposed Pregnancy, Nursing Mothers, and Pediatric Use subsections of Linzess labeling, with specific comment on labeling to address the finding of lethality in neonatal mice.

Materials Reviewed:

- Pharmacology Team Leader Review (April 17, 2012)

- Linzess Proposed Sponsor Labeling (submitted August 9, 2011 with DGIEP edits, June 4, 2012)

Introduction:

On August 9, 2011, Ironwood Pharmaceuticals, Inc submitted NDA 202-811 for Linzess (linaclotide) for the treatment of Irritable Bowel Syndrome with Constipation (IBS-C) and Chronic Idiopathic Constipation (CIC). The daily adult doses proposed for IBS-C and CIC are 290 mcg (approximately 4.8 mcg/kg for a 60 kg adult) and 145 mcg (approximately 2.4 mcg/kg for a 60 kg adult), respectively.

Background:

Linaclotide, a 14-amino acid synthetic peptide, binds to GC-C receptors in the intestine and stimulates the production of cGMP, which in turn stimulates secretion of chloride, bicarbonate, and fluid. In adult clinical pharmacology studies, Linzess is minimally absorbed and has low systemic availability following oral administration. The plasma concentrations of linaclotide and its active metabolite were found below the limit of quantitation at doses of 145 mcg or 290 mcg.

Animal Data

Oral administration of linaclotide in mice and rats stimulates gastrointestinal transit and intestinal secretion.

Although oral administration of linaclotide was generally well tolerated in rats, mice, and monkeys, markedly increased single-dose lethality was observed in neonatal/juvenile mice age 7 - 21 days, an age approximately equivalent to 1 - 23 months in humans. Adverse clinical signs and death occurred within 24 hr after the first dose, and the minimum lethal dose in 7-day old mice was 10 µg/kg, a dose approximately 2 times the maximum recommended adult dose.

The mechanism of lethality is unknown. To better characterize the nonclinical findings and evaluate the risk of linaclotide use in pediatric patients, DGIEP will require the Sponsor to conduct a series of nonclinical studies to elucidate the mechanism of lethality in neonatal/juvenile mice.

Pediatric Development:

The pediatric plan and the juvenile animal safety signal were discussed at the Pediatric Review Committee (PeRC) Meeting on May 9, 2012. The Division proposed to waive PREA studies for IBS-C in patients less than 6 years, as studies are not feasible secondary to too few patients to study. The Division also proposed to waive PREA studies for constipation in patients less than 6 months as the product fails to represent a meaningful therapeutic benefit and is unlikely to be used in a substantial number of patients. The PeRC was in agreement with the proposed age cohorts for the partial waivers and the rationales provided.

The Division proposed to defer the PREA studies for IBS-C in patients 6 years and older and the PREA studies for constipation in patients 6 months and older because the product

was ready for approval in adults. Although the PeRC agreed with a deferral of studies in the proposed age cohorts, the PeRC recommended that the deferral be based on the need for additional safety information, specifically additional nonclinical data to better characterize and understand the juvenile mouse lethality signal. The PeRC recommended that the animal studies be included in the PREA PMR.

The Division stated that Linzess contraindications will include Linzess use in pediatric patients and in nursing mothers. Given that the nonclinical safety signal is a potential concern, not an established clinical concern and that a contraindication would preclude development of linaclotide in all pediatric patients, the PeRC advised the Division to not include the juvenile animal safety concern as a contraindication but to include it in the Warning and Precautions and Pediatric Use sections of labeling. Dr. Mathis recommended consultation with the Maternal Health team for assistance with language for Pregnancy and Lactation labeling.

Reviewer Comment: If the Division contraindicates Linzess use in the pediatric population or in a subpopulation of pediatric patients, PREA required pediatric studies for that population must be waived (or partially waived) based on safety, i.e. there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups. Given that this represents a significant change from the pediatric plan discussed at the PeRC meeting in May 2012, the Division should return to PeRC for another discussion or write a memo to file explaining why the PeRC's recommendation to defer pediatric studies based on the need for additional safety data is not accepted.

PROPOSED SPONSOR LABELING (submitted August 9, 2011 with DGIEP edits, June 4, 2012)



Reviewer Comment: This contraindication was added by DGIEP.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C



Reviewer Comment: The Sponsor

DGIEP is proposing a pregnancy category C based on the available animal data.



*Reviewer Comment: The Sponsor proposed the following language for Pediatric Use:
“Safety and effectiveness of LINZESS in pediatric patients have not been established.”*

13. NONCLINICAL TOXICOLOGY



Reviewer Comment: Subsection 13.2 was added by DGIEP.

DISCUSSION AND CONCLUSIONS

Linzess acts locally on the luminal surface of the intestinal epithelium. Clinical pharmacology studies demonstrated minimal absorption with low systemic availability following oral administration. Oral bioavailability of linaclotide and its active metabolite were also extremely limited in rats, mice and monkeys. Markedly increased single-dose lethality was observed in neonatal/juvenile mice age 7 - 21 days, an age approximately equivalent to 1 - 23 months in humans. The mechanism of the lethality is unknown at this time, and DGIEP will require additional nonclinical studies to elucidate the mechanism of the lethality observed in neonatal/juvenile mice.

Because of the low bioavailability of linaclotide 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 linaclotide, fetal exposure and infant exposure through human milk is expected to be limited. However, the clinical implications of the lethality identified in juvenile mice are unclear, and labeling must clearly describe and summarize the juvenile animal data and communicate that linaclotide should not be used in pediatric patients until further data are available. Although the lethality identified in juvenile mice may not be relevant to older children and adolescents, if nonclinical data are not available to inform use in pediatric patients 2 years and older, warning about pediatric risk in all pediatric patients is reasonable.

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule published in May 2008. While the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule while still complying with current regulations. The first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount. The goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective communication tool for clinicians.

No human pregnancy data is available for Linzess. The Sponsor proposed a pregnancy

(b) (4)

DGIEP is recommending a pregnancy

category C because fetal harm was demonstrated, albeit at doses that caused maternal toxicity. An argument could be made for either category based on individual interpretation of the pregnancy labeling regulations (21 CFR 201.57(c)(9)(i). PMHS believes (b) (4)

(b) (4), PMHS would not be opposed to DGIEP classifying Linzess as a pregnancy category C drug, based on their interpretation of the science and regulations. The pregnancy categories will go away when the PLLR publishes; therefore, it is more important to appropriately format the pregnancy subsection and adequately explain available data. Linzess pregnancy labeling should be revised to include an overall summary paragraph regarding use of the drug in pregnancy, followed by the detailed description of the animal data.

Lactation should not be discouraged with maternal use of Linzess. No data is available on the excretion of linaclotide or its active metabolite in human milk; however, drug levels would be anticipated to be very low and likely not detectable in human milk due to the minimal absorption and low systemic availability of Linzess. Nursing Mothers labeling should contain the appropriate regulatory language as well as cross-reference to the Clinical Pharmacology section of labeling. The Sponsor should be encouraged to conduct a milk-only lactation study, using a validated assay, in order to appropriately inform the nursing mothers subsection of labeling.

Pediatric Use Labeling

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

Proposed Language for Pediatric Use:

“Safety and effectiveness of LINZESS in pediatric patients have not been established.” (b) (4)

For products that have not been studied in pediatric patients or do not have a pediatric indication, the language “Safety and effectiveness in pediatric patients have not been established” is acceptable and consistent with regulations. However, (b) (4) implies a contraindication to use, and is not appropriate in this situation (more below). In addition, the term (b) (4) is not recommended. The terms “pediatric population” or “pediatric patients” have specific regulatory definitions and define the pediatric age group from birth to 16 years. Instead of (b) (4) the Division may consider one of the following statements:

- LINZESS is not recommended for use in pediatric patients.
- LINZESS is not indicated for use in pediatric patients.

- Avoid LINZESS use in pediatric patients.

The addition of language to Pediatric Use to clarify that the clinical significance of the nonclinical animal findings is unclear is recommended. If a boxed warning is included in labeling, Pediatric Use should provide a cross reference not only to the Nonclinical Toxicology section, but also to the boxed warning.

Juvenile Animal Safety Signal Labeling:

As noted above, labeling must clearly explain and summarize the animal data, and clearly communicate that use in pediatric patients is to be avoided. The June 4, 2012 e-room version of labeling includes data or language to communicate the juvenile animal data and potential risks of pediatric use in the (b) (4) Warnings and Precautions, Pediatric Use, and Animal Toxicology and/or Pharmacology sections of labeling. DGIEP may also wish to consider including language to address the juvenile animal safety concern in the Indication and Usage (1), and the Patient Counseling Information (17) sections, and in the FDA-Approved Patient Labeling.

In the June 4, 2012 e-room version of labeling, there is an inconsistency between sections. The Highlights Section of labeling under Warnings and Precautions states (b) (4)

The Highlights and Full Prescribing sections of labeling must be consistent; specifically, the contraindications and warnings and precautions must be the same.

Per 21CFR201.57(c)(5), a contraindication must be a known hazard and not a theoretical possibility, and implies that use clearly outweighs any possible therapeutic benefit. A contraindication in the pediatric population should be supported by data. Given that the pharmacology toxicology review states that the studies demonstrating lethality in juvenile mice did not provide enough information to assess the cause of the lethality and that a PMR is being required to further define the risk and to help determine the reason for the risk, the data available do not appear to be adequate to determine if the risk of lethality is more than a theoretical concern.

However, if the Division believes that the data from the animal studies are enough to preclude the use of this product in the entire pediatric population, then the data must be included in labeling. As stated above, placing a contraindication in labeling would also preclude studies in the pediatric population. Hence, the Sponsor should be granted a full waiver under PREA. In this case, if the Division has determined that this product cannot be used in pediatrics, the utility of the additional animal studies would be unclear.

If the pharmacology toxicology reviewer believes that the safety concern is limited to the youngest animals and that the product would be safe in an older subgroup of the pediatric population, this will also need to be delineated in the label. In this case, additional nonclinical and clinical studies could be performed to support labeling in the relevant population.

The proposed contraindication, [REDACTED] (b) (4) provides the following information:

[REDACTED] (b) (4)

Although the juvenile animal data may not be sufficient to contraindicate use in the entire pediatric population, including this information in a boxed warning is recommended. Per 21CFR201.57(c)(5), serious animal toxicity may be the basis of a boxed warning in the absence of clinical data. Instead of [REDACTED] (b) (4) PMHS recommends that the Division consider a title that describes the risk, for example, Pediatric Risk (see below). Additional information to clearly explain and summarize the nonclinical findings and a statement that the clinical implications of the nonclinical findings are unclear is also recommended (more below). The warning and precaution should also cross-reference Pediatric Use (8.4).

The Animal Toxicology and/or Pharmacology section of labeling provides a brief summary of the neonatal mice data.

