

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202811Orig1s000

CHEMISTRY REVIEW(S)

Initial Quality Assessment
Branch 3
Pre-Marketing Assessment Division 2

OND Division: Division of Gastroenterology and Inborn Error Products
NDA: 202-811
Applicant: Ironwood Pharmaceuticals, Inc.
Stamp Date: 8/9/2011
Review Date: 9/9/2011
PDUFA Date: 6/9/2011
Filing Meeting: 9/30/2011
Proposed Trademark: LINZESS
Established Name: linaclotide
Dosage Form: Ironwood Pharmaceuticals, Inc.
Route of Administration: Oral
Indication: Irritable Bowel Syndrome and Chronic Constipation

PAL: Marie Kowblansky, PhD

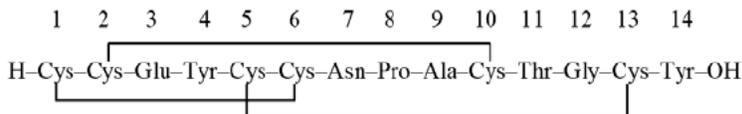
	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	<input checked="" type="checkbox"/>

A. Summary

Linzess (linaclotide) Capsules is an immediate release formulation intended for once daily administration in the treatment of irritable bowel syndrome with constipation (IBS-C) and chronic constipation (CC). This product, which was developed under IND 63,290, contains 145 µg or 290 µg of linaclotide in a hard gelatin capsule. Because linaclotide is a new molecular entity, according to the Chemical Classification Code this is a Type 1 application.

Drug Substance

The drug substance, linaclotide, is a 14-amino acid synthetic peptide with three disulfide bonds



The peptide contains [REDACTED] (b) (4)
[REDACTED] The molecular mass is 1526 daltons. The molecule is highly soluble with low permeability: according to the applicant, it is a Class III compound in the BCS classification system.

There are three intended manufacturers for the drug substance

PolyPeptide Laboratories, Inc. (PPL Torrance, CA)	DMF	(b) (4)
PolyPeptide Laboratories, AB (PPL Sweden)	DMF	(u) (v)
[REDACTED] (b) (4)	DMF	(u) (v)

A comparable manufacturing process is used by all three manufacturers: [REDACTED] (b) (4)

To establish comparability of linaclotide from each of the manufacturers, the structure of linaclotide from each of the manufacturers was evaluated using conventional approaches, (b) (4)

. In addition, at least one lot of drug substance manufactured by each of the commercial manufacturers has been evaluated in long term and accelerated stability studies. Phase 3 clinical trial material was also produced from at least one lot of linaclotide from each of the manufacturers.

The drug substance specification includes testing for identity (mass spectrometry, amino acid analysis, HPLC), assay (HPLC), (b) (4), residual solvents, water content, optical rotation, and impurities (HPLC). The specification specifies limits for a number of identified impurities, each not to exceed (b) (4) unidentified impurities, each not to exceed (b) (4) and total impurities not to exceed (b) (4). Due to the presence of (b) (4)

The specification limits these multimers at (b) (4) in the drug substance, but the (b) (4) content is not included in the total impurity limit.

A retest period of (b) (4) is proposed for drug substance stored at the recommended long-term storage condition of (b) (4).

Drug Product

Linaclotide capsules are prepared in two composition-proportional strengths, 145 µg and 290 µg by filling different amounts of an immediate release linaclotide bead formulation into the capsules. The linaclotide bead formulation contains (b) (4) of linaclotide per (b) (4) resulting in the following capsule compositions (reproduced from the submission):

Component	Function	Quality Standard	Theoretical Weight (mg/capsule)		Theoretical Weight (% w/w)
			Linaclotide Capsules, 145 µg	Linaclotide Capsules, 290 µg	
Linaclotide	Active Ingredient	In House Standard ^a	(b) (4)		
Calcium chloride dihydrate	(b) (4)	USP			
L-leucine	(b) (4)	USP			
Hypromellose	(b) (4)	USP			
Microcrystalline cellulose	(b) (4)	NF			
(b) (4)	(b) (4)	USP			
(b) (4)	(b) (4)	NF			
Total			(b) (4)	100.00	

The bead formulation (b) (4)

The specification includes testing for identity, content uniformity, (b) (4), assay, microbial limits, dissolution, and impurities. Most noteworthy are the impurity limits (reproduced from the submission):

Impurities	(b) (4)
Unspecified (each)	(b) (4)
Total (Specified and Unspecified)	(b) (4)
Total Disulfide-Bonded Multimers	(b) (4)

Two of the identified impurities (b) (4) 1% ICH qualification limits, but these limits were tentatively agreed to by FDA at a meeting where the applicant indicated that these levels were toxicologically qualified through animal studies.

Similarly to the drug substance, the limit of (b) (4) for total impurities does not include the (b) (4) for which an individual limit of (b) (4) is specified. (From stability studies particularly accelerated stability studies, it appears that (b) (4))

The product will be packaged with 1 gram of desiccant in 30-count and 4 count (physician sample) HDPE bottles. A shelf life of 18 months, with room temperature storage is proposed for both strengths and both packaging configurations, based on 6-month accelerated and 12-month long term (25°C/60%RH) stability data. The data show a definite decrease in assay value and increase in impurities with increasing time and increasing storage temperature so extrapolated results will need to be closely scrutinized. At the pre-NDA meeting, FDA agreed that additional stability data could be submitted while the NDA is under review, provided that the additional data were received no later than four months before the PDUFA date.

