Formulary Drug Reviews

Linaclotide

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Generic Name:	LINACLOTIDE
Proprietary Name:	Linzess (Forest Labs/Ironwood Pharmaceuticals)
Approval Rating:	1S
Therapeutic Class:	Guanylate Cyclase Type-C Receptor Agonists
Similar Drugs:	None
Sound- or Look-Alike Names:	Lincocin, Lurasidone

INDICATIONS

Linaclotide is approved for the treatment of irritable bowel syndrome with constipation (IBS-C) and the treatment of chronic idiopathic constipation.¹

IBS is the most common form of functional bowel disorder. It is more frequent in females than in males and declines with age. IBS is characterized by at least 3 months of continuous or recurrent abdominal pain or discomfort. Relief may occur after defecation or change in stool frequency or consistency.²⁻⁷

The criteria established for diagnosis of IBS is predominately symptom-based. The criteria used in the clinical trials to ascertain the efficacy of various newer drugs for the treatment of IBS were established by the International Working Party (eg, Rome II, Rome III) (see **Table 1**).⁸⁻¹⁰ The criteria used for diagnosis in the linaclotide clinical studies were Rome II or modified Rome II.¹¹⁻¹³

The treatment of IBS is dependent upon whether it is constipation predominant, diarrhea predominant, or alternating.^{3,6,14,15} Diarrhea-predominant IBS is usually treated with antidiarrheal medications, alosetron, and rifaximin. The treatment for constipation-predominant IBS and alternating IBS should include increasing the fiber content of the diet and using bulk laxatives, osmotic laxatives, lubiprostone, or tegaserod. Reducing the amount of tea and coffee ingested and using antispasmodic, antimuscarinic, and antidepressant medications and probiotics may decrease pain and spasms.^{3-7,10,14-27}

Constipation is defined as having a bowel movement fewer than 3 times per week. It is a common complaint and affects more than 63 million people in the United States. It can be caused by a number of

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Table 1. International Working Party's Rome II and Rome III criteria for the diagnosis of irritable bowel syndrome^{4,5,10}

Rome II	Rome III
<p>≥ 3 mo of continuous or recurrent symptoms of abdominal pain or pain during the past 12 mo that has ≥ 2 of the following:</p> <ul style="list-style-type: none"> • Relieved by defecation • Change in stool consistency (appearance) • Change in stool frequency <p>Other supportive symptoms</p> <ul style="list-style-type: none"> • Altered stool frequency (>3 times per day or <3 times per wk) • Altered stool form • Altered stool passage (straining, urgency, incomplete evacuation) • Passage of mucus • Abdominal bloating 	<p>Recurrent abdominal pain or discomfort ≥ 3 days per month in the last 3 mo associated with ≥ 2 of the following:</p> <ul style="list-style-type: none"> • Improved by defecation • Change in stool frequency • Change in stool consistency (appearance) <p>• Pain/discomfort frequency of ≥2 days per wk</p>

different factors associated with diet, medications, level of physical activity, and multiple medical diseases. Treatment generally consists of changes in lifestyle, use of laxatives, and reevaluation of the need for drugs that predispose patients to constipation. Chronic idiopathic constipation is characterized by persistently difficult, infrequent, or incomplete defecation in the absence of any physiological abnormality. Individuals with chronic idiopathic constipation tend to have persistent constipation and do not respond to standard treatment. It occurs more frequently in women, individuals in lower socioeconomic groups, individuals with lower educational levels, and older individuals.^{25,28-31}

CLINICAL PHARMACOLOGY

Linacotide is an amino acid peptide homologous to bacterial heat-stable enterotoxins. These enterotoxins are produced by pathogenic bacteria to enhance their survival. The enterotoxins increase cyclic guanosine monophosphate (cGMP) by stimulating the guanylate cyclase type-C (GC-C) receptors. The increase in intracellular and extracellular cGMP results in a number of changes in the intestine, resulting in diarrhea so the bacteria can be spread to other hosts. Increases in extracellular cGMP appear to inhibit afferent nerve firing and reduce abdominal pain. Increases in intracellular cGMP cause activation of anion channels that are responsible for stimulating

Table 2. Pooled analysis of the phase 3 studies changes in irritable bowel syndrome Quality of Life Questionnaire scores⁵¹

Irritable Bowel Syndrome Quality of Life Scale	Linacotide 266 mcg (n = 748)	Placebo (n = 742)	<i>P</i>
	Least squares mean change from baseline to week 12		
Overall	17.5	13.1	< .001
Dysphoria	19.3	15.2	< .001
Interference with activity	12.8	11.3	.075
Body image	22.1	15.7	< .001
Health worry	25.2	17.9	< .001
Food avoidance	20.2	12.7	< .001
Social reaction	14.7	11.1	< .001
Sexual	14.7	10.4	< .001
Relationships	11.8	8.5	< .001

anion and fluid secretion into the intestine, resulting in accelerated intestinal transit.^{2,5,26,32-38}