Additional sections of labeling in which data and/or language may be added to communicate the juvenile animal findings and instruction to avoid pediatric use include the Indications and Usage (1), and the Patient Counseling Information (17) sections, and the FDA-Approved Patient Labeling.

PMHS recommends including a “Limitations of Use” in the Indications and Usage section of labeling that states that Linzess is not indicated in pediatric patients. In addition, the Patient Counseling Information section and FDA-Approved Patient labeling has no information about use in pediatric patients, and should state that Linzess should not be used in children. Note: the Patient Counseling Information section of labeling is a section of the Prescribing Information and therefore is intended for prescriber/physician use, not patient use. This section of labeling should provide guidance and information for counseling patients on the safe and effective use of the drug.

PMHS RECOMMENDATIONS:

Juvenile Animal Safety Signal Labeling:

1. Consider the following:

A contraindication in the pediatric population should be supported with data.

If the pharmacology toxicology reviewer believes that the safety concern is limited to the youngest animals and that the product would be safe in an older subgroup of the pediatric population, this will need to be delineated in the label. In this case, additional nonclinical and clinical studies could be performed to

support labeling in the relevant population.

If the Division believes that the data from the animal studies are enough to preclude the use of this product in the entire pediatric population, then the data must be included in labeling. A contraindication would also preclude studies in the pediatric population, and the Sponsor should be granted a full waiver under PREA. In this case, the utility of the additional animal studies would be unclear.

Of note, the extent of concern based on the animal studies was not fully communicated to the PeRC. If the Division has reconsidered the gravity of the nonclinical results, and believes they support a contraindication, then the Division should return to PeRC for another discussion or write a memo to file explaining why the PeRC's recommendation to defer pediatric studies based on the need for additional safety data is not accepted.

2. Include a boxed warning to communicate that linaclotide should not be used in pediatric patients.
3. Include information from the boxed warning in the Warnings and Precautions section.
4. Revise the title of the warning to describe the risk identified in the juvenile animal findings, e.g. Pediatric Risk.
5. Add a limitation of use to Indications and Usage to state that Linzess is not indicated in pediatric patients.
6. Although the proposed language for the Pediatric Use subsection, i.e. "Safety and effectiveness in pediatric patients have not been established", is acceptable the language (b) (4) and the term (b) (4) should not be used. PMHS recommends one of the following statements:
 - LINZESS is not recommended for use in pediatric patients.
 - LINZESS is not indicated for use in pediatric patients.
 - Avoid LINZESS use in pediatric patients.
7. Include a summary of the juvenile animal data and language to communicate that the clinical significance of the nonclinical animal findings is unclear in the Pediatric Use subsection.
8. Clearly describe and summarize the juvenile animal data in Animal Toxicology and/or Pharmacology subsection.

9. Add that Linzess should not be used in children to the Patient Counseling Information section and FDA-Approved Patient labeling.

Pregnancy and Nursing Mothers Labeling:

Pregnancy

1. Re-format the pregnancy subsection to include an overall summary paragraph regarding use of the drug in pregnancy, followed by the detailed description of the animal data, for consistency with the proposed Pregnancy and Lactation Labeling Rule while complying with the current pregnancy labeling regulations. Classify Linzess as a pregnancy category ^(b)₍₄₎ drug based on the available animal data and interpretation of the pregnancy labeling regulations; however, PMHS would not be opposed to DGIEP classifying Linzess as a pregnancy category C drug, as an argument could be made for either category based on individual interpretation of the data and the pregnancy labeling regulations.

Nursing Mothers

1. Do not discourage lactation during treatment with Linzess. Drug levels would be anticipated to be very low and likely not detectable in human milk due to the minimal absorption and low systemic availability of Linzess.

Additional Recommendations:

1. Encourage the Sponsor to conduct a milk-only lactation study, using a validated assay, in order to appropriately inform the nursing mothers subsection of labeling.
2. Given the complexities of Linzess labeling, schedule a meeting with PMHS to specifically discuss pregnancy, nursing mothers, and pediatric use labeling.

PMHS PROPOSED LABELING:

The following are the PMHS recommendations for pregnancy, nursing mothers, and pediatric use labeling.

HIGHLIGHTS OF PRESCRIBING INFORMATION

WARNING: PEDIATRIC RISK

See full prescribing information for complete boxed warning.

- **Avoid Use in Pediatric Patients**
- **Juvenile Animal Lethality**
In nonclinical studies, administration of a single, clinically relevant oral dose of linaclotide was lethal in young mice. (5.1, 13.2)

----- **WARNINGS AND PRECAUTIONS** -----

Pediatric Risk: Juvenile Animal Lethality. Avoid Use in Pediatrics (5.1, 8.4, 13.2)

-----**Use in Specific Populations**-----

Pediatric Use: Not indicated; Avoid use (8.4)

FULL PRESCRIBING INFORMATION

WARNING: PEDIATRIC RISK

- **Avoid Use in Pediatric Patients**
- **Juvenile Animal Lethality**
In nonclinical studies, administration of a single, clinically relevant oral dose of linaclotide was lethal in young mice. The deaths were identified in mice with ages approximately equivalent to human infants and children 1 month to 23 months. Death in the animals occurred within 24 hours of linaclotide administration [see Warnings and Precautions (5.1) and Nonclinical Toxicology (13.2)]

1 INDICATIONS and USAGE

1.1 Irritable Bowel Syndrome with Constipation

LINZESS (linaclotide) is indicated in adults for the treatment of irritable bowel syndrome with constipation (IBS-C).

1.2 Chronic Idiopathic Constipation

LINZESS is indicated in adults for the treatment of chronic idiopathic constipation (CIC).

Limitations of Use: Not Indicated in Pediatric Patients

5 WARNINGS AND PRECAUTIONS

5.1 Pediatric Risk

Juvenile animal lethality was observed in nonclinical studies. Administration of a single, oral dose of linaclotide (two times the maximum adult dose) was lethal in young mice. The deaths were identified in mice with ages approximately equivalent to human infants and children 1 month to 23 months. Death occurred within 24 hours of linaclotide administration. Avoid LINZESS use in pediatric patients [see *Use in Specific Populations (8.4) and Nonclinical Toxicology (13.2).*]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category ^(b)₍₄₎

Risk Summary

There are no adequate and well-controlled studies with LINZESS in pregnant women. In animal developmental studies, adverse fetal effects were observed only with maternal toxicity which occurred at doses of linaclotide much higher than the maximum recommended human dose. LINZESS should be used during pregnancy only if clearly needed.

Animal Data

The potential for linaclotide to cause teratogenic effects was studied in rats, rabbits and mice. Oral administration of up to 100,000 mcg/kg/day in rats and 40,000 mcg/kg/day in rabbits produced no maternal toxicity and no effects on embryo-fetal development. In mice, oral dose levels \geq 40,000 mcg/kg/day produced severe maternal toxicity including death, reduced fetal weights, effects on fetal morphology, and reduced gravid uterine weight. Oral doses of 5000 mcg/kg/day did not produce maternal toxicity or any adverse effects on embryo-fetal development in mice.

The maximum recommended human dose is approximately 5 mcg/kg/day, based on a 60-kg bodyweight. Limited systemic exposure to linaclotide was achieved at the tested dose levels in animals, whereas minimal absorption was found in humans. Therefore, animal and human doses should not be compared directly for evaluating relative exposure.

Reviewer Comment: If DGIEP chooses to classify this product as a pregnancy category C, then pregnancy category regulatory language, "Linzess should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus," should be substituted for the pregnancy category B regulatory language ("LINZESS should be used during pregnancy only if clearly needed").

8.3 Nursing Mothers

It is not known whether linaclotide is excreted in human milk; however, linaclotide and its active metabolite are not measurable in plasma following administration of the recommended clinical doses [see *Clinical Pharmacology (12.3)*]. Caution should be exercised when LINZESS is administered to a nursing woman.

8.4 Pediatric Use

See Boxed Warning

Safety and effectiveness of LINZESS in pediatric patients have not been established. LINZESS is not indicated in pediatric patients and use in the pediatric patient population should be avoided. Lethality was observed in juvenile mice after administration of a single, clinically relevant oral dose of linaclotide. The mechanism of death and the clinical significance of the juvenile animal findings are unclear [see *Nonclinical Toxicology (13.2)*].

13. NONCLINICAL TOXICOLOGY

13.2 Animal Toxicology and/or Pharmacology

Linaclotide was lethal at 10 mcg/kg/day PO in neonatal mice after administration of 1 or 2 daily doses, starting on post partum day 7. Lethality was also observed in juvenile mice after a single oral administration on post partum day 14 (100 mcg/kg) and post partum day 21 (600 mcg/kg). The mechanism for the lethality is unknown.

The maximum recommended human dose is approximately 5 mcg/kg/day, based on a 60-kg bodyweight. Limited systemic exposure to linaclotide was achieved at the tested dose levels in animals, whereas minimal absorption was found in humans. Therefore, animal and human doses should not be compared directly for evaluating relative exposure.

17 PATIENT COUNSELING INFORMATION

- Remind patients that LINZESS is not indicated for use in children. Studies in which linaclotide was administered to young animals at clinically relevant doses resulted in death.

FDA-Approved Patient Labeling

Who should not take LINZESS?

You should not take LINZESS if:

- You are currently having or frequently have diarrhea.
- A doctor has told you recently that you have a bowel blockage (intestinal obstruction).

LINZESS should not be used in children. It may cause harm.

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/s/

JEANINE A BEST
06/12/2012

ELIZABETH L DURMOWICZ
06/12/2012

MELISSA S TASSINARI
06/13/2012

HARI C SACHS
06/13/2012
I concur with these recommendations

LISA L MATHIS
06/14/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: April 6, 2012

TO: Brian Strongin, Regulatory Project Manager
Erica Wynn, M.D., Medical Officer
Division of Gastroenterology and Inborn Errors Drug Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Division Director (Acting)
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202811

APPLICANT: Forest Laboratories, Inc,

DRUG: LINZESS[®] (linaclotide)

NME: Yes

THERAPEUTIC
CLASSIFICATION: Standard Review

INDICATION: Treatment of irritable bowel syndrome (IBS) and/or Chronic
Constipation (CC)

CONSULTATION REQUEST DATE: October 24, 2011

DIVISION ACTION GOAL DATE: June 9, 2012

PDUFA DATE: June 9, 2012

I. BACKGROUND:

The Applicant submitted this NDA for the use of LINZESS® to support an indication for the treatment of subjects with Irritable Bowel Syndrome with Constipation (IBS-C) and Chronic Constipation (CC).

The following four pivotal studies were submitted and inspected in support of the indication.

