CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202811Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Risk Evaluation and Mitigation Strategy (REMS) Memo

Date:	August 7, 2012
Reviewer(s):	Yasmin Choudhry, M.D., Medical Officer, Division of Risk Management (DRISK)
	Kendra Worthy, Pharm. D., Team Leader, DRISK
Division Director	Claudia Manzo, Pharm. D., DRISK
Drug Name(s):	Linzess (linaclotide) Capsules 145 mcg and 290 mcg
Therapeutic Class:	Guanylate cyclase C (GC-C) receptor agonist (first in Class)
Indication(s):	1) Treatment of irritable bowel syndrome with constipation (290 mcg) in patients ≥ 18 years of age
	2) Treatment of chronic idiopathic constipation (145 mcg)
Application Type/Number:	NDA 202811
Applicant:	Ironwood Pharmaceuticals, Inc.
OSE RCM #:	2011- 3246

INTRODUCTION

An application for Linzess (linaclotide) NDA 202811 was submitted to the Division of Gastroenterology and Inborn Errors Products (DGIEP) by Ironwood Pharmaceuticals on August 9, 2011. Even though the Applicant did not propose a risk evaluation and mitigation strategy (REMS), DRISK was consulted by the Division of Gastroenterology and Inborn Errors Products for participation in the approval process because the proposed drug is a new molecular entity (NME).

Linaclotide, a synthetic analog of the endogenous guanylin peptide family, is the first GC-C receptor agonist in clinical development. It is indicated in adult patients for the treatment of:

1. Irritable bowel syndrome with constipation - 290 mcg capsule orally once a day
2. Chronic idiopathic constipation (CIC) - proposed dosages of 145 mcg capsule orally once a day

1.1 MATERIALS REVIEWED

- Midcycle review slides
- Clinical reviews by Lara Dimick-Santos, M.D., FACS. and Erica Wynn, M.D., M.P.H.

1.2 OVERVIEW OF CLINICAL PROGRAM

Linaclotide's mechanism of action[1] is due to binding to and activation of GC-C receptors on the luminal surface of the epithelial cells in the gastrointestinal tract; activation of the GC-C receptor causes secretion of fluid and electrolytes into the intestinal lumen resulting in an increase in transit. Linaclotide may also result in reduced visceral pain secondary to decrease in pain-fiber activity.

Linaclotide has very low systemic bioavailability and does not interact with P450 or P-gp. It is metabolized within the gastrointestinal tract to a single active metabolite (MM-419447); the active metabolite is further degraded intralumenally to smaller peptides and naturally occurring amino acids and no toxic intermediaries have been identified.

Efficacy for both indications was demonstrated in > 4000 patients in randomized, placebo controlled clinical trials. Common adverse events included diarrhea, flatulence, abdominal pain, upper respiratory tract infections and nausea. Diarrhea was the most common adverse event occurring in approximately 17% of treated patients in the placebo-controlled clinical trials; serious diarrhea was rare (seen in 2-3% of patients). In long term clinical trials, postural hypotension, attributed to concomitant dehydration, was seen in 3 chronic idiopathic constipation patients, and two cases of documented ischemic colitis were identified which were not thought to be related to the drug; the clinical

[1] Ironwood Pharmaceuticals, Inc.'s New Drug Application Submission No. 202811, Sequence 0000 for Linaclotide (Linzess) dated August 9, 2011.

reviewers recommended that these be monitored by routine post-marketing surveillance. No deaths related to the drug were reported[2].

Note: The Linzess dosages and indications of use initially proposed by the Applicant were:

- 290 mcg for irritable bowel syndrome
- 145 mcg [redacted] for chronic constipation [redacted]

The clinical reviewer (Dr. Erica Wynn) recommended that linaclotide be approved for use in patients with CIC and not for use for use in patients with chronic constipation due to other etiologies such as gastroparesis, biochemical or underlying anatomical defects. In clinical trials, patients with "functional constipation" were enrolled, (functional constipation by definition has no known etiology). The clinical reviewer also recommended that [redacted] not be approved for the treatment of CIC as the clinical reviewer believes that the term [redacted] is subjective and has not been completely established; the sponsor agreed to remove the [redacted] dose from the CIC indication[3]

The labeling will carry a boxed warning with a contraindication for use of linaclotide in pediatric patients up to 6 years of age and a warning against use in pediatric patients 6 through [redacted] years of age; the Medication Guide reflects these changes[4]. The pediatric clinical trials were deferred in light of preclinical data showing a large number of deaths in infant mice. Linzess is labeled as Pregnancy [redacted].

2 DISCUSSION

IBS-C affects about 2% of the US population, while chronic idiopathic constipation affects between 2-28 % of Americans. There is a lack of prescription therapies available for chronic constipation and none of the available over-the-counter (OTC) products are designed to be used chronically; there is also concern for the potential misuse of taking OTC products at unsafe doses. Currently, there is only one other agent approved for chronic idiopathic constipation on the market Lubiprostone (Amitizal). Hence, linaclotide may fulfill an unmet need particularly for those patients who have failed other options for both indications.

Linaclotide showed clinical benefit in patients for both proposed indications; the adverse event profile of linaclotide was generally favorable and clinical trials demonstrated an overall low risk with an acceptable safety profile of Linzess (linaclotide).

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[2] Clinical Review, Linzess (linaclotide) Capsules NDA 202811 dated April 12, 2012 by Lara Dimick-Santos M.D., F.A.C.S.

[3] Clinical Review, Linzess (linaclotide) Capsules NDA 202811 dated July 17, 2012 by Erica Wynn, M.D., M.P.H., and Robert Fiorentino, M.D., M.P.H.

[4] Patient Labeling Review by Sharon R. Mills, BSN, RN, CCRP, dated June 28, 2012

3 CONCLUSION

DRISK believes that a REMS for Linzess (linaclotide) is not necessary at this time. The Applicant's proposal for labeling and routine pharmacovigilance is reasonable. Should DGIEP identify additional safety information that warrants risk mitigation measures, please send a consult to DRISK.

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/s/

YASMIN A CHOUDHRY
08/07/2012

KENDRA C WORTHY
08/07/2012