Linaclotide and its active metabolite are agonists of the GC-C receptors.¹ Linaclotide is a 14-amino acid peptide analog of guanylin and the heat-stable *Escherichia coli* enterotoxin. By stimulating the GC-C receptors found in the luminal surface of the intestine, it induces intestinal chloride and fluid secretion, enhances colonic transit, increases bowel movement frequency, and alters fecal consistency.^{1,7,25,34,36,39-43}

PHARMACOKINETICS

Systemic absorption of linaclotide from the gastrointestinal (GI) tract is minimal following oral administration. The concentration of linaclotide and its active metabolite in plasma is below the limit of quantitation after the 145 and 290 mcg doses; therefore, standard pharmacokinetic parameters cannot be calculated.¹ Food had no effect on the absorption of linaclotide, but administration with a high-fat breakfast was associated with a higher incidence of loose stools and stool frequency.¹

COMPARATIVE EFFICACY

Indication: Irritable Bowel Syndrome

With Constipation

Studies

Drug: Linaclotide vs Placebo

Reference: Johnston JM, et al, 2010^{11,44,45}

Study Design: Phase 2b dose-ranging study in patients with IBS-C; double-blind, multicenter, placebo-controlled study

Study Funding: Ironwood Pharmaceuticals

Patients: 420 patients with IBS-C

Intervention: Treatment with linaclotide (75, 150, 300, or 600 mcg) or placebo once daily for 12 weeks

Results:

Primary Endpoint(s):

- Mean change in complete spontaneous bowel movements (CSBMs) from pretreatment baseline to the 12-week treatment period was improved with all doses; mean change from baseline was 2.9 with linaclotide 75 mcg, 2.5 with 150 mcg, 3.6 with 300 mcg, 2.7 with 600 mcg, and 1 with placebo ($P < .01$ vs placebo).

Secondary Endpoint(s):

- All doses of linaclotide were better than placebo in improving abdominal pain, increasing the frequency of SBMs, increasing the frequency of CSBMs, decreasing the severity of straining on defecation, and improved stool consistency.

- Abdominal pain, assessed using a 5-point scale, was decreased by -0.71 with linaclotide 75 mcg, -0.71 with 150 mcg, -0.9 with 300 mcg, -0.86 with 600 mcg, and -0.49 with placebo ($P \leq .05$ for all doses).

Comments: Post hoc analysis found the time to onset of the effect of linaclotide treatment on IBS-C symptoms to be within the first week of therapy. Global endpoints were improved with linaclotide therapy. Improvements in CSBMs, straining, and stool consistency were seen within the first week of therapy.⁴⁶ The dose of linaclotide 300 mcg produced a significant change in IBS global assessment scores and the IBS-C symptom-specific composite endpoints.⁴⁷

Reference: Rao S, et al, 2011^{13,39}

Study Design: Phase 3 randomized, double-blind, placebo-controlled study

Study Funding: Ironwood Pharmaceuticals

Patients: 800 patients with IBS-C; average baseline for CSBMs was less than 3, number of SBMs per week was less than or equal to 5, and abdominal pain scores (0 to 10 scale) were greater than or equal to 3 during the 2-week baseline observation period. During the 2-week baseline period, 88% of the patients had abdominal pain every day (average pain score, 5.6) and 76% of the patients had no CSBMs (average rate, 0.2/week).

Intervention: Treatment with either oral linaclotide 266 mcg or placebo once daily for 12 weeks

Results:

Primary Endpoint(s):

- Achievement of the composite endpoint (greater than or equal to 30% reduction in abdominal pain, greater than or equal to 3 CSBMs per week, an increase of greater than 1 CSBM per week for at least 9 of the 12 weeks) occurred in 5.1% of the placebo group and 12.1% of the linaclotide group ($P < .001$), while 6.3% and 19.5% ($P < .001$), respectively, achieved greater than or equal to 3 CSBMs per week and an increase of greater than or equal to 1 CSBM per week for at least 9 of 12 weeks, and 27.1% and 34.3% ($P = .026$), respectively, had a greater than or equal to 30% reduction in abdominal pain for at least 9 of 12 weeks. The percentage of patients who achieved a greater than or equal to 30% reduction in pain and an increase of greater than or equal to 1 CSBM per week for at least 6 or 12 weeks was 21% in the placebo group and 33.6% in the linaclotide group ($P < .001$).

Secondary Endpoint(s):

- Improvements were also noted in all secondary endpoints (eg, abdominal pain scores, abdominal discomfort scores, bloating, straining, stool consistency, CSBMs per week, SBMs per week, abdominal pain-free days). Patients were re-randomized at the end of the 12-week treatment period; a portion of the linaclotide-treated patients was randomized to placebo therapy and the other portion was maintained on linaclotide therapy for an additional 4-week period, while the original placebo-treated patients were switched to linaclotide therapy. The group that was maintained on linaclotide continued improvement in abdominal pain; those switched to placebo had an increase in abdominal pain, and the placebo-treated patients who were switched to linaclotide therapy had a reduction in their abdominal pain scores.

Limitations: Information is only published as an abstract from a meeting and a press release from the manufacturer.