Protocol LIN-MD-01, entitled “A Phase III, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Trial of Linaclotide Administered Orally for 12 Weeks in Patients With Chronic Constipation”, and

Protocol LIN-MD-31, entitled “Parallel-Group Trial Of Linaclotide Administered Orally For 12 Weeks Followed By a 4-Week Randomized Withdrawal Period In Patients With Irritable Bowel Syndrome With Constipation”, and

Protocol MCP-103-302, entitled “A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial of Linaclotide Administered Orally for 26 Weeks in Patients with Irritable Bowel Syndrome with Constipation”, and

Protocol MCP-103-303, entitled “A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Trial of Linaclotide Administered Orally for 12 Weeks Followed by a 4-Week Randomized Withdrawal Period in Patients with Chronic Constipation”.

Protocol LIN-MD-01

The objective of this randomized, double-blind, placebo-controlled, parallel-group study was to determine the efficacy and safety of linaclotide administered to subjects with CC. The test drug product, linaclotide 150 or 300 µg/day, or placebo (1:1:1 ratio), was administered orally for 12 weeks to subjects with CC. Subjects used an interactive voice response system (IVRS) to record daily bowel habits, symptom severity score, use of per-protocol rescue medications, and their assessment of degree of relief of constipation symptoms. The primary efficacy parameter was the 12-week complete spontaneous bowel movement (CSBM) overall responder. A 12-week CSBM overall responder was a subject who was a CSBM weekly responder for at least 9 of the 12 weeks of the treatment period.

Protocol LIN-MD-31

The objective of this multicenter, randomized, double-blind, placebo-controlled, parallel-group, 12-week trial was to determine the efficacy and safety of linaclotide administered to subjects with IBS-C. Subjects received either a 300 µg linaclotide oral capsule or matching placebo. Subjects used an IVRS to record daily bowel habits, symptom severity assessments, and use of per-protocol rescue medications. The primary efficacy assessments were abdominal pain (AP) and bowel movements (BMs) that met the criteria for CSBMs, based on the IVRS information. There were four primary efficacy parameters that were based on AP and CSBM assessments.

Protocol MCP-103-302

The objective of this multicenter, randomized, double-blind, placebo-controlled, parallel-group trial was to determine the efficacy and safety of linaclotide administered to subjects with IBS-C. Subjects were to be randomized to either the active test article or to placebo and used the IVRS to record daily bowel habits, symptom severity assessments, and use of per-protocol rescue medications. The primary efficacy parameters consisted of two components: 1) AP at its Worst and 2) CSBMs.

Protocol MCP-103-303

The objective of this multicenter, randomized, double-blind, placebo-controlled, parallel-group study was to determine the efficacy and safety of linaclotide administered to subjects with CC. Subjects were randomized to linaclotide at 133 ug or 266 ug or to placebo. Subjects used the IVRS to record daily bowel habits, symptom severity assessments, and use of per-protocol rescue medications. The primary efficacy parameter was the 12-week CSBM overall response.

The sites below were selected for inspection because of the following reasons:

Site 5 was selected for Protocols MCP-103-302 and MCP-103-303 due to high enrollment and efficacy results.

Site 10 was selected for Protocols MCP-103-302 and MCP-103-303 due to high enrollment and efficacy results.

Site 61 was selected for Protocol LIN-MD-01 due to high enrollment, significant efficacy results, and an increased average number of adverse events.

Site 95 was selected for Protocols LIN-MD-01 and LIN-MD-31, due to relatively high enrollment and efficacy results.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects	Inspection Dates	Final Classification
Raj Bhandari, M.D. 608 Grammont Street Delta Research Partners Monroe, LA 71201-7517	MCP-103-302/ Site #10/ 36 subjects and MCP-103-303/ Site #10/ 37 subjects	17-20 Jan 2012	NAI
Arthur Poch, M.D. Louisiana Research Center, L.L.C. 3217 Mable Street Shreveport, LA 71103	MCP-103-302/ Site #5/ 35 subjects and MCP-103-303 Site #5/ 37 subjects	30 Jan – 1 Feb 2012	VAI
Mark A. Ringold, M.D. New River Valley Research Institute 110 Akers Farm Road Christiansburg, VA 24073	LIN-MD-01/ Site #61/ 17 subjects and LIN-MD-31 Site #61/ 10 subjects	9-17 Jan 2012	VAI
Curtis S. Horn, M.D. Quality Research, Inc. 303 West Sunset Road, Suite 102 San Antonio, TX 78209	LIN-MD-01/ Site #95/ 22 subjects and LIN-MD-31 Site #95/ 29 subjects	30 Jan-13 Feb 2012	VAI
David Ford, M.D. Toronto Digestive Disease Associates, Inc., Suite 225 4600 Highway 7 Vaughan, ON L4L 4Y7 Canada	LIN-MD-01/ Site #8/ 13 subjects and LIN-MD-31 Site #8/ 37 subjects	6-10 Feb 2012	VAI Pending final classification
Dr. Marco Taglietti Forest Research Institute, Inc. (sponsor) Harborside Financial Center Plaza V, 19 th Floor Jersey City, NJ 07311	MCP-103-302 MCP-103-303 LIN-MD-01 LIN-MD-31	23 Jan-14 Feb 2012	VAI Pending final classification

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

1. Bal Raj Bhandari, M.D.
608 Grammont Street
Delta Research Partners
Monroe, LA 71201-7517

- a. **What was inspected:** At this site, for Protocol 302, 52 subjects were screened, 36 subjects were enrolled, and 28 subjects completed the study. For Protocol 303, 42 subjects were screened, 37 subjects were enrolled, and 29 subjects completed the study. The records of 20 subjects for each protocol were reviewed. The records reviewed included, but were not limited to, all informed consent forms for both studies, medical histories, laboratory test results, concomitant medications, inclusion/exclusion criteria, adverse events, protocol deviations, IRB, sponsor, and monitor correspondence, financial disclosure, and test article accountability.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations. With regard to the verification of primary efficacy data, the FDA investigator was erroneously informed by the clinical site during conduct of the inspection that the CDs provided by the sponsor to the clinical site contained only eCRF data. Only after the conclusion of the inspection, during follow-up communication with the site, was the investigator informed that a CD of IVRS diary responses (the basis for the determination of efficacy) had been sent to the site and was available for inspection.
- c. **Assessment of data integrity:** The primary efficacy data was not verified as noted above. Otherwise, the study appears to have been conducted adequately. The medical officer may wish to consider the limitations, if any, resulting from a lack of verification of the primary efficacy data at this site.

2. Arthur Poch, M.D.
Louisiana Research Center, L.L.C.
3217 Mable Street
Shreveport , LA 71103

- a. **What was inspected:** At this site, for Protocol 302, 59 subjects were screened and 35 subjects completed the study. For Protocol 303, 62 subjects were screened and 35 subjects completed the study. All screened subjects signed consent forms. The records of 20 subjects for each protocol were reviewed. The records reviewed included, but were not limited to, IRB and sponsor correspondence, financial disclosure, drug accountability, adverse events, subject records, source documents, and case report forms.

- b. General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection. Observations included a lack of the investigator's name and date on inclusion/exclusion documents for Subject 3020, the enrollment of subject 3061 into the study by an individual not delegated that authority, and physical examinations conducted on 13 subjects (Subjects 3001, 3003, 3004, 3005, 3006, 3007, 3008, 3010, 3012, 3013, 3014, 3016, and 3017) by individuals who had not received documented protocol-specific training prior to conducting the examinations. Dr. Poch's written response of February 15, 2012, was adequate, stating that appropriate documentation and training practices would be implemented to address these deficiencies.

Primary endpoint data were entered by study subjects into the IVRS system. According to our FDA investigator, this data was not returned to the site in a CD or other format that could be verified against line listings of the primary efficacy data.

- c. Assessment of data integrity:** The inability to verify the primary efficacy data at the site was discussed with the review division. The medical officer may wish to consider the limitations, if any, resulting from the inability to verify the primary efficacy data at this site.

The endpoint for the studies was derived from IVRS daily diary response data which the CRO forwarded to the Sponsor. Based upon OSI review of the process whereby data was collected by the CRO and transferred to the Sponsor, there is no suggestion that the data was not collected appropriately. Additionally, no other significant issues have been identified during the inspections. Therefore, an inspection of the CRO at this time does not appear to be warranted. This was discussed with the review division, and the review division determined that an inspection of the CRO was not necessary. Given that there is no suggestion that the data were not collected adequately, an inspection of the CRO is not planned.

3. Mark A. Ringold, M.D.
New River Valley Research Institute
110 Akers Farm Road
Christiansburg, VA 24073

- a. What was inspected:** At this site, both Protocols LIN-MD-01 and LIN-MD-31 were inspected. For Protocol LIN-MD-01, 23 subjects were screened and 17 subjects completed the study. For Protocol LIN-MD-31, 20 subjects were screened and eight subjects completed the study. An audit of all of the subjects' records was conducted for Protocol 01 and of nine of the subject records for Protocol 31. Signed informed consent forms were present for all enrolled subjects for both studies. Records reviewed included, but were not limited to, training documentation, sponsor/monitor/IRB correspondence, source documents (included with the source documents were two CDs for each of the two studies, one containing copies of the eCRFs and the other containing the IVRS information), study responsibility delegation logs, case report forms, inclusion/exclusion criteria, laboratory results, concomitant medications, patient self-assessment records and questionnaires, test article storage temperature logs, instrumentation calibration records, financial disclosure forms, and test article accountability.

- b. General observations/commentary:** A Form FDA 483 was issued. Observations included, but were not necessarily limited to, a lack of training documentation, inadequate washout periods or documentation thereof for three subjects, evaluation of a chronic condition (endometriosis) potentially affecting randomization to the study for one subject, and the omission of an adverse event (nail breakage) from the adverse event log. Dr. Ringold's written response of February 6, 2012, adequately addresses each of these issues.
- c. Assessment of data integrity:** Follow up communications with the FDA investigator indicated that IVRS diary data was spot-checked for accuracy against case report forms and line listings for those subjects whose records were reviewed for Protocol LIN-MD-31. Similar spot-checks appear to have been conducted for Protocol LIN-MD-01. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

4. Curtis S. Horn, M.D.
Quality Research Inc.
303 West Sunset Road, Suite 102
San Antonio, TX 78209

- a. What was inspected:** At this site, both Protocols LIN-MD-01 and LIN-MD-31 were inspected. For Protocol LIN-MD-01, 43 subjects were enrolled, 22 subjects were randomized, and 20 subjects completed the study. For Protocol LIN-MD-31, 82 subjects were enrolled, 29 subjects were randomized, and 24 subjects completed the study. An audit of 20 subjects' records was conducted for each of the above two protocols. Signed informed consent forms were present for all enrolled subjects for both studies. Records reviewed included, but were not necessarily limited to sponsor/monitor/IRB correspondence, source documents, case report forms, and test article storage conditions. Follow up communications with the FDA investigator indicated that primary efficacy data (i.e. IVRS diary data) was verified using CDs sent to the clinical site by the sponsor.
- b. General observations/commentary:** A Form FDA 483 was issued with multiple observations for both studies. The bulk of the observations concerned the use of protocol-prohibited medications. These observations were documented, forwarded to the study medical monitor, and reported in the NDA line listings. Other observations included, a failure to conduct triplicate ECGs for Subject 3103 at Visit 6 (triplicate ECGs were performed at subsequent visits), inclusion of Subject 0113 with an exclusionary family history of colon cancer, failure to collect a PK sample at visit 5 for Subject 3123, failure to perform rectal examinations at the screening visit for Subjects 3137, 3158, and 3167 (for Subject 3137 conflicting information existed regarding the scheduling of a colonoscopy, for Subject 3158 the missed exam was conducted at Visit 2 and was unremarkable, and for Subject 3167, a colonoscopy conducted seven days previously rendered a rectal exam unnecessary in the investigator's opinion), a lack of a urine drug screen at the screening visit for Subject 3138 was subsequently performed at Visit 2, and three observations of excursions in refrigerator temperatures (the sponsor was notified regarding two of these excursions [including the excursion to the maximum temperature of 49°F] and cited data in Report PRO-RPT-PDV-00205 to state that the product quality would not be affected). Dr. Horn submitted an undated written response received by OSI on March 1, 2012,

that satisfactorily addressed these observations and noted that additional training and documentation had been implemented to avoid any recurrence of similar issues in future trials.

