

Brand Name: Linzess

Generic Name: linaclotide

Manufacturer: Forest Laboratories, Inc

Drug Class: Gastrointestinal Agent

Uses: ^{1,2,3,4,5,6}

Labeled: Chronic constipation (Idopathic), Irritable bowel syndrome associated with constipation

Unlabeled: Unknown

Mechanism of Action ^{1,2,3}: Linaclotide is a guanylate cyclase-C (GC-C) agonist. Linaclotide and its metabolite express its agonist action on the luminal surface of the intestinal epithelium. When the GC-C agonist binds to the receptors on the luminal surface, intracellular and extracellular levels of cyclic guanosine monophosphate (cGMP) is increased. Increase levels of cGMP encourage the release of chloride and bicarbonate into the intestinal lumen; this causes an increase in intestinal fluid and more rapid transit.

Pharmacokinetics ^{1,2,3}:

Absorption: Linaclotide is minimally absorbed which creates very low systemic bioavailability. Pharmacokinetic parameters such as AUC, Cmax, Tmax, half-life cannot be calculated .

Distribution: Due to lack of measurable plasma concentrations, distribution to the tissue is theoretically minimal.

Metabolism: Metabolized within the intestinal lumen (GI tract) into its active metabolite by losing its terminal tyrosine moiety. Both linaclotide and its active metabolite are proteolytically degraded into smaller peptides and amino acids.

Elimination: Linaclotide active metabolite was found in feces samples about 5% of fasting patients and 3% of fed patients.

Efficacy ^{4,5,6}:

Citation: Satish Rao MD, Anthony J Lembo MD, Steven J Shiff MD, Bernard J Lavins MD, Mark G Currie PhD, Xinwei D Jia PhD, ect. A 12-Week, Randomized, Controlled Trial With a 4-Week Randomized Withdrawal Period to Evaluate the Efficacy and Safety of Linaclotide in Irritable Bowel Syndrome With Constipation . Am J Gastroenterol. 2012 Sep 18.

Study design: multi-center, randomized, double-blind, parallel-group, placebo-controlled trial

Description of study:

The study included 800 patients randomized to placebo (395) or linaclotide (405). The dose of linaclotide was 290 micrograms daily (capsule).

Primary outcomes included a FDA end point defined as a patient who met both of the following criteria in the same week for at least 6 of the 12 weeks of the treatment period: (i) an improvement of $\geq 30\%$ from baseline in the average of the daily worst abdominal pain scores and (ii) an increase of ≥ 1 complete spontaneous bowel movement (CSBM) from baseline: other primary outcomes were an improvement of $\geq 30\%$ in abdominal pain, ≥ 3 CSBMs and an increase of ≥ 1 CSBM from baseline, and a combination of the previous two end points in the same week for at least 9 of 12 weeks. Secondary outcome included change from baseline in abdominal pain, abdominal discomfort, abdominal bloating, stool frequency, stool consistency, severity of straining, cramping, IBS symptom severity, constipation severity, adequate relief of IBS-C symptoms, degree of relief of IBS symptoms, and treatment satisfaction.

The result of the FDA end point was achieved P value < 0.0001 and a NNT of 8. Other primary outcomes and secondary outcomes appear to show statistical significance favoring linaclotide.

Limitations: The study was funded by Ironwood pharmaceuticals and the Forest Research Institute and all authors were paid by the companies leading to a concern of bias. The study design did not take into account outside factors that may have skewed the results such as diet and exercise—both of which can improve bowel symptoms.

Conclusion:

Although the study design was golden standard and linaclotide showed significant difference between treatment groups clinically linaclotide is limited to only a certain patient population. Adverse drug events appear to be a bigger concern (diarrhea) than the actual difference in improvement in abdominal pain and constipation. Due to the studies limitations, absolute clinical relevance has yet to be determined, but may be an option in patient refractory to other treatments.

Citation: Lembo AJ, Schneier HA, Shiff SJ, Kurtz CB, MacDougall JE, Jia XD, Shao JZ, ect. Two Randomized Trials of Linaclotide for Chronic Constipation. The New England Journal of Medicine 365;6. August 11, 2011.

Study design: The study conducted two randomized, multicenter, double-blind, parallel-group, placebo-controlled, dual-dose trials.

Description of study:

The study consisted of two trials: trial 303 and trial 01. The study's 1272 patients were included in the intent-to-treat analysis (642 in Trial 303 and 630 in Trial 01). The study groups were well balanced with respect to demographic characteristics, baseline bowel and abdominal symptoms, and constipation severity.

The primary outcome for each trial was defined as three or more complete spontaneous bowel movement (CSBMs) per week and an increase of at least one CSBM per week from baseline for 9 or more weeks during the 12-week treatment period. The secondary outcomes

included stool frequency, stool consistency, severity of straining, abdominal discomfort, bloating, and constipation severity during the 12 week study.

The primary end point was reached by 21.2% and 16.0% of the patients who received 145 µg of linaclotide, by 19.4% and 21.3% of the patients who received 290 µg of linaclotide, compared with 3.3% and 6.0% of those who received placebo ($P < 0.01$ for all comparisons of linaclotide with placebo) in trial 303 and 01 respectively. Improvements in all secondary end points were significantly greater in both linaclotide groups than in the placebo groups.

Limitations: Bias is a concern because the study was funded by the pharmaceutical and research companies, along with authors being financially associated with the companies. Individual factors that were not addressed during the study were outside factors such as diet and exercise and compliance.