Reference: Chey WD, et al, 2011^{12,40,48-50}

Study Design: Phase 3 clinical trial

Study Funding: Ironwood Pharmaceuticals

Patients: 805 patients with IBS-C; the average baseline for CSBMs was less than 3, the number of SBMs per week was less than or equal to 5, and abdominal pain scores (0 to 10 scale) were greater than or equal to 3 during the 2-week baseline observation period. During the 2-week baseline period, 87% of the patients had abdominal pain every day (average pain score, 5.6) and 76% of the patients had no CSBMs (average rate, 0.2/week).

Intervention: Treatment with either oral linaclotide 266 mcg or placebo once daily for 26 weeks

Results:

Primary Endpoint(s):

- Achievement of the composite endpoint (greater than or equal to 30% reduction in abdominal pain, greater than or equal to 3 CSBMs per week, an increase of greater than or equal to 1 CSBM per week for at least 9 of the 12 weeks) occurred in 3% of the placebo group and 12.7% of the linaclotide group ($P < .001$) at 12 weeks. The results at the end of 26 weeks were 2.5% and 12% ($P < .001$), respectively; 5% and 18% ($P < .001$), respectively, achieved greater than or equal to 3 CSBMs per week and an increase of greater than or equal to 1 CSBM per week for at least 9 of 12 weeks, and 3.5% and 15.7%, respectively, achieved this endpoint

after 26 weeks. A greater than or equal to 30% reduction in abdominal pain for at least 9 of 12 weeks occurred in 19.6% and 38.9% ($P < .001$), respectively, for at least 9 of the 12 weeks, and 17.4% and 36.9% ($P < .001$), respectively, achieved this endpoint after 26 weeks.

Secondary Endpoint(s):

- Improvements were also noted in all secondary endpoints (eg, abdominal pain scores, abdominal discomfort scores, bloating, straining, stool consistency, CSBMs per week, SBMs per week, abdominal pain-free days). The effects seen during weeks 9 to 12 of therapy were sustained through week 26 of treatment.

Limitations: Information is only published as abstracts at several different medical meetings.

Reference: Carson R, et al, 2011^{1,51-61}

Study Design: Pooled analysis of the 2 phase 3 studies

Study Funding: Ironwood Pharmaceuticals

Patients: 1,602 patients with IBS-C

Intervention: Post hoc analysis of 2 clinical studies that evaluated the efficacy of linaclotide and placebo therapy in the treatment of IBS-C

Results:

Other Endpoint(s):

- Improvements in abdominal and bowel symptoms, constipation severity, and treatment satisfaction.
- Treatment satisfaction was greater in patients treated with linaclotide than in those treated with placebo, regardless of baseline characteristics and whether patients experienced diarrhea. However, it was more strongly correlated with abdominal symptoms than bowel symptoms.
- Linaclotide therapy was associated with a reduction in overall work productivity loss and daily activity impairment with improvement seen by week 4 and maintained through week 12.
- Both studies used the same Irritable Bowel Syndrome Quality of Life questionnaire that was completed at baseline and end of treatment. This questionnaire consists of 34 items, each with a 5-point response scale (1 = *not at all* to 5 = *extremely or a great deal*); it is scored overall and by 8 subscales (dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual, relationships). The only scale that did not show improvement after 12 weeks of linaclotide therapy was interference with activity (see Table 2).

Limitations: Information is only published as abstracts from different medical meetings.

Indication: Chronic Constipation Studies

Drug: Linaclotide vs Placebo

Reference: Lembo AJ, et al, 2011^{1,62-65}

Study Design: Randomized, double-blind, parallel-group, placebo-controlled, multicenter study

Study Funding: Ironwood Pharmaceuticals

Patients: 1,276 patients with chronic constipation, defined as fewer than 3 SBMs per week and having 1 or more signs or symptoms of constipation (eg, straining, lumpy or hard stools, sensation of incomplete evacuation) during more than 25% of bowel movements for at least 12 weeks plus an average of 6 or fewer SBMs per week and fewer than 3 CSBMs per week during the 14-day baseline period. A number of drugs (eg, anticholinergic drugs, narcotics) were prohibited during the study and at least 14 days prior to the baseline period. Laxatives were also prohibited, but they could be used up to 24 hours before the baseline period.

Intervention: Treated with placebo, linaclotide 145 mcg, or linaclotide 290 mcg once daily at least 30 minutes before breakfast for 12 weeks

Results:

Primary Endpoint(s):

- At least 3 CSBMs per week and an increase of at least 1 CSBM per week from baseline for 9 or more weeks during the 12-week treatment period.
- The intent-to-treat cohort consisted of 1,272 patients (642 from trial 303 and 630 from trial 01).
- Achieved by 21.2% of the patients treated with linaclotide 145 mcg ($P < .01$ vs placebo), 19.4% of the patients treated with linaclotide 290 mcg ($P < .01$ vs placebo), and 3.3% of the patients treated with placebo in trial 303. The number needed to treat is 5.6 for linaclotide 145 mcg and 6.2 for linaclotide 290 mcg.
- Achieved by 16% of the patients treated with linaclotide 145 mcg ($P < .01$ vs placebo), 21.3% of the patients treated with linaclotide 290 mcg ($P < .01$ vs placebo), and 6% of the patients treated with placebo in trial 01. The number needed to treat is 10 for linaclotide 145 mcg and 6.5 for linaclotide 290 mcg.
- The overall response rate between the 2 doses of linaclotide was not different; trial 303: 145 mcg versus 290 mcg ($P = .63$), trial 01: 145 mcg versus 290 mcg ($P = .19$).