- c. **Assessment of data integrity:** The above observations appear to be isolated in nature and most were addressed and corrected in the course of the study; thus, these issues would not appear to have a significant effect on the analyses of safety and/or efficacy. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

5. David Ford, M.D.

Toronto Digestive Disease Associates, Inc., Suite 225
4600 Highway 7
Vaughan, ON L4L 4Y7
Canada

- a. **What was inspected:** At this site, the records for nine subjects each were audited for Protocol LIN-MD-01 and Protocol LIN-MD-31. For Protocol LIN-MD-01, 23 subjects were screened, 13 subjects were enrolled, and 11 subjects completed the study. For Protocol LIN-MD-31, 62 subjects were screened, 37 subjects were enrolled, and 33 subjects completed the study. Signed informed consent forms were present for all subject records reviewed. Other records reviewed included, but were not necessarily limited to, financial disclosure statements, duty delegation rosters, adverse events, IVRS diary data (primary efficacy data), and records of receipt, storage and accountability of the test article.
- b. **General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection. Observations included, administration of informed consent to all subjects in both studies by individuals not delegated that responsibility in the Delegation of Duties Log. This responsibility was delegated to research nurses/study coordinators in the site's SOP, and these individuals routinely obtained informed consent from subjects. These individuals were retrospectively assigned responsibility, in writing, to obtain informed consent. This inspection noted no unreported adverse events; however, adverse events were initially assessed by study nurses/coordinators who were not authorized to do so in the Delegation of Duties Log. Adverse events were then assessed by study physicians though not always in a timely manner. Review of test article storage conditions noted that test articles for different studies were stored in a refrigerator with minimal physical separation; only a single incident of incorrect test article dispensation was noted (Subject 3159 received bottle 90696 instead of bottle 78096). This incident was reported approximately four months later when noticed by a study monitor. This incident was attributed to extremely small lettering on the bottles, not storage conditions. Study Supply Accountability Logs had many instances in which source data was crossed out and transcribed elsewhere in the log. Though the FDA investigator noted that this transcription made drug reconciliation very difficult, the investigator did not note any dispensation errors (other than the one reported above), and these findings are unlikely to significantly impact data reliability.

- c. Assessment of data integrity:** The observations noted above constitute deviations from Good Clinical Practice; however, a comparison of the IVRS primary efficacy data against line listings for multiple subjects in both studies did not reveal any data discrepancies. Therefore, despite the presence of some objectionable conditions and/or practices, the study appears to have been conducted adequately, and the data appear acceptable in support of the respective indication.

Note: The observations noted above are based on a review of a draft of the Establishment Inspection Report (EIR). An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

6. Dr. Marco Taglietti
Forest Research Institute, Inc. (sponsor)
Harborside Financial Center
Plaza V, 19th Floor
Jersey City, NJ 07311

- a. What was inspected:** The sponsor's role in the conduct of the following four studies was inspected: LIN-MD-01, LIN-MD-31, MCP-103-302, and MCP-103-303. Issues covered included the firm's history, organization, personnel responsibilities, the training program for principal investigators involved in these four studies, and the training and experience of the firm's clinical research associates (CRAs). Other study elements reviewed included, but were not necessarily limited to, the protocol, IRB involvement, monitoring procedures and activities, subject records, Form FDA 1572s, investigator qualifications, test article integrity and accountability, data collection and handling, adverse event documentation, quality assurance, and annual reporting.
- b. General observations/commentary:** A 21 CFR Part 11-validated IVRS was used for data collection. Study coordinators and investigators had read-only access to this data via the study's official clinical web-site; however, the protocols did not require the sites to track subject progress. Data was collected by the CRO, ICON, who was responsible for alerting sites of subject non-compliance with the daily reporting requirements. Study data was stored on duplicate CDs sent to Forest: one copy to remain with the sponsor and the other to be forwarded to the clinical site for archival purposes. The FDA investigator noted that there were multiple primary and secondary efficacy assessments for the various studies. Because each subject was to address each bowel movement in detail with respect to parameters such as completeness of evacuation, bloating, frequency, stool consistency, severity of straining, constipation and abdominal discomfort, it was possible to generate a data file of more than 3,600 discrete data points over the course of the study. The FDA investigator requested and received raw data files for four subjects, each one representing a subject in each of the four audited studies. This data was compared with the line listings in the final clinical study report and no deficiencies were noted.

A Form FDA 483 was issued noting that Subject 0101 was enrolled in Protocol LIN-MD-01 despite having been previously enrolled in Protocol MCP-103-201 (prior enrollment in a linaclotide study was an exclusion criterion). Data generated by this subject was subsequently deleted from the efficacy analysis. Similarly, Subject 3004 in Protocol MCP-103-303 was previously enrolled in Protocol MCP-103-201. Other observations on the Form FDA 483 included not following the applicable SOP for

drug accountability record management for Protocols MCP-103-302 and 303, not following the established monitoring plan for Protocol MCP-103-303 in that at least one visit for Site 045 was four weeks outside the established timeframe for such visits, and not following an SOP requiring that action items from one report be carried over into the subsequent report resulting in a monitoring visit for Site #095 for Protocol LIN-MD-01 that was two weeks outside the established timeframe.

- c. Assessment of data integrity:** These studies generated exceptionally large amounts of data per subject. As a result, data verification was problematic. This inspection reviewed monitoring practices, data collection and handling, IVRS data flow, and raw data files, to assess the overall quality of data generation, collection, and handling. No deficiencies were noted with respect to the sponsor's treatment of the data. The observations noted above would not appear to adversely affect the evaluation of safety and/or efficacy. The studies appear to have been conducted adequately, and the data submitted by the sponsor appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Bhandari, Poch, Ringold, Horn, and Ford, were inspected in support of this NDA. A sponsor inspection of Forest Laboratories, Inc., was also conducted. Dr. Bhandari's site was not issued a Form FDA 483. The remaining clinical sites of Drs. Poch, Ringold, Horn, and Ford and the sponsor were issued Form FDA 483s. The review division may wish to consider the limitations, if any, resulting from a lack of verification of the primary efficacy data at Drs. Bhandari and Poch's clinical sites. To a limited extent, primary efficacy data were verified at the sites of Drs. Ringold, Horn, and Ford. The inspectional observations made at those clinical sites receiving Form FDA 483s would not appear to have a substantive effect on safety and/or efficacy evaluations. The inspection of the sponsor indicated that its procedures for collecting, handling, and archiving the large amounts of data generated by these studies appear to be adequate. Other observations noted during the inspection of the sponsor would not appear to have a substantive effect on safety and/or efficacy evaluations. Overall, the data generated by the clinical sites and submitted by the sponsor appear adequate in support of the respective indication.

Note: The observations noted above for Dr. Ford's site are based on a review of a draft of the Establishment Inspection Report (EIR). An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

{See appended electronic signature page}

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

/s/

ROY A BLAY
04/06/2012

JANICE K POHLMAN
04/06/2012

TEJASHRI S PUROHIT-SHETH
04/06/2012

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

Office of Surveillance and Epidemiology Consult

Date: March 21, 2012

To: Donna Griebel, MD, Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III, CDER

Division Director Solomon Iyasu, MD, MPH, Division Director
Division of Epidemiology I (DEPI I),
Office of Pharmacoepidemiology and Epidemiology (OPE)
OSE, CDER

Through Tarek Hammad, MD, PhD, Deputy Division Director,
DEPI I, OPE, OSE, CDER

From: Carolyn McCloskey, MD, MPH, Epidemiologist
DEPI I, OPE, OSE, CDER

Drug Name(s): Linzess (linaclotide)

Subject: Incidence of Gallbladder Disease in the US &
Expected Number in Linaclotide Studies

Application Type/Number: NDA 202-811

Submission Number: NA

Applicant/sponsor: Ironwood Pharmaceuticals, Inc.

OSE RCM #: 2012-103

TSI #: NA

CONTENTS

EXECUTIVE SUMMARY	3
1 Background.....	3
1.1 Regulatory History	4
2 METHODS AND MATERIALS.....	4
2.1 Data and Information Sources	4
2.2 Criteria used.....	4
2.3 Analysis techniques	4
3 RESULTS	5
3.1 Sponsor Use of Incidence Rates From Corazziari et al (2008).....	5
3.2 Other Incidence Rates from the Literature	7
4 DISCUSSION.....	9
5 CONCLUSIONS.....	10
6 RECOMMENDATIONS.....	10
7 REFERENCES	11

EXECUTIVE SUMMARY

Linaclotide is under a New Drug Application (NDA) review and has not been approved. The sponsor's safety summary of linaclotide (Linzess) reported 20 cases of gallbladder disease in the linaclotide-exposed patients and found them to be less than the expected number, 21, based on incidence rates of gallstones and cholecystectomies in an Italian study by Corazziari et al (2008). Questions presented by DGIEP are if the incidence rates and the expected number are accurate reflections of the rate in the general and irritable bowel syndrome (IBS) populations in the US.

After multiple PubMed searches for information on gallbladder disease incidence rates in the general US and the IBS populations, the Corazziari study is best suited for the linaclotide data even though there are multiple differences between them. Given the conservative estimates from Corazziari study, the linaclotide gall bladder safety finding is reassuring at this time.

1 BACKGROUND

The Division of Gastroenterology and Inborn Errors Products (DGIEP) requested the Office of Surveillance and Epidemiology (OSE) to assess the accuracy of 1) the quoted incidence rate for gallbladder disease in the US population and 2) the calculation of expected events from a report by Ironwood Pharmaceuticals, Inc. titled "Linaclotide: Summary of Clinical Safety (Module 2.7.4), Integrated Summary of Safety (Module 5.3.35.3), 01 Jul 2011" (called 'the Safety Report' throughout this memorandum).