The full CMC review of this NDA will be done by Jane Chang, PhD; the Biopharmaceutics information will be reviewed by Karen Riviere, PhD.

The firm requests a claim for categorical exclusion from an environmental assessment on the basis that the estimated concentration of the drug substance at the point of entry into the aquatic environment is expected to remain below one part per billion with approval of this product.

Inspection requests for the facilities involved in the manufacture of the drug substance and drug product have been entered into EES. (See appended list.)

Established name: linaclotide, which is the USAN for this drug substance.

B. Critical issues for review

The following issues will require particularly close scrutiny during the course of the review

-- Correct placement of the (b) (4) is critical to the identity of linaclotide. While it appears that placement of (b) (4) is ascertained as part of the formal structural characterization of the drug substance, it is not clear that this attribute is routinely determined for every batch. In a meeting with the applicant in November of 2008, FDA stressed the need for including such testing in the release specification "unless you can provide unequivocal justification that testing for this attribute in the finished drug substance is not required based on control of the manufacturing process."

-- In one of the many meetings with the applicant regarding this product, it was discussed that the (b) (4) are impurities and should be included in the reporting of total impurities. It is not clear why the applicant chooses not to do so (perhaps because this would require a total impurities limit of (b) (4))

-- With regard to the (b) (4), the applicant claims that that the (b) (4) are qualified at a level (b) (4) the (b) (4) specification limit because drug substance lots containing between (b) (4) were used in toxicology studies. In fact, significant discussion was devoted at one of the FDA/sponsor meetings to establish that the (b) (4) were not qualified at these (b) (4) levels because of the heterogeneity of the (b) (4) that would vary with changes in the manufacturing conditions. As a consequence, the applicant (b) (4) the (b) (4) limit to (b) (4) (agreed to by the toxicology group) and acknowledges this heterogeneity in the submission, stating that "identification of individual (b) (4) is not feasible", but still states that the (b) (4) are qualified at (b) (4). It is important to prominently capture this information in the executive summary of the NDA review, otherwise the applicant may come back in the future with the same claim accompanied with a request for a (b) (4) limit in the drug substance and drug product specification.

-- The equivalency of drug substance from the three manufacturers will need to be evaluated.

-- The toxicology reviewer should be contacted regarding the acceptability of the impurity limits (b) (4) the 1% ICH qualification limit.

-- In addition to assay, the applicant uses a (b) (4) approach should be carefully evaluated.

-- The data show a definite decrease in assay value and increase in impurities with increasing time and increasing storage temperature so extrapolated results will need to be closely scrutinized.

C. Comments for 74-Day Letter -- None

D. Recommendation – From the CMC perspective this application is fileable

Marie Kowblansky, PhD
CMC Lead

9/27/2011
Date

Moo-Jhong Rhee, PhD
Branch Chief

Drug product manufacturers

<i>Facility and Address</i>	<i>Registration Number</i>	<i>Contact Person</i>	<i>Function</i>
Forest Laboratories, Ireland Ltd. Clonshaugh Business and Technology Park Clonshaugh, Dublin 17, Ireland	(b) (4)	(b) (4)	Manufacture (b) (4)
(b) (4)			(b) (4)
<i>Facility and Address</i>	<i>Registration Number</i>	<i>Contact Person</i>	<i>Function</i>
			(b) (4)

FILING CHECKLIST

NDA Number: **Supplement Number and Type:** **Established/Proper Name:**

NDA 202-811 original linaclotide

Applicant: **Letter Date:** **Stamp Date:**

Ironwood
Pharmaceuticals, Inc. August 9, 2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	√		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	√		
3.	Are all the pages in the CMC section legible?	√		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	√		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			Not applicable
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		

8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		
9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	√		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	√		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	√		Claim of categorical exclusion

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?		√	Referenced to DMFs (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		√	Referenced to DMFs (b) (4)
14.	Does the section contain information regarding the characterization of the DS?		√	Referenced to DMFs (b) (4)
15.	Does the section contain controls for the DS?		√	Referenced to DMFs (b) (4)
16.	Has stability data and analysis been provided for the drug substance?		√	Referenced to DMFs (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		√	Not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		√	Not a filing issue

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	√		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	√		
21.	Is there a batch production record and a proposed master batch record?	√		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	√		
23.	Have any biowaivers been requested?	√		waiver of pediatric studies
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	√		
25.	Does the section contain controls of the final drug product?	√		
26.	Has stability data and analysis been provided to support the requested expiration date?	√		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		√	Not a filing issue
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		√	Not a filing issue

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?		√	Although no separate validation package has been submitted, there appears to be sufficient methods validation information in the body of the submission Contact information to request reference standard is provided

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		√	Not required

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	√		

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	√		
33.	Have the immediate container and carton labels been provided?	√		

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	√		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Not applicable
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		√	No issues for inclusion in the 74-day letter

{See appended electronic signature page}

Marie Kowblansky, Ph.D.
CMC Lead
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment #
Office of New Drug Quality A

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/s/

MARIE KOWBLANSKY
09/28/2011

MOO JHONG RHEE
09/28/2011
Chief, Branch IV

MEMORANDUM

Date: August 15, 2012

To: NDA 202-811

From: Terrance Ocheltree, Ph.D., R.Ph.
Director
Division of New Drug Quality Assessment II
ONDQA

Subject: Tertiary review and Concurrence of ONDQA recommendation for NDA 202-811, Linzess™, linaclotide, capsules (145 ug, and 290 ug). Linaclotide is a new molecular entity (NME).