Secondary Endpoint(s):

- Significant improvements were observed in all secondary endpoints: changes in bowel symptoms (number of weekly CSBMs, SBMs, stool consistency, and straining severity), abdominal symptoms (discomfort and bloating), and constipation severity.
- Weekly CSBMs increased during the first week of treatment with linaclotide and were maintained throughout the 12-week treatment period.
- The quality of life score was increased by at least 1 point over the baseline value, with both doses of linaclotide in both studies better than placebo.^{51,62,66-69} This improvement in the Patient Assessment of Constipation Quality of Life score was achieved by 44.9% of the linaclotide 145 mcg group ($P < .01$ vs placebo), 35.5% of the linaclotide 290 mcg group ($P < .01$ vs placebo), and 18.7% of the placebo group in trial 303, and 42.2% ($P < .01$ vs placebo), 46.8% ($P < .01$ vs placebo), and 27.8%, respectively, in trial 01.⁶²
- No evidence of rebound chronic constipation symptoms or adverse reactions following discontinuation of linaclotide therapy.^{62,70}

Comments: The 2 studies (trial 303 and trial 01) were identical, with the only difference being that in trial 303 the patients were also randomized to a 4-week period of withdrawal at the conclusion of the 12-week treatment period.⁶² The information in the product labeling only summarizes these efficacy data from the linaclotide 145 mcg and placebo arms of the study.¹ Post hoc analysis of the pooled results from both trials for those patients with at least moderate bloating at baseline treated with either dose of linaclotide had better improvements in their bowel and abdominal symptoms compared with placebo therapy.^{71,72}

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS
Contraindications

The product labeling has a boxed warning that states that linaclotide is contraindicated in pediatric patients up to 6 years of age and use should be avoided in pediatric patients 6 through 17 years of age based on the occurrence of death in young juvenile mice.¹ In addition, linaclotide is contraindicated in patients with known or suspected mechanical GI obstruction.¹

Warnings and Precautions

Severe diarrhea (2%) may occur during linaclotide therapy. If this should occur, the next dose should be held or therapy stopped.¹

The drug is classified in Pregnancy Category C. No adequate and well-controlled studies have been conducted in pregnant women. Animal studies observed some adverse fetal effects but only with maternal toxicity and at doses of linaclotide much higher than the maximum recommended human dose.¹

The amount of drug excreted in human milk is unknown. Neither the drug nor its metabolites are measurable in plasma following oral administration, but caution should be observed if linaclotide is used in the treatment of a breast-feeding mother.¹

ADVERSE REACTIONS

The most common adverse reactions associated with the use of linaclotide in the treatment of IBS-C were diarrhea, abdominal pain, flatulence, and abdominal distension (see **Table 3**).¹ The diarrhea generally started within the first 2 weeks of therapy.¹ It was classified as severe in 2% of the linaclotide-treated patients and less than 1% of the placebo-treated patients. Diarrhea was the reason given for discontinuation of therapy by 5% of the linaclotide-treated patients and less than 1% of the placebo-treated patients.¹

The most common adverse reactions associated with the use of linaclotide in the treatment of chronic idiopathic constipation were diarrhea (16% vs 5%), abdominal pain, flatulence, abdominal distension, upper respiratory tract infection, and sinusitis (see **Table 4**).^{1,62} The diarrhea generally started within the first 2 weeks of therapy.¹ It was classified as severe in 2% of the linaclotide-treated patients and less than 1% of the placebo-treated patients. Fecal incontinence occurred in 1% of the linaclotide-treated patients and less than 1% of the placebo-treated patients. The most common reasons given for discontinuation of therapy due to

adverse reactions were diarrhea in 5% and abdominal pain in 1% of the linaclotide-treated patients and diarrhea or abdominal pain in less than 1% of placebo-treated patients.¹

Other reported adverse effects have included urinary tract infections, nausea, gastroesophageal reflux disease, dyspepsia, fecal incontinence, vomiting, fatigue, nasopharyngitis, hematochezia, allergic reactions, urticaria or hives, and upper respiratory tract infections.^{1,11}

DRUG INTERACTIONS

No drug-drug interaction studies were conducted with linaclotide. However, linaclotide does not affect cytochrome P450 or P-glycoprotein and should have no effect on drugs eliminated through either of these pathways.¹

RECOMMENDED MONITORING

If diarrhea occurs, the patients should be monitored for changes in electrolyte and fluid status.