Linaclotide is under a New Drug Application (NDA) review and has not been approved. The sponsor, Ironwood Pharmaceuticals, Inc., reported that the number of "gallstone disease" cases in their Phase 3 placebo-controlled trials and long-term safety studies (n=20) were less than the expected number of cases (n=21.2) (page 132 of the Safety Report).

The proposed indication for linaclotide is for the treatment of chronic constipation (CC) and for irritable bowel syndrome with constipation (IBS-C). Linaclotide stimulates the guanylate cyclase receptor subtype C (GC-C) found on the apical surface of the epithelial cells in the gastrointestinal (GI) tract from the duodenum to the rectum (Safety report, reference Li 2009). The end result is an increase in intestinal fluid secretion and intestinal transit, and, in animals, a decrease in visceral pain.

Chronic constipation (CC), defined by the Rome Criteria (Rome Foundation; references on page 21 of Safety Report), includes bowel and abdominal symptoms such as straining, hard stools, abdominal discomfort, infrequent bowel movements (BM), bloating, sense of incomplete evacuation, and abdominal pain in the absence of structural, biochemical, or organic abnormalities or diseases.

Irritable bowel syndrome (IBS), a functional bowel disorder, consists of abdominal pain and discomfort with altered defecation thought to be related to visceral hypersensitivity, altered GI motility and psychosocial factors. IBS has four subtypes: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), IBS with mixed symptoms of constipation and diarrhea (IBS-M), and unsubtyped IBS (IBS-U).

Gallbladder disease is more common in Western industrialized countries as are cholecystectomies, the surgical removal of the gallbladder most often for gallstones. Most gallbladder diseases are related to gallstones or cholelithiasis. Other diseases of the gallbladder include cholecystitis, acalculous biliary pain, choledocholithiasis & cholangitis, sclerosing cholangitis, AIDS cholangiopathy, and tumors of the gallbladder and bile ducts. (Merck Manual 19th Ed)

Gallstones may be symptomatic with abdominal pain but about 20% - 80% are asymptomatic and often not discovered until necropsy. (Shaffer 2006 & Merck Manual) The most common type of gallstone in the US is made of cholesterol and is usually found in the gallbladder rather than the biliary ducts. Gallstones are usually found in adults with an increasing prevalence with increasing age. A greater number of women have gallstones compared to men but this difference decreases with increasing age over 65 years. (Friedman 1966)

The prevalence of gallstones and cholecystectomy in the US in the general population or whites for females and males ranges from 16.6-20.2% and 7.9-8.6% respectively; for Mexican Americans it is 26.7% and 8.9%; for black Americans it is 13.9% and 5.3%; and for American Indians (13 tribes) it is 64.1% and 29.5%. In Europe the prevalence tends to be a bit lower, for females and males: Italian studies report 6.3-14.4%, range 0-31.6% & 6.7-8.2%, range 0-19.4%; Swedish study 11-25% & 4-15%. (Shaffer 2005 & Stinton 2010)

Patients with IBS may have more cholecystectomies, possibly secondary to abdominal pain thought to be due to gallbladder disease. In a survey study in a 1997 UK population of IBS patients, the age- and sex-adjusted prevalence for females, males and overall were 22.6% (95% confidence interval (CI) 20.8-24.8%), 10.5% (8.9-12.1%), and 16.7% (15.4-18.0%) compared to the adjusted prevalence of cholecystectomies in females, males, and overall of 3.9% (3.0-4.8%), 1.2% (0.7-1.8%), and 2.6% (2.1-3.0%). (Kennedy 2000 & Shaffer 2006)

Most studies do not address the incidence rates of gallbladder diseases or gallstones because the asymptomatic nature of most gallstones makes them difficult to identify and to follow a population “free” of gallbladder disease. Studies on gallbladder surgery or cholecystectomy, a defined procedure, are reported in the literature. The first laparoscopic cholecystectomy was in 1987 and subsequently their use increased into the 1990’s. This resulted in an increase of outpatient and ambulatory laparoscopic cholecystectomies and concomitant decrease of inpatient surgeries for open cholecystectomies. (National Center for Health Statistics 2009, Shaffer 2005, Urbach 2005, Everhart 2009)

1.1 REGULATORY HISTORY

A mid-cycle meeting was held January 8, 2012. The review teams were on track.

2 METHODS AND MATERIALS

2.1 DATA AND INFORMATION SOURCES

Sources from DGIEP and Ironwood Pharmaceutical, Inc.:

- Ironwood Pharmaceuticals, Inc and Forest Research Institute, Inc. Lanaclootide: Summary of Clinical Safety (Module 2.7.4) & Integrated Summary of Safety (Module 5.3.5.3), 01 Jul 2011.
- Corazziari E, Attili AF, Angeletti C, De Santis A. Gallstones, cholecystectomy and irritable bowel syndrome (IBS), MICOL population-based study. *Digestive and Liver Disease*. 2008;40:944-950.
- Higgins PDR, Johanson JF. Epidemiology of constipation in North America: A systematic review. *American Journal of Gastroenterology*. 2004:750-759.

Medical literature identified via PubMed searches are referenced.

2.2 CRITERIA USED

An effort to identify the incidence of gallbladder disease in the US and specifically in IBS was undertaken by using PubMed to search the English language literature for the incidence of gallbladder disease or gallbladder stones or data that could be used to calculate an incidence rate.

2.3 ANALYSIS TECHNIQUES

Where applicable, calculations of the incidence of gallbladder disease were done (cases/persons over time or cases/person-year (PY), and stratified by gender if possible.

3 RESULTS

3.1 SPONSOR USE OF INCIDENCE RATES FROM CORAZZIARI ET AL (2008)

The Italian study reported by Corazziari et al (2008) and referenced by the sponsor to calculate reference incidence rates of gallbladder disease in males and females, was a population-based cross-sectional survey study with the second survey done 7.8 ± 1.0 years later on gallstone-free subjects from the first study who had a physical examination and abdominal ultrasonography in order to determine incidence of gallstone disease. According to Corazziari et al (2008), the multivariate adjusted prevalence odds of gallstones and cholecystectomy for gallstone disease were significantly higher in IBS than in controls:

- Gallstones: females OR 3.7, 95% confidence interval (CI) 3.2-4.2 and males OR 3.3, CI 2.7-4.0.
- Cholecystectomy: females OR 10.8, CI 8.3-13.9 and males OR 8.3, CI 5.7-12.11.

However, for those who did not know their gallbladder status, the adjusted prevalence of gallstones detected at ultrasonography in IBS subjects was: females OR 1.0, CI 0.8-1.3 and males OR 1.3, CI 0.9-1.8.

Of those gallstone-free subjects who were evaluated 7.8 ± 1.0 years later:

- The incidence odds ratio of gallstone disease in the IBS group was: females OR 1.20, CI 0.76-1.89 and males OR 0.91, CI 0.46-1.83, see Table 1 below.
- The incidence of cholecystectomy in the IBS group was: females 1.1% and males 0.8% compared to the control group females 0.7% and males 0.4%.

Table 1. Multivariate incidence odds ratio of gallstone disease (Corazziari's Table 4, page 948, added information in italics, totals)

	Number of subjects	Number of gallstone disease cases	OR ^a	95% CI	p-value
Females					
Controls	2501	145	1.00		
IBS	354	24	1.20	0.76-1.89	0.45
AP	332	18	0.92	0.55-1.53	0.74
AB	449	25	0.97	0.62-1.51	0.88
<i>Totals</i>	<i>3636</i>	<i>212</i>			
Males					
Controls	3775	159	1.00		
IBS	241	9	0.91	0.46-1.83	0.80
AP	373	17	1.12	0.66-1.89	0.68
AB	435	19	1.04	0.64-1.71	0.87
<i>Totals</i>	<i>4824</i>	<i>204</i>			

IBS: irritable bowel-like symptoms; AP: abdominal pain and normal bowel; AB: altered bowel and no abdominal pain.

a Adjusted for age, body mass index (BMI), level of education, smoking habits and concomitant disease previously shown to be significantly related to gallstone disease (diabetes, cirrhosis, myocardial infarction and peptic ulcer).

According to the sponsor’s Safety Report (page 132 of 13586), there were 20 cases of gallbladder disease in the linaclotide-exposed group (2 gallstones in Phase 3 placebo-controlled trials and, in the long-term safety studies, 11 gallstones, 5 gallbladder dyskinesia, and 2 gallbladder cholesterolosis). Using all the gallbladder disease cases reported in the publication (controls + IBS + Abdominal Pain with normal bowel + Altered Bowel without abdominal pain), they calculated an incidence rate of 748/100,000 person-years (PY) for females and 542/100,000 PY for males. If the same calculation method for incidence is used for just the IBS group, the incidence rates are 869 and 479 per 100,000 PY for females and males respectively:

Sponsor’s calculated incidence rate from Corazziari’s (2008) Italian study:

- total n females (or males)*7.8 years = PY; n cases/PY*100,000 = incidence rate per 100,000 PY
- Females (Corazziari): 212 cases/(3636 females*7.8 years) *100,000 = 748 cases/100,000 PY
- Males (Corazziari): 204 cases/(4824 males*7.8 years) *100,000 = 542 cases/100,000 PY

IBS Incidence rate calculated from Corazziari’s (2008) Italian study IBS group:

- IBS Females (Corazziari): 24 cases/(354 females*7.8 years) *100,000 = 869 cases/100,000 PY
- IBS Males (Corazziari): 9 cases/(241 males*7.8 years) *100,000 = 479 cases/100,000 PY

The Corazziari Italian study differs from the linaclotide studies in many aspects: objective, study type, time period, population (country & patient types, specifically gallstone-free patients for the Italian study), patient selection, cases of gallbladder disease, follow-up time and sample size. These are summarized in Table 2 below.

