Linaclotide Capsules (LINZESS)

National Drug Monograph

January 2014

VA Pharmacy Benefits Management Services,   
Medical Advisory Panel, and VISN Pharmacist Executives

*The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.*

# Executive Summary:

* Linaclotide is a guanylate cyclase-C agonist that was FDA-approved in adults for the treatment of chronic idiopathic constipation and irritable bowel syndrome characterized by constipation.
* The dose is 145 mcg once daily at least 30 minutes prior to the first meal of the day for chronic idiopathic constipation and 290 mcg once daily at least 30 minutes prior to the first meal of the day for irritable bowel syndrome characterized by constipation.
* In chronic idiopathic constipation, linaclotide increased the rate of responders (those with at least three complete spontaneous bowel movements in a week and an increase from baseline of at least one). The rate of responders was 3.3%–6% for placebo, 16%–21.2% for linaclotide 145 mcg (NNT 5.6–10.1), and 19.4%–21.3% for linaclotide 290 mcg (NNT 6.2–6.6).
* In irritable bowel syndrome characterized by constipation, linaclotide also increased the rate of responders. Several definitions of responders were used. For responders defined as having at least a 30% improvement in abdominal pain and at least 1 additional complete spontaneous bowel movement per week, rates of responders were 13.2%–21.0% for placebo and 32.4%–33.7% for linaclotide 290 mcg (NNT 5.1-8.0). For responders defined as having at least a 30% improvement in abdominal pain, rates of responders were 17.4%–27.1% for placebo and 34.3%–38.9% for linaclotide 290mcg (NNT 5.2-13.8). For responders defined as having at least a 30% improvement in abdominal pain, at least 3 complete spontaneous bowel movements per week and at least 1 additional complete spontaneous bowel movement per week from baseline, rates of responders were 2.5%–5.1% for placebo and 12.0%–12.7% for linaclotide 290 mcg (NNT 10.3-14.2).
* The most common adverse event was diarrhea, which occurred in about 12%–20% of linaclotide patients. Other gastrointestinal effects occurred less frequently, including nausea, flatulence, abdominal pain, and abdominal distension.
* Linaclotide is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction and in pediatric patients up to 6 years of age.
* **Conclusion:** Prescription medication options are limited for patients with chronic idiopathic constipation (CIC) or irritable bowel syndrome with a constipation component (IBS-C). Linaclotide was shown to be an effective and safe medication in the treatment of adults with CIC or IBS-C. Lubiprostone, a chloride channel activator, is the only other option available to treat patients with these conditions, and currently there are no head-to-head trials comparing the two medications. Based on indirect comparisons of placebo-controlled trial results, neither agent seems to be superior to the other in regards to efficacy. Both have similar adverse event profiles, with diarrhea being a common problem with each medication. Nausea and dyspnea, both of which may be severe, seem to be more common in lubiprostone treated patients based on indirect comparisons. There is more clinical experience with lubiprostone, but both agents lack long-term safety data. However, neither drug is systemically absorbed at detectable levels. Patient adherence may be easier with linaclotide, as it is dosed once daily whereas lubiprostone is twice daily. Linaclotide is also slightly less expensive than lubiprostone. For CIC, the American Gastroenterological Association considers lubiprostone and linaclotide to be third line agents in patients whose symptoms do not respond to fiber and laxatives. At this time, guidelines do not make specific recommendations for one agent over another in the treatment of IBS-C. Expert opinion suggests initiating pharmacologic therapy in patients with moderate symptoms, with the choice of agent based on patient-specific response. Head-to-head trials are needed in both conditions to determine whether one agent is better than the others.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating linaclotide for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics

## Mechanism of Action

Guanylate cyclase-C agonist. Activating guanylate cyclase-C on the luminal surface of intestinal epithelium increases levels of cyclic guanosine monophosphate, which stimulates secretion of chloride and bicarbonate into the intestinal lumen, causing an increase in intestinal fluid and faster transit

## Pharmacokinetics

Table 1 Pharmacokinetics of Linaclotide[[1]](#endnote-1)

|  |  |
| --- | --- |
| Absorption | Oral bioavailability is low. Plasma concentrations are below limit of quantitation for parent drug and metabolite. AUC, clearance and half-life cannot be calculated. |
| Distribution | Not measurable. Expected to be minimally distributed to tissues. Protein binding is not anticipated. |
| Metabolism: | Proteolytic degradation within intestinal lumen to active metabolite |
| Elimination | Fecal: 3% (fed) to 5% (fasted), mainly active metabolite |

# FDA Approved Indication(s)

Indicated in adults for treatment of both

* Chronic idiopathic constipation (CIC) and
* Irritable bowel syndrome with constipation (IBS-C)

# Potential Off-label Uses

*This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety’s* [*Guidance on “Off-label” Prescribing*](http://vaww.national.cmop.va.gov/PBM/Directives%20Policies%20and%20Information%20Letters/Guidance%20on%20Off%20Label%20Prescribing.pdf) *(available on the VA PBM Intranet site only).*

There are no current trials assessing additional uses of linaclotide.