DOSING

The recommended dosage for the treatment of IBS-C is 290 mcg orally once daily. The dosage recommended for the treatment of chronic idiopathic constipation is 145 mcg orally once daily. The capsules should be taken on an empty stomach at least 30 minutes prior to the first meal of the day. The capsules should be swallowed whole and should not be opened or chewed.¹

PRODUCT AVAILABILITY

Linaclotide was approved by the US Food and Drug Administration on August 30, 2012.⁷³ It is available as 145 and 290 mcg capsules in bottles of 30. The inactive ingredients in each capsule include calcium chloride

Table 3. Adverse reactions reported in $\geq 2\%$ of linaclotide-treated (290 mcg) patients and at an incidence greater than in placebo group patients in the 2 phase 3, placebo-controlled trials (1 and 2) in irritable bowel syndrome with constipation¹

Adverse reactions	Linaclotide 290 mcg (n = 807)	Placebo (n = 798)
Diarrhea	20%	3%
Abdominal pain	7%	5%
Flatulence	4%	2%
Headache	4%	3%
Viral gastroenteritis	3%	1%
Abdominal distension	2%	1%

Table 4. Adverse reactions reported in $\geq 2\%$ of linaclotide-treated (145 mcg) patients and at an incidence greater than in placebo group patients in the 2 phase 3, placebo-controlled trials (1 and 2) in irritable bowel syndrome with constipation¹

Adverse reactions	Linaclotide 145 mcg (n = 430)	Placebo (n = 423)
Diarrhea	16%	5%
Abdominal pain	7%	6%
Flatulence	6%	5%
Upper respiratory tract infection	5%	4%
Sinusitis	3%	2%
Abdominal distension	3%	2%

dihydrate, L-leucine, hypromellose, microcrystalline cellulose, gelatin, and titanium dioxide.¹

The product should be stored at room temperature (25°C [77°F]) in the original container, with excursions permitted between 15°C and 30°C (59°F and 86°F). The desiccant should not be removed from the container, and the bottle should be protected from moisture.¹

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Postmarketing studies are required to determine the mechanism of death in neonatal and juvenile mice treated with linaclotide (due April 2014), a safety and efficacy evaluation in pediatric patients with chronic idiopathic constipation ages 7 months up to 17 years (due December 2023), and a safety and efficacy evaluation in pediatric patients with IBS-C ages 7 years up to 17 years (due December 2023). The manufacturer is also required to determine whether linaclotide is excreted in the breast milk of healthy lactating but non-breast-feeding female volunteers, develop and validate sensitive and precise assays for the detection of antilinaclotide antibodies, and develop a clinical trial in adults to assess the development of antilinaclotide antibodies during treatment with linaclotide.⁷³

CONCLUSION

Linaclotide is a new drug for the treatment of IBS-C and idiopathic chronic constipation. Its mechanism of action is different from the current and previously approved agents for the treatment of IBS and constipation. Linaclotide works by stimulating the GC-C receptors in the luminal surface of the intestine, resulting in increased cGMP production and causing decreased abdominal pain, increased anion and fluid secretion into the intestine, and accelerated intestinal transit. Linaclotide 290 mcg once daily was better than placebo at improving CSBMs, SBMs, abdominal pain, and quality of life in patients with IBS-C. Linaclotide 145 mcg once daily was better than placebo at decreasing the signs and symptoms of constipation and improving CSBMs and SBMs in patients with idiopathic chronic constipation. The most common adverse reaction in both medical conditions was diarrhea. The long-term efficacy and safety of linaclotide in the treatment of either of these medical conditions remains to be established.

REFERENCES

1. *Linzess* [package insert]. St. Louis, MO: Forest Pharmaceuticals; August 2012.
2. Kennedy TM, Jones RH, Hungin AP, O'Flanagan H, Kelly P. Irritable bowel syndrome, gastro-oesophageal reflux, and bronchial hyper-responsiveness in the general population. *Gut*. 1998;43(6):770-774.
3. American Gastroenterological Association medical position statement: irritable bowel syndrome. *Gastroenterology*. 1997;112(6):2118-2119.
4. Drossman DA, Whitehead WE, Camilleri M. Irritable bowel syndrome: a technical review for practice guideline development. *Gastroenterology*. 1997;112(6):2120-2137.
5. Camilleri M, Prather CM. The irritable bowel syndrome: mechanisms and a practical approach to management. *Ann Intern Med*. 1992;116(12, pt 1):1001-1008.
6. Mayer EA. Clinical practice: irritable bowel syndrome. *N Engl J Med*. 2008;358(16):1692-1699.
7. Gale JD. The use of novel promotility and presecretory agents for the treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation. *Adv Ther*. 2009;26(5):519-530.
8. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut*. 1999;45(suppl 2):II43-II47.
9. Jellema P, van der Windt DA, Schellevis FG, van der Horst HE. Systematic review: accuracy of symptom-based criteria for diagnosis of irritable bowel syndrome in primary care. *Aliment Pharmacol Ther*. 2009;30(7):695-706.
10. Grundmann O, Yoon SL. Irritable bowel syndrome: epidemiology, diagnosis and treatment: an update for health-care practitioners. *J Gastroenterol Hepatol*. 2010;25(4):691-699.
11. Johnston JM, Kurtz CB, MacDougall JE, et al. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome with constipation. *Gastroenterology*. 2010;139(6):1877-1886.e2.
12. Chey WD, Lembo A, MacDougall JE, et al. Efficacy and safety of once-daily linaclotide administered orally for 26 weeks in patients with IBS-C: results from a randomized, double-blind, placebo-controlled phase 3 trial [abstract]. *Gastroenterology*. 2011;140(suppl 1):S-135.
13. Rao S, Lembo A, Shiff SJ, et al. Efficacy and safety of once daily linaclotide in patients with irritable bowel syndrome with constipation: a 12-week, randomized, double-blind, placebo-controlled phase 3 trial followed by a 4-week randomized withdrawal period [abstract]. *Gastroenterology*. 2011;140(suppl 1):S-138.
14. Szkotak J, Shek A. An evidence-based review of treatment options for irritable bowel syndrome. *Formulary*. 2012;47:319-329.
15. Camilleri M, Di Lorenzo C. Brain-gut axis: from basic understanding to treatment of IBS and related disorders. *J Pediatr Gastroenterol Nutr*. 2012;54(4):446-453.
16. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther*. 1999;13(suppl 2):3-14.
17. Francis CY, Whorwell PJ. Bran and irritable bowel syndrome: time for reappraisal. *Lancet*. 1994;344(8914):39-40.
18. Jailwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review