Table 2. Characteristics of the Linaclotide Studies and the Corazziari Italian Study

	Linaclotide studies	Corazziari Italian Study
Objective	New Drug Application – US	Determine the prevalence and incidence of gallstones and cholecystectomy in IBS patients
Study Type	Cohort – Prospective placebo-controlled trials for New Drug Application and Long-Term Safety follow-up	Cross-sectional survey – case-control Physical exam & abdominal ultrasonography at first survey
Time Period	Prior to October 11, 2010	Prior to publication in 2008
Population – Country	US	Italy
Population – Patient Type	2 Groups: IBS-C and CC patients	4 Gallstone-free Groups: IBS, Abdominal Pain with normal bowel, Altered Bowel with no abdominal pain, and controls
Patient Selection	NDA study enrollment of IBS-C and CC patients	Random selection of patients
Cases	All gallbladder diseases	Gallstones and Cholecystectomies following an interview, a physical exam and an upper abdomen ultrasonography.
Follow-Up Time	Up to 78 weeks (6.5 years)	7.8 ± 1.0 years after determined to be gallstone-free at first survey
Sample Size	“Group 4”: 4380 patients = IBS-C 2753 and CC 1627 ; 2838 PY	8460 patients: 3636 F : 4824 M

DEPI I Comment: *Even though these two studies, linaclotide safety studies and Corazziari’s Italian study, have many differences, this reviewer found no other data on gallbladder disease incidence rates, especially in US IBS patients. The sponsor’s estimate of expected cases in their linaclotide-exposed group is based on an incidence rate calculated from Corazziari’s cases of gallbladder disease in all study groups including the control group. Since linaclotide is expected to be used in IBS-C and CC, it is prudent to use the incidence rate from the IBS group; however, since the Corazziari IBS incidence rate in women is greater than the overall incidence rate, and since linaclotide will probably be used more in women, the expected number of linaclotide cases from the IBS incidence rate probably would be greater than the sponsor’s stated expected number of 20 cases.*

In addition, the incidence rate of gallbladder disease in CC, one of linaclotide’s expected indications, may reflect that of the general population and may not be as high as in the IBS group which would lead to fewer expected linaclotide cases. Therefore the sponsor’s application of their calculated incidence rates from all patients in the Italian study to estimate the expected number of linaclotide-exposed gallbladder diseases probably is more conservative than using the Italian IBS incidence rates.

A significant aspect of the Corazziari Italian study is that patients enrolled for the incidence study were gallstone-free. It is possible that patients with asymptomatic gallstones could be included in the linaclotide study which might lead to a higher observed rate of gallbladder disease in the linaclotide patients.

There is one other point that could affect the number of gallbladder disease cases in the linaclotide-exposed patients. Although not believed to be the case, if patients with gallbladder disease risk factors were inadvertently excluded from the Phase 2 and 3 trials, the observed number of gallbladder cases could be lower since linaclotide-exposed patients were rolled-over from Phase 2 and 3 trials into the Long-Term Safety (LTS) study. Some gallstone risk factors are obesity, female gender, American Indian race, drugs (e.g. ceftriazone, somatostatin), etc.

3.2 OTHER INCIDENCE RATES FROM THE LITERATURE

There are few studies on incidence rates for gallbladder disease in the US population. Table 3 below summarizes the gallbladder information from the Safety Report and the Corazziari paper in addition to gallbladder disease incidence information found through multiple searches of the literature via PubMed.

Table 3. Incidence Rates of Gallbladder Disease: Source, GB Event, Population, & Incidence Rates

Source Location, F/U	Cases	Population	Overall Rate	Rate in Women	Rate in Men	Expected Linaclotide Cases
Safety Report Phase 3: up to 26 weeks Long Term: Roll-over patients, up to 78 weeks Gallbladder Disease	20	Linaclotide 2838 PY Phase 3 + Long Term Safety Studies	20/2838PY =705/ 100,000PY			
Safety Report calculations: Corazziari 2008 Italy, 7.8 years	212 F 294 M			748/ 100,000PY Calculated	542/ 100,000PY Calculated	21

Source Location, F/U	Cases	Population	Overall Rate	Rate in Women	Rate in Men	Expected Linaclotide Cases
Corazziari 2008 Italy, 7.8 years Reported incidence rates of gallstones and cholecystectomy	212 F (all pts) 204 M (all pts)	All Pts: Controls, IBS , Abd Pain normal bowel, Altered bowel no abd pain	Incidence Cholecystectomy Control Group IBS Group	0.7% 1.2% Per article	0.5% 0.8% Per article	
Corazziari 2008 Calculated IBS group incidence rates by PY	24 F 9 M	IBS Only		869/100,000PY Calculated	479/100,000PY Calculated	
Friedman 1966 US-Mass Framingham Cholelithiasis or cholecystitis or both	226 over 10 years	5008 subjects, population-based (5209 - 201 previous cases = 5008)	45/1000 Over 10 years = 450/100,000 PY	59/1000 Over 10 years = 590/100,000PY	29/1000 Over 10 years = 290/100,000PY	12.8 cases
Maram 1990 US-Minn Rochester, 20 yrs Gallstones (by chart review for surgery, radiograph, pathology, autopsy)		Rochester, Minn	301/100,000 Annually	370/pop 100,000 Annually	217/pop 100,000 Annually	8.5 cases
			Age-adjusted average annual incidence rate:	Adjusted: 376/pop 100,000 annually	Adjusted: 255/pop 100,000 annually	
Steiner 1994 US-Maryland Cholecystectomies (hosp discharges)	67,537 1985-1992	Maryland hospital discharges	Adj Annual rates 165 (1985) - 217 (1992) per 100,000 gen pop			6.2 cases
Urbach 2005 Ontario, Canada Hospitalized Cholecystectomies			Adjusted 260.8/pop 100,000 Annually (1988-2000)	Adjusted 367.5/pop 100,000 Annually	Adjusted 134.6/pop 100,000 Annually	7.4 cases
Mallon 2006 Ireland Laparoscopic cholecystectomy 1998-2000	401 Lap 69 IBS Lap	Londonderry Operating theatre records Pop-based	All laparoscopic cholecystectomies 75.9/100,000/yr IBS 26% of Lap (~19.7/100,000/yr)			2.2 ~0.6 cases
Natl Center for Health Statistics, CDC, 2009 report 2006 data # Cholecystectomies		Natl Hosp Discharge Survey Natl Survey of Ambulatory Surgery	Cholecystectomy 181 discharges per 100,000 pop Ambulatory surg cholecystectomy 212 visits per 100,000 pop	2006: Ambulatory surgery: 34.2 visits per 10,000 pop = 342/100,000	2006: Ambulatory surgery: 7.3 visits per 10,000 pop = 73/100,000	(No single incidence rate for all cholecystectomies for the US pop.)

Hospital Cholecystectomy (77% Laparoscopy) & Ambulatory Cholecystectomy (almost all Laparoscopic)

The two earlier studies from Framingham, Massachusetts, (Friedman 1966) and Rochester, Minnesota, (Maram 1990) report on gallstones and, in the case of Massachusetts, also cholecystitis. Their incidence rates are 590 and 370 (adjusted 376) cases per 100,000 annually for females and 290 and 217 (adjusted 255) cases per 100,000 annually for males. The Maryland study (Steiner 1994), the Canadian study (Urbach 2005), and the Irish study (Mallon 2006) reported incidence rates for hospitalized cholecystectomies: Maryland hospitalized cholecystectomies (open & laparoscopic) of 217 per 100,000 general population, Canadian hospitalized cholecystectomies (severe gallstones) of 260.8 per 100,000 Ontario general population annually (367.5 per 100,000 annually for females and 134.6 for males), and Irish hospitalized laparoscopic cholecystectomies averaged annually of 75.9 per 100,000 Londonderry general population with 26% of these in IBS patients (~19.7 per 100,000). The most recent publication on incidence rates gallbladder diseases, besides the Corazziari study, is from the National Center for Health Statistics which reported hospital discharges for cholecystectomies of 181 discharges per 100,000 population in 2006 and for ambulatory cholecystectomies (almost all are laparoscopic) of 212 visits per 100,000 population for 2006 and, for females and males, 342 and 73 visits per 100,000 population.

DEPII Comment: *The Corazziari Italian study published in 2006 had the highest incidence rate for gallstones and cholecystectomies of all the studies but it was the only study reporting IBS data from which to calculate IBS incidence rates for females and males. All of the other studies reported only on cholecystectomies (hospitalized) except the two earlier studies in Massachusetts (Friedman 1996) and Minnesota (Maram 1990) which most likely did not include many, if any, laparoscopic cholecystectomies since they were introduced in the late 1980's and all of these studies report lower incidence rates than Corazziari in Italy.*

There were only two reports of cholecystectomies in IBS patients: The Irish study (Mallon 2006) on hospitalized cholecystectomies and the UK survey study (Kennedy 1998) on the general population. Mallon's Irish study (2006) reported incidence rates for open (1988-1990) and laparoscopic (1998-2000) cholecystectomies with IBS patients representing 20 and 26% respectively which was not statistically significant. The second publication on cholecystectomies in IBS patients was a UK survey study by Kennedy et al (1998) and they found more cholecystectomies in IBS patients than the general population but they did not have incidence data.

The reported incidence rates in the US population studies for cholecystectomies are less than that reported by Corazziari for Italians and specifically IBS patients; however, Corazziari established a gallstone-free group following an interview, a physical exam and an ultrasonography. None of the other studies established a gallbladder disease-free group with such rigor.

4 DISCUSSION

DGIEP asked for information on the incidence rate of gallbladder disease in the US in reference to the incidence rate that the sponsor calculated from the Corazziari Italian study on gallstones and cholecystectomies.

Unfortunately, the linaclotide safety studies do not have a control group for comparison with the linaclotide-exposed patients. It would have been especially helpful to have a separate control group for the linaclotide IBS-C and for the CC group.

Most cholecystectomies are a matter of the patients' medical records but the status of their gallbladder prior to symptoms is often not known; therefore, it is difficult to know the true GB disease "free" population to follow for new onset of GB disease and to determine the incidence rate of GB disease. There are, however, published studies that focus on gallstones and cholecystectomies from which incidence rates were reported (Table 3). Unlike the other studies, the Italian Corazziari study established a gallstone-free group after an interview, physical exam and ultrasonography and it had an IBS group.

The two linaclotide-exposed groups, IBS-C and CC, are unique and they are not representative of the general population. Only the Corazziari study lends itself to application to the linaclotide patients, despite the differences between the linaclotide and Corazziari studies (Table 2).

It is possible that an increase in the incidence of cholecystectomies may be due to an increase in the incidence of gallstones, an increase in symptomatic gallstones, improved diagnosis of gallstones (especially with the use of ultrasonography), or a higher tendency for surgery (especially with laparoscopy). (Shaffer 2006)

5 CONCLUSIONS

The Italian Corazziari study is the best source for a comparator incidence rate for gallstones in IBS patients and therefore for use in the linaclotide safety study. Even though other studies report incidence rates for the general US population, it is possible that their gallstone/cholecystectomy incidence rates are lower than the Corazziari study because the Corazziari study established a truer gallstone-free group using ultrasonography. The expected number of gallbladder cases is 21 and the linaclotide safety studies had 20 cases.

6 RECOMMENDATIONS

Given the conservative estimates from Corazziari study, the linaclotide gall bladder safety finding is reassuring at this time.