I have assessed the ONDQA reviews of NDA 202-811 by Jane Chang, Ph.D. and Karen Riviere Ph.D. and concur with the ONDQA recommendation of Approval. The initial ONDQA CMC review was entered into DARRTS on April 12, 2012, with a recommendation for a Complete Response due to an absence of a recommendation from the Office of Compliance on the manufacturing testing sites and pending labeling issues. The ONDQA Biopharmaceutics review was entered into DARRTS on April 10, 2012 with a recommendation for Approval. A second CMC review was entered into DARRTS on August 15, 2012 updating the status of the recommendation from the Office of Compliance. On August 15, 2012 the Office of Compliance entered an Overall Recommendation of "Acceptable" into EES.

All CMC related label/labeling issues were satisfactorily resolved through amendments dated July 25, 2012.

Linaclotide in NDA 202-811 is proposed for the treatment of irritable bowel syndrome with constipation and chronic constipation.

The drug substance, Linaclotide is manufactured by PolyPeptide Laboratories, Torrance, CA (DMF (b)(4)), PolyPeptide Laboratories, Sweden (DMF (b)(4)) and Corden Pharma Inc. (DMF (b)(4)). All three DMFs were reviewed and found to be adequate to support this NDA. For more information see DMF reviews for DMF (b)(4) completed on March 26, 2012, March 28, 2012 and March 29, 2012, respectively. A (b)(4) month retest date is recommended

The drug product, linaclotide capsules, is manufactured by Forest Laboratories, Ireland. Two strengths are proposed for commercialization, 145 ug and 290 ug, packaged in 4-count and 30-count HDPE bottle configurations and recommended to be stored at room temperature. The 145 ug strength capsules are supplied as a (b)(4) size 3, white to off-white opaque hard gelatin capsule with a gray imprint "FL 145" on the cap. The 290 ug strength capsules are supplied as a (b)(4) size 2, white to off-white opaque hard gelatin capsule with a gray imprint "FL 290" on the cap. The following expiration periods are approved:

- 15 months expiration dating period for 4-count and 30-count bottle configurations for 290 ug strength
- 15 months expiration dating period for 30-count bottle configuration for 145 ug strength
- 12 months expiration dating period for 4-count bottle configuration for 145 ug strength

I concur with the determination that the information as provided in the NDA is adequate to assure the identity, strength, purity, and quality of the drug product and support the recommended drug product shelf life as described above for the proposed commercial product when it is stored at controlled room temperature.

No Phase 4 recommendations are proposed.

The secondary review of the CMC reviews was performed by Moo-Jhong Rhee, Ph.D. The secondary review of the ONDQA Biopharmaceutics review was performed by Sandra Suarez, Ph.D.

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/s/

TERRANCE W OCHELTRIE
08/15/2012

MEMORANDUM

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

DATE: August 15, 2012

TO: Review #1 of NDA 202811

FROM: Jane Chang, Ph.D.
Review Chemist, ONDQA

SUBJECT: Final ONDQA Recommendation on
NDA 202811
Linzess (linaclotide) Capsules

SUMMARY

The previous CMC Review #1, dated 03-Apr-2012, made a recommendation of not approval of this NDA because of the following deficiencies:

1. Labeling issues were not resolved.
2. An overall recommendation by the Office of Compliance was still pending.

On 25-Jul-2012, revised Prescribing Information was provided, where 'Dosage Forms and Strengths', 'Description' and 'How Supplied/Storage and Handling' sections were updated per ONDQA's recommendation, and it is now deemed satisfactory.

On August 15, 2012, an overall "Acceptable" recommendation was issued from the Office of Compliance (see the **Attachment 1**).

RECOMMENDATION

This NDA is now recommended for approval from the ONDQA perspective.

Reviewer's Assessment: Whether (b) (4) should be used for the designation of the pharmacological/therapeutic class was discussed in the 5/31/2012 team labeling meeting. It was concluded that the proposed "guanylate cyclase-C agonist" as the pharmacological/therapeutic class is acceptable.

