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Linaclotide: A New Option for Irritable Bowel Syndrome with Constipation (IBS-C)

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Linaclotide (Linzess®) manufactured by Forest Laboratories, Inc. was FDA approved in August 2012 for treatment of irritable bowel syndrome with constipation (IBS-C) in adults.[1] This is the first guanylate cyclase-C (GC-C) agonist indicated for use in IBS-C on the market. Irritable bowel syndrome is a chronic gastrointestinal disorder characterized by abdominal pain and disturbed defecation not explained by known structural or biochemical abnormalities.[2]

IBS-C is defined as the presence of hard or lumpy stools with ≥25 percent of bowel movements and loose or watery stools with <25 percent of bowel movements (Table 2).[2] Irritable bowel syndrome has an estimated prevalence of 14.1% with women being more affected (60%-75% of cases).[3,4] The proportion of cases described as IBS-C range from 5.2% to 66%.[5] Irritable bowel syndrome has a considerable economic impact with estimated direct medical costs (excluding prescription and over-the-counter drug costs) ranging between $1.7 billion to $10 billion and indirect medical costs around $20 billion.[6]

Treatment of irritable bowel syndrome should be based on the patient's predominant symptom and subtype.[7] Treatment of IBS-C is aimed at producing more bowel movements, improving stool consistency, reducing abdominal pain, and reducing the severity of straining. Treatment options include: fiber (e.g., psyllium), osmotic laxatives (e.g., polyethylene glycol), locally acting chloride channel activators (e.g., lubiprostone), and guanylate cyclase agonists (e.g., linaclotide).

The objective of this article is to review the pharmacology, pharmacokinetics, clinical trials, precautions and adverse reactions, dosing and administration, and cost associated with linaclotide.

Table 1 | Subtypes of Irritable Bowel Syndrome[2]

Subtypes	Definition
IBS with Constipation	Hard or lumpy stools ≥ 25% of bowel movements Loose or watery stools < 25% of bowel movements
IBS with diarrhea	Loose or watery stools ≥ 25% of bowel movements Hard or lumpy stools < 25% of bowel movements
Mixed IBS	Hard or lump stools ≥ 25% of bowel movements Loose or watery stools ≥ 25% of bowel movements
Unsubtyped IBS	Stool consistency unable to be characterized by above definitions

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Pharmacology

Linaclotide is a GC-C agonist designed to increase intestinal fluid and accelerate transit. Stimulation of GC-C on the luminal surface of the intestinal epithelium increases intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP).[1] Elevated levels of intracellular cGMP activate the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel. Activation of the CFTR channel causes secretion of chloride and bicarbonate into the intestinal lumen leading to the increased intestinal fluid and accelerated transit.

Pharmacokinetics

Linaclotide has minimal absorption following oral administration.[1] At standard oral doses, linaclotide bioavailability is below the limit of quantitation and standard pharmacokinetic parameters (e.g. area under the curve, maximum concentration, and half-life) cannot be determined. Since the bioavailability of linaclotide is minimal, the distribution is expected to be negligible as well.

Linaclotide is metabolized to an active metabolite in the gastrointestinal tract. Both linaclotide and its active metabolite are then degraded further to smaller peptides and naturally occurring amino acids. Elimination is mainly through the feces for linaclotide, its active metabolite and degradation products.

The effect of food does not appear to alter the pharmacokinetics of linaclotide. In clinical trials, linaclotide was administered at least 30 minutes before breakfast on an empty stomach.

At this time, linaclotide has not been adequately studied in pediatric (≤ 17 years of age) or geriatric (≥ 65 years of age) patients to determine the effects of age on pharmacokinetics.

Clinical Trials

Currently all published trials of linaclotide are placebo controlled. A reliable measure to evaluate improvement in signs and symptoms associated with IBS-C has been a challenge. At this time, patient reported outcome measures are the only available measures to characterize the effect of treatment in a clinical trial. On May 2012, the FDA released a statement containing nonbinding recommendations to the pharmaceutical industry in an attempt to standardize the primary endpoint for clinical trials involving IBS.[8] The FDA recommended primary endpoint for IBS-C is a multi-item patient reported outcome instrument that measures the effect of treatment on abnormal defecation and abdominal pain. According to the FDA, an IBS-C patient is characterized as a weekly responder if the following criteria are met in the same week for ≥ 6 out of 12 weeks[8]:

1. Improvement of ≥ 30% from baseline in average daily worst abdominal pain score
2. Increase of ≥ 1 complete spontaneous bowel movement from baseline

The efficacy and safety of linaclotide was evaluated in one phase II trial and two phase III trials (Table 2). In the phase II trial, Johnston et al, evaluated multiple doses of linaclotide (75 mcg, 150 mcg, 300 mcg, 600 mcg) once daily on change from baseline in normalized weekly complete spontaneous bowel movement rate over a 12 week period.[9] The two phase III trials, described by Chey et al and Rao et al, studied the impact of linaclotide 290 mcg once daily on the FDA's endpoint for IBS-C.[10-11] There is no clear reason why 290 mcg was chosen in the phase III trials when 300 mcg was studied in the phase II trial.

