CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

202811Orig1s000

Trade Name: Linzess Capsules, 145 mcg and 290 mcg.

Generic Name: linaclotide

Sponsor: Forest Laboratories, Inc.

Approval Date: August 30, 2012

Indications: Linzess (linaclotide) Capsules for the treatment of irritable bowel syndrome with constipation and for treatment of chronic idiopathic constipation.

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202811Orig1s000

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202-811

NDA APPROVAL

Forest Laboratories, Inc.
Attention: Linda Kunka
Senior Manager, Regulatory Affairs
Harborside Financial Center, Plaza V
Jersey City, NJ 07311

Dear Ms. Kunka:

Please refer to your New Drug Application (NDA) dated August 8, 2011, received August 9, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Linzess (linaclotide) Capsules, 145 mcg and 290 mcg.

We acknowledge receipt of your amendments dated August 10, August 22, August 23, October 7, October 20, October 25, October 28, November 3, November 7, November 16, November 18, December 3, December 5, December 6, December 9, December 16, December 23, and December 29, 2011 and January 18, January 19, January 20, January 30, February 2, February 3, February 6, February 8, February 17, February 29, March 1, March 2, March 9, March 16, March 19, March 26, March 27, April 4, April 17, April 18, April 19, April 20, May 7, May 11, May 23, June 6, June 25, July 25, July 30, August 14, August 17, August 20, August 21, August 27, August 28, and August 29, 2012.

This new drug application provides for the use of Linzess (linaclotide) Capsules for the treatment of irritable bowel syndrome with constipation and for treatment of chronic idiopathic constipation.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on August 21, 2012, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 202-811**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for Linzess Capsules was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure mitigation, treatment or prevention of disease, and outside expertise was not necessary.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for chronic idiopathic constipation in ages birth to six months and for irritable bowel syndrome in ages birth to six years because necessary studies are impossible or highly impracticable. This is because there are too few children with these conditions to study.

We are deferring submission of your pediatric studies for ages seven months to seventeen years for chronic idiopathic constipation and for ages seven years to seventeen years for irritable bowel syndrome with constipation for this application because pediatric studies should be delayed until additional nonclinical safety data have been collected. Death was seen in neonatal and juvenile mouse studies of linaclotide. Data regarding the mechanism of these deaths must be gathered before studies may proceed in pediatric patients.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

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

Final Protocol Submission – January 2013
Study Completion – October 2013
Final Report Submission – April 2014

1915-2 A safety and efficacy study in pediatric patients with chronic idiopathic constipation ages seven months up to 17 years treated with Linzess (linaclotide).

Final Protocol Submission – April 2015
Study Completion – December 2022
Final Report Submission – December 2023

1915-3 A safety and efficacy study in pediatric patients with irritable bowel syndrome with constipation ages seven years up to 17 years treated with Linzess (linaclotide).

Final Protocol Submission – April 2015
Study Completion – December 2022
Final Report Submission – December 2023

Submit the protocols to your IND 063290, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious

risks associated with the presence of linaclotide or its active metabolite in human breast milk, to assess known serious risks of immune-mediated reactions, or to identify unexpected serious risks of the development of anti-drug antibodies that may cross react with endogenous guanylin peptide family members and lead to deficiency syndromes.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

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.

The timetable you submitted on August 28, 2012, states that you will conduct this study according to the following schedule:

Final Assay Validation Report: March 2014

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify unexpected serious risks associated with the presence of linaclotide or its active metabolite in human breast milk, to assess known serious risks of immune-mediated reactions, or to identify unexpected serious risks of the development of anti-drug antibodies that may cross react with endogenous guanylin peptide family members and lead to deficiency syndromes

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1915-5 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.

The timetable you submitted on August 14, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	March 2013
Trial Completion:	September 2014
Final Report Submission:	September 2015

1915-6 A clinical trial in adults receiving Linzess (linaclotide) to assess development of anti-drug antibody (ADA) responses in patient samples. Validated assays capable of

sensitively detecting ADA responses that may be present at the time of patient sampling, developed under PMR 1915-4 above, will be used. Sampling will occur at 0 and 2 weeks, and at 1, 3, 6 and 12 months. Immunogenicity rates and individual patient titers will be evaluated. Adverse events will be collected.

The timetable you submitted on August 28, 2012 states that you will conduct this trial according to the following schedule:

Final Protocol Submission: November 2013
Trial Completion: March 2018
Final Report Submission: December 2018

Submit the protocols to your IND 063290, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Brian Strongin, R.Ph., MBA, Chief, Regulatory Project Management Staff, at (301) 796-1008.

Sincerely,

{See appended electronic signature page}

Victoria Kusiak, M.D.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

JULIE G BEITZ
08/30/2012
Signing for Dr. Victoria Kusiak