<i>Item</i>	<i>Comments on the Information Provided in NDA</i>	<i>Conclusions</i>
<i>Proprietary name and established name</i>	<i>LINZESS Established name, linaclotide, was provided.</i>	<i>Satisfactory</i>
<i>Dosage form and route of administration</i>	<i>capsule, oral</i>	<i>Satisfactory</i>
<i>Inactive ingredient information</i>	<i>All inactive ingredients are listed as follows: calcium chloride dihydrate, L-leucine, hypromellose, microcrystalline cellulose, gelatin, and titanium dioxide. They are not listed in alphabetical order, but since it is not an OTC product, it is acceptable.</i>	<i>Satisfactory</i>
<i>Pharmacological/ therapeutic class per 21 CFR 201.57(c)(12)(E)</i>	<i>guanylate cyclase-C agonist</i>	<i>Satisfactory</i>
<i>Chemical name, structural formula, molecular weight</i>	<i>Structural formula, molecular weight, and chemical name are provided correctly.</i>	<i>Satisfactory</i>
<i>Other important chemical or physical properties (such as pKa or pH)</i>	<i>Linaclotide is slightly soluble in water and aqueous sodium chloride (0.9%).</i>	<i>Satisfactory</i>

Conclusion: Satisfactory

c. Section 16 How Supplied/Storage and Handling

How Supplied

- 145 mcg Capsules: White to off-white opaque hard gelatin capsules with grey imprint "FL 145"
Bottle of 30: NDC 0456-1201-30
- 290 mcg Capsules: White to off-white opaque hard gelatin capsules with grey imprint "FL 290"
Bottle of 30: NDC 0456-1202-30

Storage

Store at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

Keep LINZESS in the original container. Do not subdivide or repackage. Protect from moisture. Do not remove desiccant from the container. Keep bottles tightly closed in a dry place.

Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
<i>Strength of dosage form in metric system</i>	<i>Strengths are correctly described as 145 mcg and 290 mcg per capsule</i>	Satisfactory
<i>Units of dosage form e.g. bottles of 30 tablets</i>	<i>Available units are correctly described as 30 capsules per bottle</i>	Satisfactory
<i>Identification of dosage forms, shape, color, coating, scoring, imprinting, NDC number</i>	<i>The identification of the dosage form is described as white to off-white opaque hard gelatin capsules, imprinted with "FL 145" in grey color for 145 mcg capsules and white to off-white opaque hard gelatin capsules, imprinted with "FL 290" in grey color for 290 mcg capsules. NDC Numbers are stated: NDC 0456-1201-30 for 145 mcg capsules; NDC 0456-1202-30 for 290 mcg capsules.</i>	Satisfactory
<i>Special handling (e.g., protect from light)</i>	<i>Keep LINZESS in the original container. Do not subdivide or repackage. Protect from moisture. Do not remove desiccant from the container. Keep bottles tightly closed in a dry place.</i>	Satisfactory
<i>Storage condition</i>	<i>Storage condition is described as "Store at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature]."</i>	Satisfactory

Conclusion: **Satisfactory**

d. Manufacturer's or Distributor's name

Distributed by:
 Forest Pharmaceuticals, Inc.
 Subsidiary of Forest Laboratories, Inc.
 St. Louis, Missouri, 63045

Marketed by:

Forest Pharmaceuticals, Inc. Subsidiary of Forest Laboratories, Inc. St. Louis, Missouri, 63045	Ironwood Pharmaceuticals, Inc. Cambridge, MA, 02142
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Reviewer's Assessment: *The information in this section, which is provided at the end of Prescribing Information, remains the same as that provided in the original submission.*

Conclusion: **Satisfactory**

2. EES Status

An update was provided by the Office of Compliance. All manufacturing and testing facilities were determined to be acceptable as recommended by M. Stock on August 15, 2012. The EES Summary Report is included in **Attachment 1**.

3. Biopharmaceutics Review Status

At the completion of CMC Review #1, an agreement was reached for dissolution method and acceptance criterion, but the Biopharmaceutics review had not been

finalized (see CMC Review #1, page 142). Subsequently, a recommendation of approval was made on 10-Apr-2012 by the Biopharmaceutics Reviewer, Dr. Karen Riviere.

II. Attachment 1: EES report

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 202811/000	Sponsor:	FOREST LABS INC
Org. Code:	180		HARBORSIDE FINANCIAL CENTER PLAZA V
Priority:	1		JERSEY CITY, NJ 07311
Stamp Date:	09-AUG-2011	Brand Name:	LINZESS
PDUFA Date:	09-SEP-2012	Estab. Name:	
Action Goal:		Generic Name:	Linaclotide
District Goal:	10-APR-2012	Product Number; Dosage Form; Ingredient; Strengths	
			001; CAPSULE; LINACLOTIDE; 145MCG 002; CAPSULE; LINACLOTIDE; 290MCG
FDA Contacts:	C. TRAN-ZWANETZ	Project Manager	(HFD-800) 3017963877
	J. CHANG	Review Chemist	3017961973
	M. KOWBLANSKY	Team Leader	3017961390

Overall Recommendation:	ACCEPTABLE	on 15-AUG-2012	by M. STOCK	(HFD-320)	3017964753
	PENDING	on 15-MAR-2012	by EES_PROD		
	PENDING	on 12-OCT-2011	by EES_PROD		
	PENDING	on 12-OCT-2011	by EES_PROD		
	PENDING	on 05-OCT-2011	by EES_PROD		
	PENDING	on 05-OCT-2011	by EES_PROD		