# Current VA National Formulary Alternatives

There are no current formulary alternatives to linaclotide.

Lubiprostone is a nonformulary alternative for both CIC and IBS-C.

# Dosage and Administration

Hard gelatin capsules, oral: 145 mcg, 290 mcg

Chronic idiopathic constipation (CIC): 145 mcg orally once daily at least 30 minutes prior to the first meal of the day.

Irritable bowel syndrome characterized by constipation (IBS-C): 290 mcg orally once daily at least 30 minutes prior to the first meal of the day.

Swallow whole; do not break or chew.

Loose stools and increased frequency of stools may occur after administration with a high-fat breakfast.

## Dosage in Specific Populations

Renal Impairment: no dose adjustment necessary

Hepatic Impairment: no dose adjustment necessary

# Storage

Store at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).

Keep capsules in the original container. Do not subdivide or repackage.

Protect from moisture. Do not remove desiccant from container. Keep bottles tightly closed in a dry place.

# Efficacy

## Efficacy Measures

The chronic idiopathic constipation efficacy measure was the rate of responders, which was defined as the percentage of patients with at least 3 complete spontaneous bowel movements and an increase from baseline of at least 1 complete spontaneous bowel movement during a particular week for at least 9 of the 12 weeks of the treatment period. A complete spontaneous bowel movement was defined as a bowel movement for which the patient reported a feeling of complete evacuation without the use of a laxative, enema, or suppository within the preceding 24 hours.[[2]](#endnote-2)

For IBS-C, the efficacy measure was also rate of responders. Several definitions of responders were used that took into account improvements in abdominal pain from baseline and increases in complete spontaneous bowel movements. One trial also evaluated patient assessment of overall IBS severity on a 5 point scale, with responders defined as those with at least a 1 point decrease in at least 6 of the 12 weeks. It also evaluated the percentage of patients who said they had adequate relief of their symptoms with the study treatment.[[3]](#endnote-3),[[4]](#endnote-4)

## Summary of efficacy findings

### Chronic idiopathic constipation:

* Two high-quality RCTs consistently showed that linaclotide increased the rate of responders2:
  + Trial 01: 6% placebo vs. 16% linaclotide 145 mcg (NNT = 10.1) vs. 21.3% linaclotide 290 mcg (NNT = 6.6)
  + Trial 303: 3.3% placebo vs. 21.2% linaclotide 145 mcg (NNT = 5.6) vs. 19.4% linaclotide 290 mcg (NNT = 6.2)
* A meta-analysis of available treatments for chronic idiopathic constipation included placebo-controlled trials of laxatives, lubiprostone, and linaclotide[[5]](#endnote-5)
  + Laxatives: 40.1% failed to respond vs. 73.3% placebo, RR 0.52 (95% CI 0.46-0.60), NNT 3
  + Lubiprostone: 45.1% failed to respond vs. 66.9% placebo, RR 0.67 (95% CI 0.56-0.80), NNT 4
  + Linaclotide: 79.0% failed to respond vs. 94.9% placebo, RR 0.84 (95% CI 0.80-0.87), NNT 6

### IBS-C:

Two high-quality RCTs consistently showed that linaclotide increased the rate of responders for all definitions of responder. In Rao, the average baseline severity was 3.7-3.8 on a 5 point scale, with 5 being the most severe3,4:

* ≥ 30% improvement in abdominal pain and ≥ 1 complete SBM increase in ≥ 6 of 12 weeks:
  + Chey (2012): (Weeks 1-12) 13.9% placebo vs. 33.7% linaclotide (NNT = 5.1)
  + Rao (2012): 21.0% placebo vs. 33.6% linaclotide, OR 1.9 (95% CI 1.4-2.7), p <0.0001, NNT = 8
* ≥ 30% improvement in abdominal pain and ≥ 1 complete SBM increase in ≥ 13 of 26 weeks:
  + Chey: (Weeks 1-26) 13.2% placebo vs. 32.4% linaclotide (NNT = 5.2)
* ≥ 30% improvement in abdominal pain for ≥ 9 of 12 weeks:
  + Chey: (Weeks 1-12) 19.6% placebo vs. 38.9% linaclotide (NNT = 5.2)
  + Rao: 27.1% placebo vs. 34.3% linaclotide, OR 1.4 (95% CI 1.0-1.9), p=0.0262, NNT=13.8
* ≥ 30% improvement in abdominal pain for ≥ 20 of 26 weeks:
  + Chey: (Weeks 1-26) 17.4% placebo vs. 36.9% linaclotide (NNT = 5.1)
* ≥ 3 complete SBM and increase of ≥ 1 from baseline for ≥ 9 of 12 weeks:
  + Chey: (Weeks 1-12) 5.0% placebo vs. 18.0% linaclotide (NNT = 7.7)
  + Rao: 6.3% placebo vs. 19.5% linaclotide, OR 3.7 (95% CI 2.3-5.9), p < 0.0001, NNT = 7.6
* ≥ 3 complete SBM and increase of ≥ 1 from baseline for ≥ 9 of 12 weeks:
  + Chey: (Weeks 1-26) 3.5% placebo vs. 15.7% linaclotide (NNT = 8.2)
* ≥ 30% improvement in abdominal pain, ≥ 3 complete SBM and increase of ≥ 1 from baseline for ≥ 9 of 12 weeks:
  + Chey: (Weeks 1-12) 3.0% placebo vs. 12.7% linaclotide (NNT = 10.3)
  + Rao: 5.1% placebo vs. 12.1% linaclotide, OR 2.6 (95% CI 1.5-4.5) p=0.0004, NNT=14.2
* ≥ 30% improvement in abdominal pain, ≥ 3 complete SBM and increase of ≥ 1 from baseline for ≥ 20 of 26 weeks:
  + (Weeks 1-26) 2.5% vs. 12.0% linaclotide (NNT = 10.5)
* IBS severity responders:
  + Rao: 37.5% placebo vs. 56.3% linaclotide, p<0.0001 NNT=5.3
* Adequate relief of symptoms:
  + Rao: 34.2% placebo vs. 48.9% linaclotide, p<0.0001 NNT 6.8

For further details on the efficacy results of the clinical trials, refer to *Appendix: Clinical Trials* (page 12).

# Adverse Events (Safety Data)1,[[6]](#endnote-6)

Adverse event data is available for 1275 CIC patients. Of those, 642 patients had data available for trials up to 26 weeks. Adverse event data is available for 1605 IBS-C patients. Of those, 599 patients had data available for trials up to 26 weeks.

**CIC**

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

**IBS-C**

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

When indirectly comparing the adverse event rates in patients taking linaclotide or lubiprostone for IBS-C it was found both had similar side effect profiles with diarrhea being a common problem among both medications. Patients taking lubiprostone experienced a considerable amount of nausea whereas those treated with linaclotide experience little or negligible amounts of nausea. Dyspnea was an uncommon but possible side effect with lubiprostone but not linaclotide.

When indirectly comparing the adverse event rates in patients taking linaclotide or lubiprostone for CIC it was found both had similar side effect profiles with diarrhea being a common problem among both medications. Patients taking lubiprostone experienced a considerable amount of nausea whereas those treated with linaclotide experience little or negligible amounts of nausea. Dyspnea was an uncommon but possible side effect with lubiprostone but not linaclotide.

## Deaths and Other Serious Adverse Events

None

For further details on the safety results of the clinical trials, refer to *Appendix: Clinical Trials* (page 12).

# Contraindications

Pediatric patients up to 6 years of age

Mechanical gastrointestinal obstruction, known or suspected1

# Warnings and Precautions

Pediatric patients, ages 6 through 17 years; avoid use.

Severe diarrhea has been reported; consider interruption of dose.

Report suspected adverse reactions to the US Food and Drug Administration at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

Pregnancy Category C (All Trimesters): Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.1

# Specific Populations

Renal Impairment: no dose adjustment necessary

Hepatic Impairment: no dose adjustment necessary1

# Sentinel Events

No data

# Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a Joint Commission standard, LASA names are assessed during the formulary selection of drugs.  Based on clinical judgment and an evaluation of LASA information from three ~~four~~ data sources (Lexi-Comp, ~~USP Online LASA Finder,~~ First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| NME Drug Name | Lexi-Comp | First DataBank | ISMP | Clinical Judgment |
| Linaclotide | None | None | None | Lanreotide  Lacosamide  Liraglutide |
| Linzess | None | None | None | Lessina  Linezolid |

# Drug Interactions

## Drug-Drug Interactions

None have been identified1

## Drug-Lab Interactions

None have been identified1

# Pharmacoeconomic Analysis

There are no published pharmacoeconomic evaluations of this drug.