- of randomized, controlled trials. *Ann Intern Med.* 2000; 133(2):136-147.
19. Pimentel M, Lembo A, Chey WD et al; TARGET Study Group. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med.* 2011;364(1):22-32.
20. Camilleri M. Review article: new receptor targets for medical therapy in irritable bowel syndrome. *Aliment Pharmacol Ther.* 2010;31(1):35-46.
21. Moayyedi P, Ford AC, Talley NJ et al. The efficacy of probiotics in the treatment of irritable bowel syndrome: a systematic review. *Gut.* 2010;59(3):325-332.
22. Andresen A, Montori VM, Keller J, West CP, Laver P, Camilleri M. Effects of 5-hydroxytryptamine (serotonin) type 3 antagonists on symptoms relief and constipation in non-constipated irritable syndrome: a systematic review and meta-analysis of randomized controlled trials. *Clin Gastroenterol Hepatol.* 2008;6(5):545-555.
23. Ford AC, Talley NJ, Spiegel BM, et al. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis [published correction appears in *BMJ.* 2009;338:b1881]. *BMJ.* 2008;337.a2313 10.1136/bmj.a2313.
24. Ford AC, Talley NJ, Schoenfeld PS, Quigley EM, Moayyedi P. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. *Gut.* 2009;58(3):367-378.
25. Tack J. Current and future therapies for chronic constipation. *Best Pract Res Clin Gastroenterol.* 2011;25(1):151-158.
26. Manabe N, Rao AS, Wong BS, Camilleri M. Emerging pharmacologic therapies for irritable bowel syndrome. *Curr Gastroenterol Rep.* 2010;12(5):408-416.
27. Shad ED, Chong K, Pimentel M. Evaluation of treatment-associated harm for irritable bowel syndrome with constipation [abstract]. Digestive Disease Week 2012; May 19-22, 2012; San Diego, CA. Abstract Mo1042.
28. Constipation. National Digestive Disease Information Clearinghouse Web site. <http://digestive.niddk.nih.gov/ddiseases/pubs/constipation>. Published July 2007. Updated February 21, 2012. Accessed October 10, 2012.
29. FDA approves *Linzess* to treat certain cases of irritable bowel syndrome and constipation [news release]. Silver Spring, MD: Food and Drug Administration; August 30, 2012. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm317505.htm>. Accessed October 10, 2012.
30. Shahid S, Ramzan Z, Maurer AH, Parkman HP, Fisher RS. Chronic idiopathic constipation: more than a simple colonic transit disorder. *J Clin Gastroenterol.* 2012;46(2):150-154.
31. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. *Gut.* 2011;60(2):209-218.
32. Bharucha AE, Waldman SA. Taking a lesson from microbial diarrheagenesis in the management of chronic constipation. *Gastroenterology.* 2010;138(3):813-817.
33. Bharucha AE, Linden DR. Linaclotide—a secretagogue and antihyperalgesic agent—what next? *Neurogastroenterol Motil.* 2010;22(3):227-231.
34. Busby RW, Bryant AP, Bartolini WP, et al. Linaclotide, through activation of guanylate cyclase C, acts locally in the gastrointestinal tract to elicit enhanced intestinal secretion and transit. *Eur J Pharmacol.* 2010;649(1-3):328-335.
35. Eutamene H, Bradesi S, Larauche M, et al. Guanylate cyclase C-mediated antinociceptive effects of linaclotide in rodent models of visceral pain. *Neurogastroenterol Motil.* 2010;22(3):312-e84.
36. 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.
37. Castro J, Martin C, Hughes PA, et al. A novel role of cyclic GMP in colonic sensory neurotransmission in healthy and TNBS-treated mice [abstract]. Digestive Disease Week 2011; May 7-10, 2011; Chicago, IL. Abstract SU2030.
38. MacDougall JE, MacKinnon DP, Lavins BJ, et al. Mediation analysis supports a direct effect of linaclotide on relief of abdominal pain independent of constipation improvement [abstract]. Digestive Disease Week 2012; May 19-22, 2012; San Diego, CA. Abstract Sa1098.
39. Ironwood and Forest to present linaclotide results from phase 3 trials in patients with irritable bowel syndrome with constipation [news release]. Cambridge, MA: Ironwood Pharmaceuticals; May 4, 2011. <http://www.ironwoodpharma.com/newsPDF/DDW.Schedule.IRWD.FRX.05.04.11.pdf>. Accessed August 6, 2011.
40. Ironwood and Forest announce positive linaclotide results from second phase 3 trial in patients with irritable bowel syndrome with constipation [news release]. Cambridge, MA: Ironwood Pharmaceuticals; November 1, 2010. <http://www.ironwoodpharma.com/newsPDF/IRWD.FRX.Ph3.MCP-103-302.11.01.10.pdf>. Accessed August 6, 2011.
41. Andresen V, Camilleri M, Busciglio IA, et al. Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. *Gastroenterology.* 2007;133(3):761-768.
42. Lembo A, Lavins B, MacDougall J, et al. Linaclotide treatment results in significant improvements in abdominal and bowel symptoms in IBS-C patients with severe abdominal pain at baseline [abstract]. *Am J Gastroenterol.* 2010;105(suppl 1):1341.
43. Castro J, Harrington AM, Hughes PA, et al. Mechanism of action for linaclotide induced abdominal pain relief [abstract]. Digestive Disease Week 2012; May 19-22, 2012; San Diego, CA. Abstract Mo1849.
44. Lavins B, MacDougall J, Shiff S, et al. Comparison of abdominal pain endpoints: results from a phase 2b study of linaclotide in adults with IBS-C [abstract]. *Am J Gastroenterol.* 2009;104(suppl 3):1303.
45. Carson R, Williams V, Nelson L, et al. Psychometric evaluation of patient-reported outcomes measures for assessing IBS-C symptom severity and global change: results from a phase 2b study of linaclotide [abstract]. *Am J Gastroenterol.* 2009;104(suppl 3):S-409.