Establishment:	CFN:	(b) (4)	FEI:	(b) (4)
DMF No:			AADA:	
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER			
Profile:	CONTROL TESTING LABORATORY			OAI Status: NONE
Last Milestone:	OC RECOMMENDATION			
Milestone Date:	30-MAY-2012			
Decision:	ACCEPTABLE			
Reason:	DISTRICT RECOMMENDATION			

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER

Profile: CAPSULES, PROMPT RELEASE OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-OCT-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-OCT-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 04-JUN-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment:	CFN: (b) (4)	FEI: (b) (4)
	(b) (4)	
DMF No:		AADA:
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER	
Profile:	CONTROL TESTING LABORATORY	OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	06-OCT-2011	
Decision:	ACCEPTABLE	
Reason:	BASED ON PROFILE	
<hr/>		
Establishment:	CFN: (b) (4)	FEI: (b) (4)
	(b) (4)	
DMF No:		AADA:
Responsibilities:	DRUG SUBSTANCE OTHER TESTER	
Profile:	CONTROL TESTING LABORATORY	OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	15-AUG-2012	
Decision:	ACCEPTABLE	
Reason:	DISTRICT RECOMMENDATION	
<hr/>		
Establishment:	CFN: (b) (4)	FEI: (b) (4)
	(b) (4)	
DMF No:		AADA:
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER	
Profile:	CONTROL TESTING LABORATORY	OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	15-MAR-2012	
Decision:	ACCEPTABLE	
Reason:	BASED ON PROFILE	
<hr/>		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-OCT-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
FOREST LABORATORIES IRELAND, LTD.
CLONSHAUGH BUSINESS AND TECHNOLOGY PARK
DUBLIN 17, CLONSHAUGH, IRELAND

DMF No: AADA:

Responsibilities: (b) (4) MANUFACTURER
(b) (4) TESTER
(b) (4) TESTER

Profile: CAPSULES, PROMPT RELEASE OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-APR-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER

Profile: CAPSULES, PROMPT RELEASE OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-OCT-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-APR-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-OCT-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-OCT-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: [REDACTED] FEI: [REDACTED] (b) (4)
[REDACTED] (b) (4)

DMF No: [REDACTED] AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 15-AUG-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: [REDACTED] (b) (4) FEI: [REDACTED] (b) (4)
[REDACTED] (b) (4)

DMF No: [REDACTED] AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-OCT-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: [REDACTED] (b) (4) FEI: [REDACTED] (b) (4)

POLYPEPTIDE LABORATORIES (SWEDEN) AB
HOGERUDSGATAN 21, LIMHAMM
LIMHAMN, SWEDEN

DMF No: [REDACTED] (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: NON-STERILE API [REDACTED] (b) (4) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-OCT-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
POLYPEPTIDE LABORATORIES INC

DMF No: TORRANCE, , UNITED STATES 905032602 (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 12-OCT-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Profile: NON-STERILE API (b) (4) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 07-MAR-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: NON-STERILE API (b) (4) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 18-OCT-2011

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

/s/

JANE L CHANG
08/15/2012

MOO JHONG RHEE
08/15/2012
Chief, Branch IV

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Dr. Jane Chang, CMC Reviewer
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: jane.chang@fda.hhs.gov
Phone: (301)-796-1973
Fax: (301)-796-9877

FROM: FDA
Division of Pharmaceutical Analysis
James Allgire, Team Leader
Suite 1002
1114 Market Street
St. Louis, MO 63101
Phone: (314) 539-3813

Through: Benjamin J. Westenberger, Deputy Director
Phone: (314) 539-3869

SUBJECT: Methods Validation Report Summary

Application Number: NDA 202811

Name of Product: Linzess (linoclotide) Capsules, 145 mcg and 290 mcg

Applicant: Ironwood Pharmaceuticals, Inc.

Applicant's Contact Person: Mark Currie, VP R&D, Chief Scientific Officer

Address: 301 Binney Street, Cambridge, MA 02142

Telephone: 617-621-8419 Fax: FAX Number

Date Methods Validation Consult Request Form Received by DPA: 10/18/11

Date Methods Validation Package Received by DPA: 10/18/11

Date Samples Received by DPA: 11/10/11

Date Analytical Completed by DPA: 04/16/12

Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes.
2. Methods are acceptable with modifications (as stated in accompanying report).
3. Methods are unacceptable for regulatory purposes.

Comments:

The cover memo and summary of results are attached



Date: April 11, 2012
To: Dr. Jane Chang, CMC Reviewer, ONDQA
Through: B.J.Westenberger, Deputy Director, Division of Pharmaceutical Analysis (HFD-920)
From: Anjanette Smith, Chemist, Division of Pharmaceutical Analysis (HFD-920)
Subject: Method Validation for NDA 202-811
Linzess (linaclotide) Capsules, 145 mcg
Ironwood Pharmaceuticals, Inc.