Johnston et al performed a multi-center, randomized, double-blind, parallel-group, placebo-controlled study. Patients were men and women 18 years of age or older who met the Rome II (Table 3) criteria for IBS and who reported having < 3 spontaneous bowel movements per week and ≥ 1 of the following symptoms for at least 12 weeks in the 12 months prior to the study: (1) straining during ≥ 25% of bowel movements; (2) lumpy or hard stools during ≥ 25% of bowel movements; or (3) sensation of incomplete evacuation during >25% of bowel movements. Patients were randomly assigned to one of five treatment arms: placebo; linaclotide 75 mcg; linaclotide 150 mcg; linaclotide 300 mcg; or linaclotide 600 mcg. The primary endpoint, mean change in complete spontaneous bowel movement rate from baseline to 12 weeks, was 2.90, 2.49, 3.61, and 2.68 for linaclotide doses of 75, 150, 300, and 600 mcg, re-

Table 2 | Primary Endpoints of Clinical Trials Involving Linaclotide

Study	Patients	Treatment Arms	Primary Endpoints	Results	Author's Conclusions
Johnston[9], 2010	N = 419 ≥18 yrs of age Rome II criteria for IBS-C	PL 75 mcg L 150 mcg L 300 mcg L 600 mcg L	Δ from BL in normalized wk CSBMR (per wk) during the 12-wk period	The mean Δ from BL to the 12-wk period in CSBMR (per wk) = 2.90, 2.49, 3.61, and 2.68 for L doses of 75, 150, 300, and 600 mcg, respectively, compared with 1.01 for PL (P≤0.01, for each L dose)	The responder rate was 2- to 3-fold > for L vs. PL; an approximate 10-fold improvement over BL
Chey[10], 2012	N = 805 ≥18 yrs of age Rome II criteria for IBS-C	PL 290 mcg L	Difference in % of patients meeting FDA criteria	A total of 33.7% receiving 290 mcg L vs. 13.9% receiving PL (P<0.0001) met the FDA criteria	Treatment with L resulted in a significantly greater % of patients who experienced improvements in IBS-C symptoms vs. PL
Rao[11], 2012	N = 800 ≥18 yrs of age Rome II criteria for IBS-C	PL 290 mcg L	Difference in % of patients meeting FDA criteria	A total of 33.6% receiving 290 mcg L vs. 21.0% receiving PL (P<0.0001) met the FDA criteria	Treatment with L resulted in a statistically significant improvement in IBS-C symptoms vs. PL

PL = placebo, L = linaclotide, FDA = Food and Drug Administration, IBS-C = irritable bowel syndrome with constipation, CSBMR = complete spontaneous bowel movement rate, BL = baseline, Δ = change

spectively, compare with 1.01 for placebo (P≤0.01, for each of the linaclotide doses). In regards to the primary endpoint, there is no clear reason why the 600 mcg dose appeared to be less effective than the 300 mcg dose. This dose-range-finding study concluded that the 300 mcg per day dose provided the best risk-benefit ratio for continued evaluation in future clinical trials since the 300 mcg dose provided comparable efficacy to the 600 mcg dose and was associated with less gastrointestinal side effects.

Chey et al studied 805 IBS-C patients in a double-blind, parallel-group, placebo-controlled trial with 403 patients receiving placebo and 402 patients receiving 290 mcg linaclotide for 26 weeks. Patients were men and women aged 18 years or older who met modified Rome II criteria for IBS-C. The study showed statistical significance in the percentage of patients defined as weekly responders by the FDA primary endpoint with 33.7% of patients responding in the linaclotide 290 mcg group compared to 13.9% of patients in the placebo group (P<0.0001).