# Conclusion

Prescription medication options are limited for patients with chronic idiopathic constipation (CIC) or irritable bowel syndrome with a constipation component (IBS-C). Linaclotide was shown to be an effective and safe medication in the treatment of adults with CIC or IBS-C. Lubiprostone, a chloride channel activator, is the only other option available to treat patients with these conditions, and currently there are no head-to-head trials comparing the two medications. Based on indirect comparisons of placebo-controlled trial results, neither agent seems to be superior to the other in regards to efficacy. Both have similar adverse event profiles, with diarrhea being a common problem with each medication. Nausea and dyspnea, both of which may be severe, seem to be more common in lubiprostone treated patients based on indirect comparisons. There is more clinical experience with lubiprostone, but both agents lack long-term safety data. However, neither drug is systemically absorbed at detectable levels. Patient adherence may be easier with linaclotide, as it is dosed once daily whereas lubiprostone is twice daily. Linaclotide is also slightly less expensive than lubiprostone. For CIC, the American Gastroenterological Association considers lubiprostone and linaclotide to be third line agents in patients whose symptoms do not respond to fiber and laxatives. At this time, guidelines do not make specific recommendations for one agent over another in the treatment of IBS-C. Expert opinion suggests initiating pharmacologic therapy in patients with moderate symptoms, with the choice of agent based on patient-specific response. Head-to-head trials are needed in both conditions to determine whether one agent is better than the others.

# References

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# Appendix: Clinical Trials

A literature search was performed on PubMed (1966 to August 2004) using the search terms linaclotide and Linzess. The search was limited to studies performed in humans and published in English language. Reference lists of review articles and the manufacturer’s AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Summary of Linaclotide Clinical Trials: Chronic Idiopathic Constipation