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

- Method for the analysis of Linaclotide by SEC for Ironwood Pharmaceuticals, Inc. (MOA-0091-01)
- Method for the analysis of identification, assay and purity of Linaclotide by HPLC (MOA-0093-04)
- Method for the analysis of identification, assay and purity of Linaclotide by HPLC (MOA-0094-03)
- Impurities testing (by HPLC) for Linaclotide capsules, 145 mcg and 290 mcg (PRD-TM-ANL-00760)
- Identification, assay and content uniformity (by HPLC) for Linaclotide capsules, 145ug and 290ug (PRD-TM-ANL-00769)
- Identification and determination of (b)(4) by HPLC for Linaclotide capsules, 145ug and 290ug (PRD-TM-ANL-00772)
- Identification, assay and content uniformity (by UPLC) for Linaclotide capsules, 145ug and 290ug (PRD-TM-ANL-00770)

The Division of Pharmaceutical Analysis (DPA) has the following comments pertaining to the methods that should be addressed.

- All methods for drug product have a problem (b)(4) The method should specify how to quantitatively (b)(4) (b)(4)
- All methods for drug product state (b)(4)
- Method for the analysis of linaclotide by SEC for Ironwood Pharmaceuticals, Inc. (MOA-0091-01)
 1. (b)(4)

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

/s/

JAMES F ALLGIRE
04/16/2012

BENJAMIN J WESTENBERGER
04/16/2012

NDA 202-811

Linzess (linaclotide) Capsules
145 mcg, 290 mcg

Forest Laboratories, Inc.

Jane L. Chang, Ph.D.

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV

For Division of Gastroenterology and Inborn Errors Products
HFD-180

Table of Contents

The Executive Summary	9
I. Recommendations.....	9
A. Recommendation and Conclusion on Approvability	9
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	9
II. Summary of Chemistry Assessments.....	9
A. Description of the Drug Product(s) and Drug Substance(s).....	9
B. Description of How the Drug Product is Intended to be Used.....	11
C. Basis for Approvability or Not-Approval Recommendation	11
III. Administrative.....	11
A. Reviewer’s Signature.....	11
B. Endorsement Block.....	11
C. CC Block.....	12
Chemistry Assessment	13
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	13
S DRUG SUBSTANCE.....	13
S.1 General Information	13
S.1.1 Nomenclature	13
S.1.2 Structure	13
S.1.3 General Properties	14
S.2 Manufacture	15
S.2.1 Manufacturers.....	15
S.2.2 Description of Manufacturing Process and Process Controls.....	16
S.2.3 Control of Materials.....	18
S.2.4 Controls of Critical Steps and Intermediates	18
S.2.5 Process Validation and/or Evaluation.....	18
S.2.6 Manufacturing Process Development.....	19
S.3 Characterization	23
S.3.1 Elucidation of Structure and other Characteristics	23
S.3.2 Impurities.....	35
S.4 Control of Drug Substance.....	49
S.4.1 Specification.....	49
S.4.2 Analytical Procedures.....	51
S.4.3 Validation of Analytical Procedures.....	57
S.4.4 Batch Analyses	64
S.4.5 Justification of Specification	70

S.5	Reference Standards or Materials	79
S.6	Container Closure System.....	81
S.7	Stability	81
S.7.1	Stability Summary and Conclusions.....	81
S.7.2	Postapproval Stability Protocol and Stability Commitment	84
S.7.3	Stability Data	84
P	DRUG PRODUCT	84
P.1	Description and Composition of the Drug Product	84
P.2	Pharmaceutical Development.....	85
P.2.1	Components of the Drug Product	85
P.2.2	Drug Product	87
P.2.3	Manufacturing Process Development.....	92
P.2.4	Container Closure System	101
P.2.5	Microbiological Attributes	102
P.2.6	Compatibility.....	102
P.3	Manufacture	104
P.3.1	Manufacturers.....	104
P.3.2	Batch Formula	105
P.3.3	Description of Manufacturing Process and Process Controls.....	106
P.3.4	Controls of Critical Steps and Intermediates	110
P.3.5	Process Validation and/or Evaluation.....	114
P.4	Control of Excipients	114
P.4.1	Specifications	114
P.4.2	Analytical Procedures.....	116
P.4.3	Validation of Analytical Procedures.....	116
P.4.4	Justification of Specifications.....	116
P.4.5	Excipients of Human or Animal Origin.....	116
P.4.6	Novel Excipients.....	116
P.5	Control of Drug Product.....	116
P.5.1	Specification	116
P.5.2	Analytical Procedures.....	118
P.5.3	Validation of Analytical Procedures.....	123
P.5.4	Batch Analyses	132
P.5.5	Characterization of Impurities	136
P.5.6	Justification of Specification	138
P.6	Reference Standards or Materials	143
P.7	Container Closure System	143
P.8	Stability	145
P.8.1	Stability Summary and Conclusion	146
P.8.2	Postapproval Stability Protocol and Stability Commitment	148
P.8.3	Stability Data	149
A	APPENDICES	152
A.1	Facilities and Equipment (biotech only)	155
A.2	Adventitious Agents Safety Evaluation	155
A.3	Novel Excipients	155
R	REGIONAL INFORMATION	155
R.1	Executed Batch Records	155
R.2	Comparability Protocols.....	155
R.3	Methods Validation Package.....	155

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	156
A. LABELING & PACKAGE INSERT.....	156
1. Physician’s Labeling Rule Prescription Drug Labeling	156
2. Labels	161
3. Drug Listing Data Elements in Structured Product Labeling.....	166
B. ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION	169
III. List Of Deficiencies	170
IV. Attachment – EES Report.....	173

