PDL NEW DRUG REVIEW

Proprietary Name: Linzess®
Common Name: linaclotide
PDL Category: GI-Antiflatulents/GI Stimulants

Comparable Products	Preferred Drug List Status
Amitiza	Non-Preferred

Summary

Indications and Usage: For the treatment of irritable bowel syndrome with constipation (IBS-C) in adults AND for the treatment of chronic idiopathic constipation (CIC) in adults. This is a pregnancy category C medication. The safety and efficacy of use in children under the age of 18 years have not been established. Furthermore, Linzess® is contraindicated in the pediatric population up to 6 years of age, and should be avoided in those aged 6-17 years.

Drug Interactions: Drug-drug interaction studies have not been performed with Linzess®. Nevertheless, linaclotide does not interfere with the CYP enzyme system with *in vitro* results.

Dosage Forms: Capsules; 145mcg, 290mcg

Recommended Dosage: IBS-C: 290mcg once daily on an empty stomach, at least 30 minutes prior to the first meal of the day; CIC: 145mcg once daily on an empty stomach, at least 20 minutes prior to the first meal of the day. Capsules should be swallowed whole, and not broken apart of chewed. Dose adjustment is not required in those with renal or hepatic impairment.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions = reported % incidence for drug minus reported % incidence for placebo (and results below were from IBS-C studies).* The most commonly reported adverse events with Linzess® include diarrhea (17%), abdominal pain (2%), flatulence (2%), abdominal distension (1%), viral gastroenteritis (2%), and headache (1%).

The use of linaclotide is associated with a warning of diarrhea. Patients should be educated that if severe diarrhea occurs, patients should discontinue treatment and contact their provider.

Contraindications: Pediatric patients up to 6 years of age; patients with known or suspected mechanical gastrointestinal obstruction.

Manufacturer: Forest Pharmaceuticals

Analysis: Linaclotide, the active ingredient of Linzess®, is a guanylate cyclase-C (GC-C) agonist. Linaclotide is a 14-amino acid peptide; it binds to GC-C and acts locally on the luminal surface of the intestinal epithelium. When GC-C is activated, it results in increases of both intracellular and extracellular levels of cyclic guanosine monophosphate (cGMP). Increases in intracellular cGMP stimulate the secretion of both chloride and bicarbonate into the intestinal lumen, which results in increased intestinal fluid and accelerated transit.

Linzess® has a boxed warning regarding the risk of use in the pediatric population. It is contraindicated in the pediatric population up to 6 years of age. Furthermore, use should be avoided in those ages 6 through 17. In non-clinical studies, young juvenile mice died when given a clinically relevant adult oral dose.

Two double-blind, placebo-controlled studies were performed to assess the safety and efficacy of linaclotide for use in adults with IBS-C (N=800 Trial 1; N=804 Trial 2). All patients had IBS and met the following criteria: a mean abdominal pain score of at least 3 on a 1-10 point scale; <3 complete spontaneous bowel movements (CSBM) per week; and ≤5 spontaneous bowel movements (SBM) per week. For the 9 out of 12 weeks combined primary responder endpoint, a patient had to have 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 for at least 9 out of 12 weeks. For the 6 out of 12 weeks combined primary responder endpoint, a patient had to have 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 for at least 6 of out of the first 12 weeks of treatment.

For the 9 out of 12 week primary endpoint, results suggest the efficacy responder rates were 12.1% of the Linzess® group as compared with 5.1% of the placebo group in trial 1, and 12.7% vs 3%, respectively, in trial 2. These results were calculated to obtain an NNT of 15 with trial 1 and an NNT of 11 with trial 2. For the 6 out of 12 week primary endpoint, results suggest that the efficacy responder rates were 33.6% with Linzess® vs 21% placebo in trial 1, and 33.7% vs 13.9%, respectively, in trial 2. The number who responded to Linzess® 290mcg was statistically significantly higher as compared with placebo. These results were calculated to obtain an NNT of 8 with trial 1 and an NNT of 6 with trial 2.

Two double-blind, placebo-controlled studies were also performed to assess the safety and efficacy of linaclotide for use in adults with CIC (N=642 Trial 1; N=630 Trial 2). All included patients met modified Rome II criteria for functional constipation, which included less than 3 SBM per week and 1 of the following symptoms for at least 12 weeks in the preceding 12 months: Straining during >25% of bowel movements, lumpy or hard stools during >25% of bowel movements, or sensation of incomplete evacuation during >25% of bowel movements. Also, all were required to have <3 CSBMs per week and ≤6 SBMs per week during a 2-week baseline period. Again, efficacy was assessed using the overall responder analysis, with a CSBM overall responder defined as one who had at least 3 CSBM and an increase of at least 1 CSBM from baseline in a given week for at least 9 out of the 12 weeks treatment period.

Results suggested that the efficacy responder rates were 20.3% with Linzess® as compared with 3.3% of the placebo group in trial 1, and 15.5% vs 5.6%, respectively, in trial 2. The number who responded to Linzess® 145mcg was statistically significantly greater as compared with placebo. These results were calculated to obtain an NNT of 6 with trial 1 and an NNT of 11 with trial 2. There was not a consistently clinically meaningful benefit with Linzess® 290mcg vs 145mg, thus only the 145mcg dose is recommended for this indication.

As there are no comparator studies, there is no evidence at this time to support that Linzess® is more efficacious or safer than the currently available, more cost effective medications. Therefore, it is

recommended that Linzess® remain non-preferred and be available to the few who are unable to tolerate any preferred medications.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☐ **Preferred with Conditions**

Definitions:

1. Number Needed to Treat (NNT): The number of subjects required to bring about one response on the primary outcome.

References

[1] Linzess [package insert]. St. Louis, MO: Forest Pharmaceuticals; 2012.