7 REFERENCES

- Everhart JE, Ruhl CE. Burden of digestive diseases in the United States Part III: Liver, biliary tract, and pancreas. *Gastroenterology*. 2005;136:1134-1144.
- Friedman GD, Kannel WB, Dawber TR. The epidemiology of gallbladder disease: observations in the Framingham Study. *J Chron Dis*. 1966;19:273-292.
- Kennedy TM, Jones RH. Epidemiology of cholecystectomy and irritable bowel syndrome in a UK population. *British Journal of Surgery*. 2000;87:1658-1663.
- Li P, Lin JE, Marszlowicz GP, et al. GCC signaling in colorectal cancer: Is colorectal cancer a paracrine deficiency syndrome? *Drug News Perspect* 2009;22; referenced in Ironwood Pharmaceuticals, Inc and Forest Research Institute, Inc. Lanacotide: Summary of Clinical Safety (Module 2.7.4) & Integrated Summary of Safety (Module 5.3.5.3), 01 Jul 2011, page 21.
- Maram ES, Linos DA, Thistle JL, Linos A, O'Fallon, Kurland LT. The incidence of cholelithiasis and cholecystitis in Rochester, Minn, 1950 through 1969. *Arch Intern Med*. 1990;150:1833-1836.
- Merck Manual of Diagnosis and Therapy, 19th Edition. Kaplan JL, Porter RS, eds. 2011. Whitehouse Station, NJ. Merck Sharp & Dohme Corp, A Subsidiary of Merck & Co, Inc. ISBN-10: 0-911910-19-0, ISBN-13: 978-0-911910-19-3. ISSN: 0076-6526. STAT!Ref Online Electronic Medical Library. <http://online.statref.com/document.aspx?fxid=21&docid=196>. 2/22/2012.
- Mallon P, White J, McMenamin M, Das N, Hughes D, Gilliland R. Increased cholecystectomy rate in the laparoscopic era. *Surg Endosc*. 2006;20:883-886.
- National Center for Health Statistics. Health, United States, 2009: With Special Feature on Medical Technology. Hyattsville, MD. 2010. US Department of Health and Human Services, Centers for Disease Control and Prevention. <http://www.cdc.gov/nchs/data/hus/hus09.pdf>
- Shaffer EA. Epidemiology and Risk Factors for Gallstone Disease: Has the Paradigm Changed in the 21st Century? *Current Gastroenterology Reports*. 2005, May. 7:132-140.
- Shaffer EA. Epidemiology of gallbladder stone disease. *Best Practice & Research Clinical Gastroenterology*. 2006. 20;6:981-996.
- Steiner CA, Bass, EB, Talamini MA, Pitt HA, Steinberg EP. Surgical rates and operative mortality for open and laparoscopic cholecystectomy in Maryland. *The New England Journal of Medicine*. 1994; 330(6):403-408.
- Stinton LM, Myers RP, Shaffer EA. Epidemiology of gallstones. *Gastroenterol Clin N Am* 2010; 39:157-169.
- Urbach DR, Stukel TA. Rate of elective cholecystectomy and the incidence of severe gallstone disease. *Canadian medical Association Journal*. 2005, Apr 12; 172 (8): 1015-9.

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/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and Labeling Review

Date: February 15, 2012

Reviewer(s): Jamie Wilkins Parker, Pharm.D.
Division of Medication Error Prevention and Analysis

Team Leader: Carlos Mena-Grillasca, RPh
Division of Medication Error Prevention and Analysis

Division Director: Carol A. Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength(s): Linzess (Linaclotide) Capsules, 145 mcg and 290 mcg

Application Type/Number: NDA 202811

Applicant/sponsor: Ironwood Pharmaceuticals, Inc.

OSE RCM #: 2011-3178

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis's evaluation of the proposed container labels, carton, and insert labeling for Linzess (Linaclotide) Capsules for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

The Applicant submitted the proposed labels and labeling for Linzess Capsules (NDA 202811) on August 8, 2011.

1.2 PRODUCT INFORMATION

- Active Ingredient: Linaclotide
- Indication of Use: Treatment of irritable bowel syndrome with constipation (IBS-C) and chronic constipation
- Route of administration: Oral
- Dosage form: Capsules
- Dose and Frequency: 145 mcg or 290 mcg taken orally once daily on an empty stomach
- How Supplied: trade bottles containing 30 capsules, with the middle NDC numbers differing for each strength
- Storage: 59° F-86° F, and should remain in the original container (should not be subdivided or repackaged)
- Container and Closure systems: HDPE bottles with (b) (4) Closure.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Insert Labeling submitted August 8, 2011 (no image)
- Trade Container Labels submitted August 8, 2011 (Appendix A)
- Professional Sample Container Labels and Carton Labeling submitted August 8, 2011 (Appendix B)

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 DISCUSSION OF DEFICIENCIES IDENTIFIED

3.1 INSERT LABELING

- The insert labeling contains information regarding storage and administration which requires greater prominence due to the potential of loss of stability of the active ingredient in sections 16 and 17 as well as in the patient counseling information.

3.2 CONTAINER LABELS AND CARTON LABELING

- Professional Sample Labels and Labeling
 - The professional sample and trade container labels and carton labeling contain graphics which appear as part of the trade name, contain a dangerous abbreviation, have improper prominence of important storage and dispensing information, improper prominence of the net quantity statement, unnecessary shading on the container labeling, and a package size of 30 capsules, which may lead to medication error.
- Trade Container Labels
 - The trade container labels contain graphics which appear as part of the trade name, contain a dangerous abbreviation, and have improper prominence of important storage and dispensing information, which may lead to medication error.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling introduce vulnerability that can lead to medication error. We recommend the following:

A. Insert Labeling

1. Warnings and Precautions section Highlights and Full Prescribing Information. We recommend the addition of the statement “Keep Linzess in the original container. Do not subdivide or repackage. Protect from moisture. Do not remove desiccant from the container. Keep bottles closed tightly in a dry place.” as Linaclotide is sensitive to moisture and formaldehyde, therefore the proposed (b) (4) expiration dating is only valid if the drug remains in the proposed commercial container closure system during the entire shelf life, and therefore needs a prominent warning of this type to prevent transferring to a pharmacy bottle or pill box.
2. How Supplied/Storage and Handling and Instructions for Patients within the Patient Counseling Information sections. Increase the prominence of the statement “Keep Linzess in the original container. Do not subdivide or repackage. Protect from moisture. Do not remove desiccant from the container. Keep bottles closed tightly in a dry

place.” as Linaclotide is sensitive to moisture and formaldehyde, therefore the proposed (b) (4) expiration dating is only valid if the drug remains in the proposed commercial container closure system during the entire shelf life and therefore needs a prominent warning of this type to prevent transferring to a pharmacy bottle or pill box.

B. Container Labels (4 count (b) (4); 30 count trade bottle)

1. (b) (4)
2. Relocate the graphic that is currently directly adjacent to the proprietary name, as it currently appears as part of the proprietary name where it is currently located, and could be misinterpreted as a modifier or extra letter.
3. Increase the size and prominence of the strength statement.
4. Relocate and revise the storage statement to read “Keep Linzess in the original container to protect from moisture. Do not remove the desiccant from inside the bottle.” to the principal display panel, in prominent text, as Linaclotide is sensitive to moisture and formaldehyde, therefore the proposed (b) (4) expiration dating is only valid if the drug remains in the proposed commercial container closure system during the entire shelf life and therefore needs a prominent warning of this type to prevent transferring to a pharmacy bottle or pill box. On the 4 count sample bottle, we recommend relocating the net quantity statement to the top right corner of the principal display panel to allow space for the above statement to fit on the principal display panel of the label.

C. Carton Labeling (4 count (b) (4); 30 count trade)

1. See Comments B 2-4.
2. Remove the blue shading from the lower portion of the panels on the carton labeling, as this color is used on both strengths, and makes the bottles look similar, which can lead to product selection errors.

D. (b) (4)

If you have further questions or need clarifications, please contact Nitin Patel, project manager, at 301-796-3904.

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

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02/16/2012

Executive CAC

Date of Meeting: January 17, 2012

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
David B. Joseph, Ph.D., DGIEP, Alternate Member/Team Leader
Niraj R. Mehta, Ph.D., DGIEP Presenting Reviewer

Author of Draft: Niraj R. Mehta

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 202811

Drug Name: LINZESS (linaclotide acetate) tablets

Sponsor: Ironwood Pharmaceuticals, Inc.

Background: Linaclotide is a first-in-class, orally active, synthetic 14-amino acid peptide structurally related to the guanylin peptide family. Linaclotide is a potent activator of GC-C (guanylate cyclase C), which increases the intracellular concentrations of the second messenger cyclic guanosine monophosphate (cGMP). The known pharmacologic effects of linaclotide include increased intestinal fluid secretion, acceleration of intestinal transit, and antinociception in rodent models of visceral pain secondary to colorectal injury. The proposed indications for linaclotide are the treatment of chronic constipation and irritable bowel syndrome with constipation.

Linaclotide was negative in the Ames assay and in the *in vitro* chromosome aberration assay. The *in vivo* micronucleus test was not conducted.

Mouse Carcinogenicity Study:

Linaclotide was administered to Crl:CD-1 mice (70/sex/group) at doses of 0 (0.5% methylcellulose in deionized water), 600, 2000, and 6000 µg/kg/day, given by oral gavage for 104 weeks. There were no significant drug-related effects on survival rates, clinical signs, masses noted during the treatment period, body weights, food consumption, hematology, macroscopic observations, or microscopic findings (neoplastic and non-neoplastic.)

Rat Carcinogenicity Study:

Linaclotide was administered to Crl:CD(SD) rats (70/sex/group) at doses of 0 (0.5% methylcellulose in deionized water), 300, 1000, and 3500 µg/kg/day, given by oral gavage for 104 weeks. Survival in control group 1 females (28.6%) was significantly lower than control group 2 females (47.1%). The test article-treated females had lower

survival rates when compared control group 2. The 300 µg/kg/day females had a statistically significant decrease in survival rate (25.7%) compared to the combined control groups. In general, there were no significant drug-related effects on survival rates, clinical signs, masses noted during the treatment period, body weights, food consumption, hematology, macroscopic observations, or microscopic findings (neoplastic and non-neoplastic). Neoplastic findings showed that benign interstitial cell (Leydig cell) adenomas of the testes (common tumor) were observed in 4/70 males (5.7%) in the 3,500 µg/kg/day group compared to 0/140 control males. Although statistical significance was achieved in the trend test, the study results were considered to be negative based on the following: the incidence in the 3500 µg/kg/day males was not significantly different from control ($p=0.0175$, $\alpha=0.01$); the incidence of testicular interstitial adenoma in the 3500 µg/kg/day males (5.7%) was within the historical control range (0-5.7%); the p value in the trend test (0.0049) was extremely close to the designated significance level for common tumors ($\alpha=0.005$); and there is no plausible mechanism for drug-related tumor induction, since no systemic exposure to the drug or its active metabolite would be expected at the doses used in this study.