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 202-811
2. REVIEW #: 1
3. REVIEW DATE: 03-APR-2012
4. REVIEWER: Jane L. Chang, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
05-15-2008 EOP2 Meeting Minutes	14-Jul-2008
11/06/2008 EOP2 CMC Meeting Minutes	01-Jun-2009
Preliminary Comments for 5/20/2010 CMC Meeting	14-May-2010
1/20/2011 CMC Meeting Minutes	07-Feb-2011
Preliminary Comments for 5/11/2011 Pre-NDA CMC Meeting Minutes	04-May -2011

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	08-Aug-2011
General Correspondence	03-Nov-2011
Administrative Change/Applicant	07-Nov-2011
Amendment	16-Nov-2011
Amendment	18-Nov-2011
Amendment	03-Dec-2011
Amendment (email response provided on 10-Feb-2012)	29-Feb-2012
Amendment	09-Mar-2012
Amendment (labeling)	16-Mar-2012
Amendment	26-Mar-2012
Amendment (labeling)	27-Mar-2012

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Ironwood Pharmaceuticals, Inc. was the original applicant of this NDA. The ownership of the NDA was changed in the 07-Nov-2011 submission. The updated information is listed below.

Name: Forest Laboratories, Inc.
Address: Harborside Financial Center, Plaza V
Jersey City, NJ 07311
Representative: Linda Kunka
Senior Manager, Regulatory Affairs
linda.kunka@frx.com
Telephone: (201) 386-2124
Fax: (631) 858-7921

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Linzess
- b) Non-Proprietary Name (USAN): linaclotide
- c) Code Name/# (ONDQA only): N/A
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 1 (new molecular entity)
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: guanylate cyclase type C (GC-C) agonist

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 145 µg and 290 µg

13. ROUTE OF ADMINISTRATION: oral

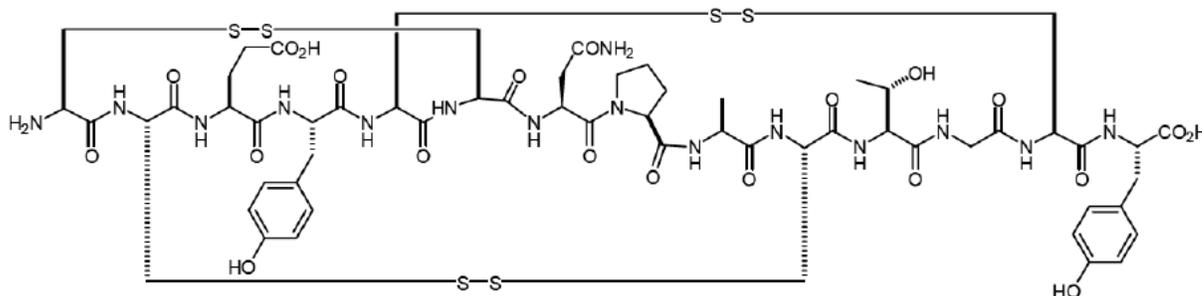
14. Rx/OTC DISPENSED: Y Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

 SPOTS product – Form Completed

 Y Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Molecular Formula:

C₅₉H₇₉N₁₅O₂₁S₆

Average Molecular Mass:

1526.8 Da

Monoisotopic Molecular Mass:

(b) (4)

CAS No:

851199-59-2

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	PolyPeptide, Torrance	Linacotide	1	adequate	3/26/2012	By J. Chang
(b) (4)	II	PolyPeptide, Sweden	Linacotide	1	adequate	3/28/2012	By J. Chang
(b) (4)	II	Corden Pharma Colorado	Linacotide	1	adequate	3/29/2012	By J. Chang
(b) (4)	IV	(b) (4)	(b) (4)	4	N/A		*
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		**
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		**
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		**
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		**
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		**
(b) (4)	III	(b) (4)	(b) (4)	4	N/A		**

*See pages 85 and 116 for details.

**See page 145 for details.

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Chemistry Review Data Sheet

Other codes indicate why the DMF was not reviewed, as follows:

- 2 – Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	63,290	Linaclootide

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending ¹		
Pharm/Tox	N/A		
Biopharmaceutics	Pending ²		
Methods Validation	Pending ³		
Office of Drug Safety	Acceptable for "Linzess: as the proprietary name"	11/17/2011	J. W. Parker
EA	N/A		
Microbiology	N/A		

¹As of the date of this review, evaluation of the following sites is still pending.

Drug substance testing sites:

- [REDACTED] (b) (4)
- [REDACTED]
- [REDACTED]

Drug product manufacturing and testing sites:

- Forest Laboratories, Ireland, Ltd.
- Forest Research Institute, Inc.
- [REDACTED] (b) (4)

²As of the date of this review, Biopharmaceutics final review is underway.

³As of the date of this review, evaluation of the methods validation by Division of Pharmaceutical Analysis is still pending. The pending status has no impact on the CMC recommendation and conclusion on approvability for the NDA per CDER policy.