46. Lembo AJ, Johnston JM, Lavins BJ, et al. Effects of linaclotide on IBS-C symptoms in the first week of treatment: results from a phase 2B study [abstract]. *Gastroenterology*. 2009;136(suppl 1):A-30.
47. Johnston JM, MacDougall JE, Lavins BJ, et al. Global endpoints in IBS clinical trials: results from a phase 2B study of linaclotide [abstract]. *Gastroenterology*. 2009;136(suppl 1):A-45.
48. Levine D, Chey WD, Lembo AJ, et al. Efficacy and safety of linaclotide administered orally once-daily for 26 weeks in patients with irritable bowel syndrome with constipation (IBS-C) [abstract]. *Neurogastroenterol Motil*. 2011;23(suppl 1):30.
49. Lembo AJ, Fortea J, Diaz C, et al. 26-week efficacy and safety of once-daily oral linaclotide in patients with irritable bowel syndrome with constipation (IBS-C): a European perspective [abstract]. *Gut*. 2012;61(suppl 2):A35.
50. Chey WD, Quigley EM, Lavins BJ, et al. Effects of 26 weeks of linaclotide treatment on adequate relief and IBS severity in patients with irritable bowel syndrome with constipation [abstract]. *Digestive Disease Week 2012*; May 19-22, 2012; San Diego, CA. Abstract Tu1381.
51. Carson R, Tourkodimitris S, Lewis BE, Johnston JM. Effect of linaclotide on quality of life in adults with irritable bowel syndrome with constipation: pooled results from two randomized, double-blind, placebo-controlled phase 3 trials [abstract]. *Gastroenterology*. 2011;140(suppl 1):S-51.
52. Carson R, Tourkodimitris S, Lewis BE, Johnston JM. Two randomized, double-blind, placebo-controlled phase 3 trials of linaclotide in adults with irritable bowel syndrome: effects on quality of life [abstract]. *Neurogastroenterol Motil*. 2011; 23(suppl 1):29.
53. Carson RT, Tourkodimitris S, Lewis BE, Johnston JM. Two randomized, double-blind, placebo-controlled phase 3 trials of linaclotide in adults with irritable bowel syndrome: effects on quality of life [abstract]. *Gut*. 2012;61(suppl 2):A348.
54. Schoenfeld PS, Chey WD, Lavins BJ, et al. Linaclotide significantly improved abdominal pain compared with placebo in patients with irritable bowel syndrome regardless of baseline pain severity in two phase 3 trials [abstract]. *Digestive Disease Week 2012*; May 19-22, 2012; San Diego, CA. Abstract Mo1856.
55. Locke GR, Chang L, Gurrie MG, et al. Comparison of responder rates and degree of agreement for symptom-specific and global-relief endpoints in two phase 3 trials of linaclotide in IBS-C [abstract]. *Digestive Disease Week 2012*; May 19-22, 2012; San Diego, CA. Abstract Tu1065.
56. Locke GR, Chey WD, Kurtz CB, et al. Effects of linaclotide treatment on patient-reported ratings of change for symptoms of irritable bowel syndrome with constipation (IBS-C): pooled 12-week findings from two phase 3 trials [abstract]. *Digestive Disease Week 2012*; May 19-22, 2012; San Diego, CA. Abstract Tu1068.
57. Schoenfeld PS, Chang L, Carson R, et al. Do baseline factors contribute to treatment satisfaction in patients with chronic constipation treated with linaclotide vs placebo? [abstract]. *Digestive Disease Week 2012*; May 19-22, 2012; San Diego, CA. Abstract Tu1069.
58. Rao SS, Chang L, Hao X, et al. Assessing the percent of days linaclotide improved abdominal symptoms and stool frequency in patients with IBS-C: a pooled analysis of two phase 3 trials [abstract]. *Digestive Disease Week 2012*; May 19-22, 2012; San Diego, CA. Abstract Tu1380.
59. Lembo A, Carson R, Shiff SJ, et al. Factors contributing to treatment satisfaction in patients with irritable bowel syndrome with constipation (IBS-C) treated with linaclotide vs placebo [abstract]. *Digestive Disease Week 2012*; May 19-22, 2012; San Diego, CA. Abstract Tu1401.