Executive CAC Conclusions and Recommendations:

Rat:

- The Committee agreed that the study was adequate, noting prior approval of the study protocol.
- The Committee concluded that the study was negative for drug-related neoplasms.

Mice:

- The Committee agreed that the study was adequate, noting prior approval of the study protocol.
- The Committee concluded that the study was negative for drug-related neoplasms.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\

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/s/

ADELE S SEIFRIED
01/20/2012

DAVID JACOBSON KRAM
01/20/2012

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 # 202811 BLA#	NDA Supplement #:S- N/A BLA STN #	Efficacy Supplement Type SE- N/A
Proprietary Name: LINZESS Established/Proper Name: linaclotide Dosage Form: Capsules Strengths: 145 mcg and 290 mcg		
Applicant: Ironwood Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: 8/9/11 Date of Receipt: 8/9/11 Date clock started after UN: N/A		
PDUFA Goal Date: 6/9/12		Action Goal Date (if different): 6/8/12
Filing Date: 10/8/11		Date of Filing Meeting: 9/30/11
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): treatment of irritable bowel syndrome with constipation and chronic 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) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track <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 [21 CFR 314.55(b)/21 CFR 601.27(b)] <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)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 63290				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>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 system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>		X		Document Room asked to add chemical classification code "1", and combination product code "N"
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><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></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><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></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>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)].</p>			<p>X</p>																	
<p>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> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, 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 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the <i>Orphan Drug Designations and Approvals</i> list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

<p>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)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 5 years</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>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)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

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

1

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

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
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), 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)?	X			
<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?	X			
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)?	X			
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)?	X			
<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?	X			
<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 FDCA 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>	X			
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>			X	
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>			X	
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, 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>	X			PeRC scheduled for March 21, 2012

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	X			
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <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? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

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? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)		X		Patient labeling consulted
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?			X	No longer necessary to consult labeling to DMEPA. Carton and container labeling to be reviewed by ONQA also.
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 <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>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
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 consult(s) and date(s) sent:</i>	X			DSI consult no longer needed. QT IRT consult not needed per CDTL 10-4-11.

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): Chronic Constipation – 5/15/08 IBS-C – 8/7/08 CMC EOP2 Mtg – 11/6/08 <i>If yes, distribute minutes before filing meeting</i>	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): Clinical and Non-Clinical PNDA Mtg - 3/22/11 CMC PNDA Mtg – 5/4/11 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 9/30/11

BLA/NDA/Supp #: NDA 202-811

PROPRIETARY NAME: LINZESS

ESTABLISHED/PROPER NAME: linaclotide

DOSAGE FORM/STRENGTH: 145 mcg and 290 mcg capsules

APPLICANT: Ironwood Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Chronic Constipation and IBS-C

BACKGROUND:

NDA 202-811 for LINZESS (linaclotide) Capsules is an eCTD submission that provides for the treatment of constipation predominant irritable bowel syndrome (IBS-C) and chronic constipation. Linaclotide is an NME.

Clinical development for LINZESS was conducted under IND 63,290. IND 63,290 was submitted by Microbia, Inc. September 30, 2004 for the treatment of IBS-C. Sponsorship of the IND changed to Ironwood Pharmaceuticals on April 14, 2008. An end-of-phase 2 (EOP2) meeting to discuss phase 3 chronic constipation protocols was held May 15, 2008. A second EOP2 meeting to discuss IBS-C phase 3 protocols was held August 7, 2008 with a follow-up meeting October 15, 2008. A Type C meeting to discuss pediatric issues was held January 26, 2010.

A pre-NDA meeting to discuss the clinical and nonclinical submission content of a planned NDA for irritable bowel syndrome with constipation and chronic constipation was held March 22, 2011. Safety and efficacy for the NDA were supported by the following phase 3 studies:

- MCP-I03-302: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group trial of Linaclotide Administered Orally for 26 weeks in Patients with Irritable Bowel Syndrome with Constipation
- LIN-MD-31: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group trial of Linaclotide Administered Orally for 12 weeks Followed by a 4- Week Randomized Withdrawal Period in Patients with Irritable Bowel Syndrome with Constipation
- LIN-MD-OI: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group trial of Linaclotide Administered Orally for 12 weeks in Patients with Chronic Constipation
- MCP-103-303: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group trial of Linaclotide Administered Orally for 12 weeks Followed by a 4-Week Randomized Withdrawal Period in Patients with Constipation.

A chemistry, manufacturing and controls (CMC) EOP2 was held November 6, 2008. A follow-up Type C CMC meeting was held January 20, 2011 and a CMC pre-NDA meeting was held May 11, 2011.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Brian Strongin	Y
	CPMS/TL:	Brian Strongin	Y
Cross-Discipline Team Leader (CDTL)	Ruyi He		Y
Clinical	Reviewer:	Lara Dimick	Y
	TL:	Ruyi He	Y
Clinical	Reviewer:	Erica Wynn	Y
	TL:	Rob Fiorentino	Y
Clinical Pharmacology	Reviewer:	Sandhya Apparaju	N
	TL:	Sue Chih Lee	Y
Biostatistics	Reviewer:	Milton Fan	Y
	Reviewer:	Freda Cooner	Y
	TL:	Mike Welch	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Niraj Mehta	Y
	TL:	David Joseph	Y
Statistics (carcinogenicity)	Reviewer:	Mohamed Nagem	Y
	TL:	Karl Lin	N
Product Quality (CMC)	Reviewer:	Jane Chang	Y
	Reviewer (Biopharm):	Kareen Riviere	Y
	TL (Biopharm):	Angelica Dorantes	N
	TL:	Marie Kowblansky	N
Quality Microbiology (for sterile products)	Reviewer:		
	TL:		

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APPEARS THIS WAY ON ORIGINAL

CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Jamie Wilkins-Parker and Lubna Merchant	
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Roy Blay	N
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers (SEALD)	Jeannie Delasko		N
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <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 <p>List comments: None</p>	<input type="checkbox"/> Not Applicable

<p>CLINICAL</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 study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <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 type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> • Abuse Liability/Potential <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
<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? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</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>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: May request reformatted data sets, site-level data and a sensitivity analysis.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" 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>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</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>PRODUCT QUALITY (CMC)</p> <p>Comments: Biopharmaceuticals may have an information request</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<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>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments: Reviewer working with OMPQ to add one site to EES.</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input checked="" type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Julie Beitz, M.D.</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	

REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List: Clin/Stat – reformatted data sets, site-level data and a sensitivity analysis may be needed. Stat reviewers to send an e-mail to RPM with wording for the request. ONDQA/Biopharmaceutics may have an information request – reviewer will send RPM wording.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<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"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<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 type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]

<input type="checkbox"/>	Other
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APPEARS THIS WAY ON ORIGINAL

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

BRIAN K STRONGIN
10/05/2011

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 202-811

Name of Drug: LINZESS (linaclotide) Capsules

Applicant: Ironwood Pharmaceuticals, Inc.

Labeling Reviewed

Submission Date: August 8, 2011

Receipt Date: August 9, 2011

Background and Summary Description

NDA 202-811 for LINZESS (linaclotide) Capsules is an eCTD submission that provides for the treatment of constipation predominant irritable bowel syndrome (IBS-C) and chronic constipation. Linaclotide is an NME.

Clinical development for LINZESS was conducted under IND 63,290. IND 63,290 was submitted by Microbia, Inc. September 30, 2004 for the treatment of IBS-C. Sponsorship of the IND changed to Ironwood Pharmaceuticals on April 14, 2008. An end-of-phase 2 (EOP2) meeting to discuss phase 3 chronic constipation protocols was held May 15, 2008. A second EOP2 meeting to discuss IBS-C phase 3 protocols was held August 7, 2008 with a follow-up meeting October 15, 2008. A Type C meeting to discuss pediatric issues was held January 26, 2010.

A pre-NDA meeting to discuss the clinical and nonclinical submission content of a planned NDA for irritable bowel syndrome with constipation and chronic constipation was held March 22, 2011. Safety and efficacy for the NDA were supported by the following phase 3 studies:

- MCP-I03-302: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group trial of Linaclotide Administered Orally for 26 weeks in Patients with Irritable Bowel Syndrome with Constipation
- LIN-MD-31: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group trial of Linaclotide Administered Orally for 12 weeks Followed by a 4- Week

Randomized Withdrawal Period in Patients with Irritable Bowel Syndrome with Constipation

- LIN-MD-OI: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group trial of Linaclotide Administered Orally for 12 weeks in Patients with Chronic Constipation
- MCP-103-303: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group trial of Linaclotide Administered Orally for 12 weeks Followed by a 4-Week Randomized Withdrawal Period in Patients with Constipation.

A chemistry, manufacturing and controls (CMC) EOP2 was held November 6, 2008. A follow-up Type C CMC meeting was held January 20, 2011 and a CMC pre-NDA meeting was held May 11, 2011.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the “Selected Requirements for Prescribing Information (SRPI)” section of this review. Labeling deficiencies are identified in this section with an “X” in the checkbox next to the labeling requirement.

Selected Requirements for Prescribing Information (SRPI)

Highlights (HL)

- **General comments**
 - HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
 - HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
 - There is no redundancy of information.
 - If a **Boxed Warning** is present, it must be limited to 20 lines. (**Boxed Warning** lines do not count against the one-half page requirement.)
 - A horizontal line must separate the HL and Table of Contents (TOC).
 - All headings must be presented in the center of a horizontal line, in **UPPER-CASE** letters and **bold** type.
 - Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.

Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading - if no contraindications are known, it must state "None")
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**
 - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**
 - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
 - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**
 - All text in the boxed warning is **bolded**.
 - Summary of the warning must not exceed a length of 20 lines.
 - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
 - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**
 - Applies only to supplements and is limited to substantive changes in five sections: **Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.**
 - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “**Dosage and Administration, Coronary Stenting (2.2) -- 2/2010.**”
 - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
 - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
 - Removal of a section or subsection should be noted. For example, “**Dosage and Administration, Coronary Stenting (2.2) -- removal 2/2010.**”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product] is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”).**”

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and bold type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in bold type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**
 - A horizontal line must separate the TOC and FPI.
 - The heading - **FULL PRESCRIBING INFORMATION** - must appear at the beginning in UPPER CASE and bold type.
 - The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).
- **Boxed Warning**
 - Must have a heading, in UPPER CASE, bold type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use bold type and lower-case letters for the text.
 - Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:
“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 clinical practice.”
- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:
“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.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.
- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
 - “See FDA-approved patient labeling (Patient Information)”

Conclusions/Recommendations

All labeling deficiencies identified in the SRPI section of this review will be conveyed to the applicant in the 74-day letter. The applicant will be asked to resubmit labeling that addresses all identified labeling deficiencies by November 14, 2011. The resubmitted labeling will be used for

further labeling discussions.

APPEARS THIS WAY ON ORIGINAL

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

/s/

BRIAN K STRONGIN
09/14/2011