| **Citation**  **Design**  **Analysis type**  **Setting** | **Eligibility Criteria** | **Interventions** | **Patient Population Profile** | **Efficacy Results** | **Safety Results** | **Author’s conclusions**  ***Critique*** |
| --- | --- | --- | --- | --- | --- | --- |
| (Trial 303) Lembo (2011)  Two Randomized Trials of Linaclotide for Chronic Constipation  MC DB PC CO RCT  ITT  Outpatient clinics (USA and Canada)2  Included a 4-week period of randomized withdrawal at conclusion of the 12-week treatment period | Inclusion criteria: >18 years old, < 3 SBMs/week and ≥ 1 of the following signs/symptoms during > 25% of BMs for at  least 12 weeks within the preceding 12 months: 1) straining, 2) lumpy or hard stools, or  3) sensation of incomplete evacuation, Mean of < 3 CSBMs and ≤ 6 SBMs per week during 14-day baseline period  Exclusion criteria: loose (mushy) or watery stools in the absence of laxatives > 25% of BM during the 12 weeks  preceding the study, > 1 BSFS 6 or 7 stool during the pretreatment baseline, Rome II criteria for IBS, history of pelvic floor dysfunction | Linaclotide 290 mcg, linaclotide 145 mcg orally once daily or placebo for treatment period  Withdrawal period: placebo group switched to linaclotide 290mcg, linaclotide group were randomized to continue same linaclotide dose or switch to placebo  Patient may  use dispensed, protocol-defined laxatives (bisacodyl 5mg tablets or bisacodyl 10mg suppositories) as rescue medicine when at least 72 hours have passed since patient’s previous BM or  when symptoms intolerable | 642 patients: linaclotide 290mcg (n = 216), linaclotide 145mcg (n = 217), placebo 209)  Average age 48, 87% female, 75% white  No significant differences in baseline characteristics | Percentage of patients with ≥ 3 CSBMs and an increase  of ≥ 1 CSBM from baseline during a particular week  for ≥ 9 weeks of the 12-week treatment period: 3.3% placebo vs. 21.2% linaclotide 145mcg (NNT = 5.6) vs. 19.4% linaclotide 290mcg (NNT = 6.2)  Secondary endpoint: weekly SBM frequency compared to baseline: 1.1 placebo vs. 3.0 linaclotide 145mcg vs. 3.0 linaclotide 290 mcg  Patient Assessment of Constipation Quality of Life (4 point scale) improved from baseline by >1 points: 18.7% placebo vs. 44.9% linaclotide 145mcg vs. 35.5% linaclotide 290mcg | No deaths  Any event 50.2% placebo vs. 56.2% linaclotide 145mcg vs. 54.8%linaclotide 290mcg  Diarrhea 6.7% placebo vs. 12.4% linaclotide 145mcg vs. 13.8% linaclotide 290mcg  Abdominal distention 1.4% placebo vs. 3.7% linaclotide 145mcg vs. 3.2% linaclotide 290mcg | Linaclotide led to improvement in bowel and abdominal symptoms and reduced the severity of  constipation  The effects of linaclotide on  symptoms of constipation were observed within  the first 24 hours and were sustained through 16  weeks  Episodes of diarrhea mostly mild or moderate; treatment discontinued  because of diarrhea in 4.2% of linaclotide-treated patients as compared with 0.5% of patients  receiving placebo  During the randomized withdrawal period, patients continuing linaclotide  and those who switched from placebo to linaclotide  had sustained increases in rate of CSBMs  similar to levels reported during  treatment period, patients who switched from linaclotide to placebo had decreased rate  of CSBMs, which was similar to rates in  placebo groups during treatment period. No evidence of “rebound” (i.e., fewer CSBMs  or worsening of other constipation symptoms), as  compared with baseline levels  Jadad Quality Rating: 5 |
| (Trial 01) Lembo (2011)  Two Randomized Trials of Linaclotide for Chronic Constipation  MC DB PC CO RCT  ITT  Outpatient clinics (USA and Canada)2 | Inclusion criteria: >18 years old, < 3 SBMs/week and ≥ 1 of the following signs/symptoms during > 25% of BMs for at  least 12 weeks within the preceding 12 months: 1) straining, 2)lumpy or hard stools, or  3) sensation of incomplete evacuation, Mean of < 3 CSBMs and ≤ 6 SBMs per week during 14-day baseline period  Exclusion criteria: loose (mushy) or watery stools in the absence of laxatives > 25% of BM during the 12 weeks  preceding the study, > 1 BSFS 6 or 7 stool during the pretreatment baseline, Rome II criteria for IBS, history of pelvic floor dysfunction | Linaclotide 290 mcg, linaclotide 145 mcg orally once daily or placebo for treatment period  Patient may  use dispensed, protocol-defined laxatives (bisacodyl tablets or bisacodyl suppositories) as rescue medicine when at least 72 hours have passed since patient’s previous BM or  when symptoms intolerable | 630 patients: linaclotide 290mcg (n = 202), linaclotide 145mcg (n = 213), placebo 215)  Average age 48, 90% female, 77% white  No significant differences in baseline characteristics | Primary endpoint: Percentage of patients with ≥ 3 CSBMs and an increase  of ≥ 1 CSBM from baseline during a particular week  for ≥ 9 weeks of the 12-week treatment period: 6% placebo vs. 16% linaclotide 145mcg (NNT = 10.1) vs. 21.3% linaclotide 290mcg (NNT = 6.6)  Secondary endpoint: weekly SBM frequency compared to baseline: 1.1 placebo vs. 3.4 linaclotide 145mcg vs. 3.7 linaclotide 290 mcg  Patient Assessment of Constipation Quality of Life (4 point scale) improved from baseline by >1 points: 27.8% placebo vs. 42.2% linaclotide 145mcg vs. 46.8%linaclotide 290mcg | No deaths  Any event 54% placebo vs. 64.8% linaclotide 145mcg vs. 56.6%linaclotide 290mcg  Diarrhea 2.8% placebo vs. 19.7% linaclotide 145mcg vs. 14.6% linaclotide 290mcg  Flatulence 6.0% placebo vs. 7.5% linaclotide 145mcg vs. 6.3% linaclotide 290mcg  Abdominal pain 2.3% placebo vs. 5.2% linaclotide 145mcg vs. 5.4% linaclotide 290mcg | Linaclotide led to improvement in bowel and abdominal symptoms and reduced the severity of  constipation  The effects of linaclotide on  symptoms of constipation were observed within  the first 24 hours and were sustained through 16  weeks  Episodes of diarrhea mostly mild or moderate; treatment discontinued  because of diarrhea in 4.2% of linaclotide-treated patients as compared with 0.5% of patients  receiving placebo  Jadad Quality Rating: 5 |
| Ford et al (2013): chronic idiopathic constipation meta-analysis4  Efficacy measures: failure to respond to therapy or effect on mean number  of stools per week during treatment | RCT of laxatives, prucalopride, lubiprostone, or linaclotide for ≥ 7 days in adults with chronic idiopathic constipation  Exclusion criteria included trials of organic constipation, drug-induced constipation, and highly selected patients (e.g. elderly institutionalized patients)  Individual trials used varying definitions for responders. | Polyethylene glycol, sodium picosulfate, bisacodyl, lactulose  Prucalopride (not approved in U.S.)  Lubiprostone  Linaclotide | Laxatives: 8 trials with 1442 total patients. 5 trials had a low risk of bias and 6 allowed rescue laxatives  Prucalopride: 7 trials with 2639 total patients. All were low risk of bias and 6 allowed rescue laxatives  Lubiprostone: 3 trials with 610 total patients. 1 was low risk of bias and all allowed rescue laxatives  Linaclotide: 2 trials with 1582 total patients. Both were low risk of bias and allowed rescue laxatives. | Laxatives: 40.1% failed to respond vs. 73.3% placebo, RR 0.52 (95% CI 0.46-0.60), NNT 3 (95% CI 2–4)  Prucalopride: 71.7% failed to respond vs. 86.7% placebo, RR 0.82 (95% CI 0.76-0.88), NNT 6 (5–9)  Lubiprostone: 45.1% failed to respond vs. 66.9% placebo, RR 0.67 (95% CI 0.56-0.80), NNT 4 (3–7)  Linaclotide: 79.0% failed to respond vs. 94.9% placebo, RR 0.84 (95% CI 0.80-0.87), NNT 6 (5–8) | Laxatives: RR any adverse event 1.94 (95% CI 1.52-2.47). RR diarrhea 13.75 (95% CI 2.82-67.14)  Prucalopride: RR any adverse event 1.14 (95% CI 1.05-1.24). RR HA 1.70 (95% Ci 1.25-2.31). RR nausea 1.98 (95% CI 1.39-2.82). RR diarrhea 2.72 (95% CI 1.80-4.13).  Lubiprostone: RR total adverse event 1.79 (95% CI 1.21-2.65). RR diarrhea 4.46 (95% CI 1.28-15.48). RR nausea 7.27 (95% CI 3.76-14.06).  Linaclotide: total adverse events 33.6% vs. 31.9% placebo. RR diarrhea 3.08 (95% CI 1.27-7.48). | Osmotic or stimulant laxatives (polyethylene glycol, sodium picosulfate, bisacodyl), prucalopride, lubiprostone, and linaclotide are superior to placebo for the treatment of CIC. 50%–85% of patients did not fulfill criteria for response to therapy. Head-to-head comparison studies are needed.  Limitations: Only 12 of 21 trials included had a low risk of bias and only 2 were conducted in primary care. Most patients were female. Few studies reported individual symptoms of CIC.  The lower NNTs for laxatives probably reflect more stringent endpoints and a more recalcitrant patient population in the trials evaluating the newer agents. |

