Drug Monograph

Drug/Drug Class:	**Linzess™ (linaclotide) capsule / guanylate cyclase-C agonist**
Prepared for:	MO HealthNet
Prepared by:	Xerox Heritage, LLC

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Each 145 mcg capsule of Linzess™ contains 145 mcg of linaclotide and each 290 mcg capsule of Linzess™ contains 290 mcg of linaclotide. Distributed by: Forest Pharmaceuticals, Inc. Subsidiary of Forest Laboratories, Inc. St. Louis, Missouri, 63045
Summary of Findings:	Linaclotide is a guanylate cyclase-C agonist that has demonstrated efficacy for the treatment of irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) in adults. It is the first agent approved in this class of medications and offers a new treatment option.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☒ Clinical Edit ☐ PDL Product
Type of PA Criteria:	☐ Increased Risk of ADE ☐ No PA Required ☒ Appropriate Indications ☐ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction

According to the National Institutes of Health, an estimated 63 million people are affected by chronic constipation and an estimated 15.3 million people are affected by IBS (IBS-C is a subtype).

Dosage Form(s)[1]

Each 145 mcg capsule of Linzess™ contains 145 mcg of linaclotide and each 290 mcg capsule of Linzess™ contains 290 mcg of linaclotide.

Manufacturer

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 and Ironwood Pharmaceuticals, Inc. Cambridge, MA, 02142

Indication(s)[1]

Linaclotide is FDA approved for the treatment of irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) in adults.

Clinical Efficacy[1-10] (mechanism of action/pharmacology, comparative efficacy)

Linzess is a guanylate cyclase-C (GC-C) agonist. Both Linzess and its active metabolite bind to GC-C and act locally on the luminal surface of the intestinal epithelium. Activation of GC-C results in an increase in both intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP). Elevation in intracellular cGMP stimulates secretion of chloride and bicarbonate into the intestinal lumen, mainly through activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel, resulting in increased intestinal fluid and accelerated gastrointestinal (GI) transit. In animal models, Linzess has been shown to both accelerate GI transit and reduce intestinal pain. The linaclotide-induced reduction in visceral pain in animals is thought to be mediated by increased extracellular cGMP, which was shown to decrease the activity of pain-sensing nerves.

PHARMACOKINETICS

Linzess is minimally absorbed with low systemic availability following oral administration. It is metabolized in the GI tract to an active metabolite by loss of the tyrosine moiety, and is further degraded to smaller peptides and amino acids.

EFFICACY (1-3,6-10) SUMMARY

The approval of Linzess was primarily based upon 2 double-blind, placebo-controlled, randomized clinical trials involving 1604 adult patients with IBS-C and 2 double-blind, placebo-controlled trials involving 1272 adults with CIC. Results from the studies showed that patients with IBS-C receiving Linzess experienced a significant reduction in abdominal pain and a significant increase in the number of complete spontaneous bowel movements (CSBMs) compared with patients receiving placebo. Study results also showed that Linzess therapy significantly increased CSBMs in patients with CIC compared with placebo.

IRRITABLE BOWEL SYNDROME WITH CONSTIPATION

CONCLUSION (1)
Linzess is effective in the treatment of irritable bowel syndrome with constipation (IBS-C) in adults.

STUDY DESIGN	Two multicenter, double-blind, placebo-controlled, randomized clinical trials (n=1604).
INCLUSION CRITERIA	Adult patients with IBS-C. All patients met Rome II criteria for IBS and were required to meet the following criteria during the 2-week baseline period: 1) have a mean abdominal pain score of at least 3 (numeric rating scale, 0 to 10 points); 2) have less than 3 complete spontaneous bowel movements/week (CSBMs), with a CSBM defined as a spontaneous bowel movement (SBM) that is associated with a sense of complete evacuation; and 3) have less than or equal to 5 SBMs/week, with an SBM defined as a bowel movement occurring in the absence of laxative use.
EXCLUSION CRITERIA	Not specified.
TREATMENT REGIMEN	Patients were randomized to receive Linzess 290 mcg once daily or placebo. The trial designs were identical through the first 12 weeks. Trial 1 included a 4-week randomized withdrawal period, where patients were randomized a second time to Linzess or placebo, and Trial 2 continued for 14 additional weeks of double-blind treatment. Patients were allowed to continue stable doses of bulk laxatives or stool softeners, but were not allowed to take laxatives, bismuth, prokinetic agents, or other drugs for IBS-C or chronic constipation. Linzess efficacy was assessed from self-reported diaries of changes from baseline in abdominal pain and/or CSBMs (primary endpoints). Results for abdominal pain and CSBMs were reported separately and together, which defined a combined primary efficacy responder. Group 1 included patients who responded for at least 9 out of the first 12 weeks of treatment, and Group 2 included patients who responded for at least 6 out of the first 12 weeks of treatment. In Group 1, a combined primary efficacy responder was a patient who had at least a 30% reduction from baseline in mean abdominal pain, at least 3

	CSBMs, and an increase of at least 1 CSBM from baseline, all in the same week. In Group 2, a combined primary efficacy responder was a patient who had at least a 30% reduction from baseline in mean abdominal pain and an increase of at least 1 CSBM from baseline, all in the same week.
RESULTS	In both trials, the proportion of patients who responded to Linzess was significantly higher than placebo. Combined efficacy responder rates (abdominal pain and CSBM) for at least 9 out of 12 weeks with Linzess versus placebo were 12.1% versus 5.1% (95% CI, 3.2% to 10.9%) and 12.7% versus 3% (95% CI, 6.1% to 13.4%) in Trial 1 and 2, respectively. Combined efficacy responder rates for at least 6 out of 12 weeks with Linzess versus placebo were 33.6% versus 21% (95% CI, 6.5% to 18.7%) and 33.7% versus 13.9% (95% CI, 14% to 25.5%) in Trial 1 and 2, respectively. During the 4-week withdrawal period, subjects who were initially randomized to Linzess and subsequently randomized to placebo experienced decreased frequency of CSBM and increased abdominal pain severity within 1 week, although symptoms were not worse when compared with baseline measurements.
SAFETY	Not specified.