60. Buono JL, Tourkodimitris S, Sarocco PW, et al. Impact of linaclotide treatment on work productivity and activity impairment in adults with irritable bowel syndrome with constipation [abstract]. *Digestive Disease Week 2012*; May 19-22, 2012; San Diego, CA. Abstract Tu1402.
61. Lembo A, Rao SS, Shiff SJ, et al. Effects of linaclotide on straining associated with bowel movements in patients with irritable bowel syndrome with constipation (IBS-C): a post-hoc analysis of pooled data from two phase 3 trials [abstract]. *Digestive Disease Week 2012*; May 19-22, 2012; San Diego, CA. Abstract Tu1423.
62. Lembo AJ, Schneier HA, Shiff SJ, et al. Two randomized trials of linaclotide for chronic constipation. *N Engl J Med*. 2011;365(6):527-536.
63. Lembo A, Lavins B, Shiff S, et al. Week 1 changes in bowel and abdominal symptoms following linaclotide treatment: results from two phase 3 trials in chronic constipation patients [abstract]. *Am J Gastroenterol*. 2010;105(suppl 1):1303.
64. Lembo A, Schneier H, Lavins B, et al. Correlation of global assessments with symptom endpoints in phase 3 clinical trials of linaclotide in chronic constipation [abstract]. *Am J Gastroenterol*. 2010;105(suppl 1):1304.
65. Lembo A, Schneier H, Lavins BJ, et al. Efficacy and safety of once daily linaclotide administered orally for 12-weeks in patients with chronic constipation: results from 2 randomized, double-blind, placebo-controlled phase 3 trials [abstract]. *Gastroenterology*. 2010;138(suppl 1):S-53.
66. Carson R, Tourkodimitris S, Lewis BE, Johnston JM. Effect of linaclotide on quality of life among patients with chronic constipation (CC) with abdominal symptoms [abstract]. *Gastroenterology*. 2011;140(suppl 1):S-202.
67. Carson R, Tourkodimitris S, Lewis BE, Johnston JM. Effect of linaclotide on quality of life among patients with chronic constipation (CC) with abdominal symptoms [abstract]. *Digestive Disease Week 2011*; May 7-10, 2011; Chicago, IL. Abstract SA1007.
68. Carson R, Tourkodimitris S, Lewis BE, Johnston JM. Two randomized double-blind, placebo-controlled phase 3 trials of linaclotide in patients with chronic constipation: effects on quality of life among patients with abdominal symptoms [abstract]. *Neurogastroenterol Motil*. 2011;23(suppl 1):29.
69. Carson RT, Tourkodimitris S, MacDougall JE, et al. Effect of linaclotide on quality of life in adults with chronic constipation: results from 2 randomized, double-blind, placebo-controlled phase III trials [abstract]. *Gastroenterology*. 2010; 139:e19.

70. Johnston JM, Schneier H, Lavins BJ, et al. Results from the randomized withdrawal period of a phase 3 clinical trial of linaclotide in chronic constipation [abstract]. *Digestive Disease Week* 2011; May 7-10, 2011; Chicago, IL. Abstract T1817.
71. Lembo A, Schneier H, Lavins B, et al. Efficacy and safety of once-daily linaclotide administered orally for 12-weeks in patients with chronic constipation and at least moderate bloating at baseline: pooled results from 2 randomized, double-blind, placebo-controlled phase 3 trials [abstract]. *Am J Gastroenterol*. 2011;106(suppl 2):S506-S507.
72. Lembo AJ, Schneier HA, Lavins BJ, et al. The effect of linaclotide treatment on abdominal and bowel symptom measures in patients with chronic constipation and abdominal pain: pooled results from two phase 3 trials [abstract]. *Neurogastroenterol Motil*. 2011;23(suppl 1):30.
73. Kusiak V. NDA approval letter: *Linzess* (linaclotide NDA 202-811). US Food and Drug Administration Web site. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/202811Orig1s000ltr.pdf. Published August 30, 2012. Accessed September 4, 2012. ■