Conclusion: Linaclotide appears to be effective for patients who experience chronic constipation but this trial was relatively short (12 weeks). Longer term use of linaclotide should be studied to determine the benefits and risk with its use. Overall, linaclotide helps relieve patient's symptoms and improve satisfaction, but adverse events like diarrhea may occur and clinical judgment should be used when prescribing this medication.

Citation: Chey WD, Lembo AJ, Lavins BJ, Shiff SJ, Kurtz CB, Currie MG, MacDougall JE, ect. Linaclotide for Irritable Bowel Syndrome With Constipation: A 26-Week, Randomized, Double-blind, Placebo-Controlled Trial to Evaluate Efficacy and Safety. *Am J Gastroenterol.* 2012 September 18.

Study design: multicenter, randomized, double-blind, placebo controlled, parallel-group trial lasting 26 weeks

Description of study:

805 patients were randomly assigned to receive placebo (403) or linaclotide 290 micrograms (402). Of the original 805 patients, 305 placebo and 294 linaclotide patients completed the full 26-week trial period.

Primary outcomes included a FDA end point defined as a patient who met both of the following criteria in the same week for at least 6 of the 12 weeks of the treatment period (13 of 26 weeks was also evaluated): (i) an improvement of $\geq 30\%$ from baseline in the average of the daily worst abdominal pain scores and (ii) an increase of ≥ 1 CSBM from baseline. Other primary outcomes were an improvement of $\geq 30\%$ in abdominal pain, ≥ 3 CSBMs and an increase of ≥ 1 CSBM from baseline, and a combination of the previous two in the same week for at least 9 of 12 weeks. Secondary outcomes included the 12 week and 26 week change-from-baseline for abdominal pain, abdominal discomfort, abdominal bloating, stool frequency, stool consistency, and severity of straining, cramping, IBS symptom severity, constipation severity, adequate relief of IBS-C symptoms, degree of relief of IBS symptoms, and treatment satisfaction.

33.7 % of linaclotide-treated patients were FDA end point responders, vs. 13.9 % of placebo-treated patients ($P < 0.0001$) (NNT = 5.1, 95 % confidence interval (CI): 3.9, 7.1). Remaining primary end points and all secondary end points were statistically significantly

improved with linaclotide vs. placebo. Diarrhea was reported in 19.5% of the linaclotide group vs. 2.5% of the placebo group (P<0.05).

Limitations: The study was funded by Ironwood pharmaceuticals and the Forest Research Institute and all authors were paid by the companies leading to a potential bias. The study design did not take into account outside factors that may have skewed the results such as diet and exercise—both of which can improve bowel symptoms.

Conclusion: Overall this longer duration study provided better evidence for the clinical use of linaclotide because the differences in outcomes between groups were greater than previous studies. Diarrhea as an adverse event still remains a concern because roughly 20% of the patients taking linaclotide experienced this event—most were mild to moderate, but some cases were severe. Clinical judgment should be used when prescribing linaclotide to patients with IBS-C.

Contraindications^{1,2,3,4,5,6}: pediatric patients up to 6 years of age, mechanical gastrointestinal obstruction, known or suspected

Precautions^{1,2,3,4,5,6}: pediatric patients, ages 6 through 17 years; avoid use; diarrhea, severe, has been reported; consider interruption of dose

Adverse effects^{1,2,3,4,5,6}:

Common:

- Gastrointestinal: Abdominal distension (2% to 3%), Abdominal pain (7%), Diarrhea (16% to 20%), Flatulence (4% to 6%)

Serious:

- Diarrhea (2%)

Drug Interactions^{1,2,3}: No drug-drug interaction studies have been conducted with linaclotide. Due to no bioavailability and un-measurable plasma levels after administration, no systemic drug interactions are expected.

Dosing/Administration^{1,2,3,4,5,6}:

Usual dose: Chronic constipation: 145 mcg orally, 30 minutes before the first meal, daily;

IBS-C: 290 mcg daily orally, 30 minutes before the first meal, daily

Geriatric dose: No studies were conducted in geriatric patients.

Pediatric dose: contraindicated

Renal impairment dose: specific studies not completed

Hepatic impairment dose: specific studies not completed

Use in special circumstances^{1,2,3}:

Pregnancy: Pregnancy category C. No adequate studies have been attempted with linaclotide in pregnant women. In animal studies, adverse events were seen with maternal toxicity but at doses much higher than max dose for humans.

Lactation: it is unknown if linaclotide is excreted in human milk; use with caution in nursing mothers.

Pediatrics: Studies of safety and effectiveness have not been conducted, but animal studies on juvenile mice show results of death occurring when given linaclotide.

Geriatric: IBS-C studies did not include sufficient numbers of patients 65 yrs and older to determine if there is a difference in response. Use caution.

Chronic idiopathic constipation did not include sufficient numbers of patients 65 yrs and older to determine if there is a difference in response. Use caution.

Conclusion: In conclusion, linaclotide appears to help relieve abdominal pain and improve complete spontaneous bowel movements in patients suffering from irritable bowel syndrome with constipation as well as chronic constipation. The longer duration study showed better results than the shorter studies. Diarrhea and adverse events are an issue regarding linaclotide and its use in everyday practice. Clinically, if patients do not respond to other forms of therapy, linaclotide is an appropriate choice for both chronic constipation and irritable bowel syndrome with constipation when the benefits outweighs the risk of adverse events.

Recommended References

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