CHRONIC IDIOPATHIC CONSTIPATION

CONCLUSION (1)
Linzess is effective in the treatment of chronic idiopathic constipation (CIC) in adults.

STUDY DESIGN	Two multicenter, double-blind, placebo-controlled, randomized clinical trials (n=1272).
INCLUSION CRITERIA	Adult patients with CIC who met modified Rome II criteria. The modified Rome II criteria included less than 3 spontaneous bowel movements/week (SBMs) and 1 of the following symptoms for at least 12 weeks, which need not be consecutive, in the preceding 12 months: 1) straining during greater than 25% of bowel movements, 2) lumpy or hard stools during greater than 25% of bowel movements, and 3) a sensation of incomplete evacuation during greater than 25% of bowel movements. Patients were also required to have less than 3 CSBMs/week and less than or equal to 6 SBMs/week during a 2-week baseline period.
EXCLUSION CRITERIA	Patients were excluded if they met criteria for IBS-C or had fecal impaction that required emergency room treatment.
TREATMENT REGIMEN	Patients were randomized to receive Linzess 145 mcg or 290 mcg once daily or placebo. The trial designs were identical through the first 12 weeks. Trial 1 included an additional 4-week randomized withdrawal period, where patients were randomized a second time to Linzess or placebo. Patients were allowed to continue stable doses of bulk laxatives or stool softeners, but were not allowed to take laxatives, bismuth, prokinetic agents, or other drugs to treat chronic constipation. Linzess efficacy was assessed from self-reported diaries using overall responder analysis of changes from baseline in CSBMs (primary endpoint). A CSBM overall responder was defined as a patient who had

	at least 3 CSBMs and an increase of at least 1 CSBM from baseline in a given week for at least 9 out of the 12 weeks of treatment. During the individual trials, Linzess 290 mcg did not consistently offer additional clinically meaningful benefit beyond that observed with the 145 mcg dose, which is the FDA-approved recommended dose. Only data for the 145 mcg dose of Linzess are presented.
RESULTS	The proportion of patients who were CSBM overall responders was significantly greater for Linzess 145 mcg when compared with placebo. Efficacy responder rates at least 9 out of 12 weeks for Linzess versus placebo were 20.3% versus 3.3% (95% CI, 11% to 22.8%) and 15.5% versus 5.6% (95% CI, 4.2% to 15.7%) in Trial 1 and 2, respectively.
SAFETY	Not specified.

Contraindications[1]

- Pediatric patients up to 6 years of age
- Patients with known or suspected mechanical gastrointestinal obstruction

Warnings and Precautions[1]

- Avoid use in pediatric patients 6 through 17 years of age.
- Severe diarrhea has been reported; interruption of dose or discontinuation may be necessary.

Adverse Effects[1]

Most common, >= 2%	**Linzess 290 mcg**	**Placebo**
Diarrhea	20%	3%
Abdominal pain	7%	5%
Flatulence	4%	2%
Headache	4%	3%
Viral gastroenteritis	3%	1%
Abdominal distension	2%	1%
Most common, >= 2%	**Linzess 145 mcg**	**Placebo**
Diarrhea	16%	5%
Abdominal pain	7%	6%
Flatulence	6%	5%
Upper respiratory tract infection	5%	4%
Abdominal distension	3%	2%
Sinusitis	3%	2%

Drug Interactions[1]

None noted

Dosage and Administration[1]

Irritable bowel syndrome with constipation: 290 mcg orally once daily
Chronic idiopathic constipation: 145 mcg orally once daily
The capsule should be taken on an empty stomach at least 30 minutes prior to the first meal of the day.

Cost Comparisons (at commonly used dosages)

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST/ MONTH
Linaclotide	Linzess	Forest	145 mcg capsules	1 capsule daily	$213.00 (WAC)
			290 mcg capsules	1 capsule daily	$213.00 (WAC)
Lubiprostone	Amitiza	Takeda Pharma	8 mcg capsules	1 capsule twice daily	$ 246.60 (WAC)
			24 mcg capsules	1 capsule twice daily	$ 172.80 (WAC)

*Wholesale Acquisition Cost (WAC)

Conclusion

Linzess is a guanylate cyclase-C agonist that has demonstrated efficacy for the treatment of IBS-C and CIC in adults. It is the first agent approved in this class of medications and offers a new treatment option. According to the National Institutes of Health, an estimated 63 million people are affected by chronic constipation and an estimated 15.3 million people are affected by IBS (IBS-C is a subtype). As part of the post-approval requirements, the manufacturer has agreed to a pediatric development program that will consist of additional nonclinical Linzess studies to characterize deaths previously observed in neonatal and young juvenile mice during nonclinical toxicology studies.

Recommendation

MO HealthNet Division recommends this product be placed into a clinical edit.

References

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4. Bryant AP, Busby RW, Bartolini WP et al: Linaclotide is a potent and selective guanylate cyclase C agonist that elicits pharmacological effects locally in the gastrointestinal tract. Life Sci 2010; 86(19-20):760-765.

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