Rao et al included 800 IBS-C patients in a double-blind, parallel-group, placebo-controlled trial with 397 patients receiving placebo and 406 patients receiving 290 mcg linaclotide for 12 weeks. Both male and female patients were eligible if they were at least 18 years of age and met modified Rome II criteria for IBS-C. The study demonstrated 33.6% of patients receiving linaclotide 290 mcg compared with 21.0% of patients receiving placebo met the FDA defined endpoint for weekly responder (P<0.0001). A common criticism of these three clinical trials is that the Rome II diagnostic criteria were used as opposed to the more recent Rome III. The authors reasoned that the Rome III criteria were relatively new at the time and had not yet been used in clinical trials. The Rome III criteria are notable for questioning the validity and stability of IBS subtypes in Rome II. The authors of Rome III argue that the variable nature of IBS preclude the use of defining subtypes. Therefore, conclusions drawn from IBS-C clinical trials of motility-active agents such as linaclotide should be limited because their patient populations may be heterogeneous.

Precautions and Adverse Drug Reactions

Linaclotide is considered Pregnancy Category C and therapy should be used only if the potential benefit outweighs the risk to the fetus. At this time, there is a lack of safety data for the use of linaclotide during pregnancy and lactation.[1]

Linaclotide is not indicated for use in children as safety and efficacy has not been established. Also, clinical studies of linaclotide did not enroll enough geriatric patients (≥ 65 years of age) to determine the safety and efficacy in this population.[1]

Table 3 | Rome II Criteria Vs. Rome III Criteria[12]

Rome II Criteria for IBS-C	Rome III Criteria for IBS
At least 12 weeks or more, which need not be consecutive, in the preceding 12 months, of abdominal discomfort or pain that has two out of three features:	Recurrent abdominal pain or discomfort at least 3 days/ month in last 3 months associated with two or more of the following:
• Relieved by defecation	• Improvement with defecation
• Onset associated with a change in frequency of stool	• Onset associated with a change in frequency of stool
• Onset associated with a change in form (appearance) of stool	• Onset associated with a change in form (appearance) of stool
With at least 1 of the following: A. Fewer than 3 bowel movements a week B. Hard or lumpy stools C. Straining during a bowel movement	

Overall, linaclotide 290 mcg was well tolerated in the two phase III trials. The adverse events reported in Chey et al and Rao et al that occurred in a frequency greater than 1% or greater versus placebo were diarrhea, flatulence, abdominal pain, viral gastroenteritis, headache, and abdominal distension (Table 4). Diarrhea was the most common adverse reaction of patients treated with linaclotide in IBS-C double-blind placebo-controlled trials. Patients should be instructed to stop linaclotide if severe diarrhea occurs and suspension of subsequent doses should be considered.

Dose & Cost

Linaclotide comes in capsule dosages of 145 mcg and 290 mcg. The 145 mcg dose is the strength used in chronic idiopathic constipation.[1] Linaclotide should be taken orally once daily on an empty stomach, at least 30 minutes before breakfast.

Although not specifically studied, no dosage adjustment is required in renal or hepatic impairment. Renal and hepatic impairment is not likely relevant because of linaclotide's low systemic bioavailability and its metabolism in the gastrointestinal tract.

Linaclotide is now available at many pharmacies. Three community pharmacies were called and the average cash price for a 30 day supply was $299 with a range of $290-$316.

Summary

Linaclotide is a guanylate cyclase-C agonist indicated for use in IBS-C designed to produce more bowel movements, improve stool consistency, reduce abdominal pain, and reduce the severity of straining. In two IBS-C phase III clinical trials, treatment with linaclotide 290 mcg resulted in a significantly greater percentage of patients who experienced improvements in abdominal and bowel symptoms compared with placebo. Linaclotide has minimal absorption following oral administration at standard doses. The systemic effects of linaclotide are expected to be insignificant due to the low bioavailability of the drug. Diarrhea is the most common adverse reaction. Patients should be instructed to stop linaclotide if severe diarrhea occurs and suspension of subsequent doses should be considered.

Table 4 | Rate of Common Adverse Drug Reactions with Linaclotide Seen in Clinical Trials[10,11]

Adverse Event	Linaclotide 290 mcg/day	Placebo
Chey[10], 2012	(N = 402)	(N = 403)
Diarrhea	19.7 %	2.5 %
Flatulence	3.7 %	2.2 %
Viral gastroenteritis	3.7 %	2.2 %
Rao[11], 2012	(N = 406)	(N = 396)
Diarrhea	19.5 %	3.5 %
Abdominal Pain	5.4 %	2.5 %
Flatulence	4.9 %	1.5 %
Headache	4.9 %	3.5 %
Abdominal distension	2.2 %	0.8 %

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PharmaNote would like to welcome Dr. Steve Smith back to UF Community Health and Family Medicine and the PharmaNote editorial staff.

Dr. Smith served as faculty at the University of Colorado Skaggs School of Pharmacy for the past 3 years since completing his post-doctoral fellowship in family medicine at UF.

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