Executive Summary Section

Chemistry Review for NDA 202-811

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. However, labeling issues are still pending and a site recommendation from the Office of Compliance has not been made as of the date of this review.

Therefore, from the ONDQA perspective, this NDA is *not* recommended for approval per 21 CFR 314.125(b)(6),(13) in its present form until all issues are resolved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Product

Linress (linaclotide) capsules are available as 145 µg and 290 µg immediate release capsules indicated for irritable bowel syndrome with constipation (290 µg) and chronic constipation (145 µg (b) (4)). Linaclotide capsules, 145 µg are supplied as a (b) (4) size 3, white to off-white opaque hard gelatin capsule with a gray imprint "FL 145" on the cap. The 290 µg strength capsules are supplied as a (b) (4) size 2, white to off-white opaque hard gelatin capsule with a gray imprint "FL 290" on the cap.

Linaclotide capsules are manufactured in two stages: (b) (4)

The process for each stage is controlled by respective operating ranges which are established based on developmental studies. The two strengths are (b) (4)

No novel excipients are used. The excipients (b) (4) are: calcium

Executive Summary Section

chloride dihydrate, L-leucine, hypromellose and microcrystalline cellulose. (b) (4)
gelatin and titanium dioxide.

The proposed specifications for linaclotide capsules are acceptable. The specifications include description, identification (UPLC and size exclusion chromatography), uniformity of dosage units, assay, related substances, total (b) (4), microbial limits, and dissolution. The analytical procedures and their validations were reviewed and found to be adequate to support their intended purpose. A Methods Validation request was sent to Division of Pharmaceutical Analysis (DPA) in St. Louis. As of the date of this review, evaluation of the methods validation by DPA is still pending, however, the pending status has no impact on the CMC recommendation and conclusion on approvability for the NDA per CDER policy. The applicant revised the dissolution method and acceptance criterion per Biopharmaceutics Reviewer's recommendation (see page 142), and they are acceptable.

The capsules are packaged in HDPE bottles with silica gel desiccant and capped with aluminum (b) (4) sealed (b) (4) cap. **Linaclotide capsules should be kept in the original container with the desiccant to prevent from moisture.** Two major degradation products, (b) (4), have been observed. Formation of (b) (4) degradant is attributed to the presence of (b) (4). The level of (b) (4) is dependent on the (b) (4) to which the product is exposed to. Stability data, which included both 4-count and 30-count bottle configurations, based on three registration batches and five supporting batches for each strength support the proposed expiration dating period, as listed below, when stored at 25°C (77°F); excursions permitted to 15 – 30°C (59 – 86°F).

- 15 months expiration dating period for 4-count and 30-count bottle configurations for 290 µg strength
- 15 months expiration dating period for 30-count bottle configuration for 145 µg strength
- 12 months expiration dating period for 4-count bottle configuration for 145 µg strength

The request for a categorical exclusion from the preparation of an environmental assessment (EA) under 21 CFR 25.31(b) is acceptable.

(2) Drug Substance

The drug substance linaclotide is a new molecular entity. It is a guanylate cyclase type C (GC-C) agonist. Linaclotide is a 14-amino acid peptide with three disulfides at Cys¹-Cys⁶, Cys²-Cys¹⁰, and Cys⁵-Cys¹³. Linaclotide is classified as Class III compound (high solubility, low permeability) according to Biopharmaceutics Classification System (BCS).

Executive Summary Section

Linaclotide is manufactured by PolyPeptide Laboratories, Torrance, CA (DMF (b) (4)), PolyPeptide Laboratories, Sweden (DMF (b) (4)), and Corden Pharma Inc. (DMF (b) (4)). Information on characterization of linaclotide, including elucidation of structure and other characteristics, as well as reference standard and impurities was provided in the NDA. All other CMC information is referenced to their respective DMFs and a letter of authorization has been provided from each DMF holder. All three DMFs have been reviewed by this reviewer and found to be adequate to support this NDA.

The proposed linaclotide specification includes testing for appearance, solubility, identification (mass spectrometry, amino acid analysis, RP-HPLC), assay (RP-HPLC), related substances (two different RP-HPLC), (b) (4), water, specific optical rotation, residue on ignition, microbial limits, and residual solvents. The analytical procedures and their validations were reviewed and found to be adequate to support their intended purpose.

Stability data support a retest period of (b) (4) for drug substance when stored at (b) (4).

B. Description of How the Drug Product is Intended to be Used

The recommended dose of LINZESS for irritable bowel syndrome with constipation is 290 µg taken orally once daily on an empty stomach. The recommend dose of LINZESS for chronic constipation is 145 µg (b) (4) taken orally once daily on an empty stomach.

C. Basis for Not-Approval Recommendation

- 21 CFR 314.125 (b)(6)
Labeling issues are not yet resolved (see pages 157-160).
- 21 CFR 314.125 (b)(13)
A recommendation by the Office of Compliance is still pending.

III. Administrative**A. Reviewer's Signature**

See appended electronic signature page

B. Endorsement Block

See appended electronic signature page

Executive Summary Section

C. CC Block

Entered electronically in DARRTS

167 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JANE L CHANG
04/03/2012

MOO JHONG RHEE
04/03/2012
Chief, Branch IV