Summary of Linaclotide Clinical Trials: Irritable Bowel Syndrome Characterized by Constipation

| **Citation**  **Design**  **Analysis type**  **Setting** | **Eligibility Criteria** | **Interventions** | **Patient Population Profile** | **Efficacy Results** | **Safety Results** | **Author’s conclusions (optional)**  ***Critique***  **(optional)** |
| --- | --- | --- | --- | --- | --- | --- |
| Rao (2012)  Randomized, double-blind, placebo-controlled, multicenter ITT study  Outpatient centers5 | Inclusion criteria: At least 18 years old; met modified Rome II criteria for IBS-C (in the last 12 months, at least 12 weeks of abdominal pain/ dsicomfort with at least 2 of: relieved with defecation, onset associated with change in stool frequency, onset associated with change in form of stool); in the last 12 months < 3 spontaneous bowel movements (SBM) per week and at least 1 other bowel symptom (straining, lumpy or hard stools, or sensation of incomplete evacuation) during > 25% of BMs; average abdominal pain of at least 3, average < 3 complete SBMs per week, and average 5 or less SBMs per week during baseline period.  Exclusion criteria:  Loose, mushy, or watery stools for > 25% BMs in 12 weeks before screening, BSFS score of 7 for any SBM or 6 for > 1 SBM during baseline period, history of cathartic colon or laxative abuse or ischemic colitis or pelvic floor dysfunction, history of bariatric surgery or surgical removal of a segment of the GI tract, surgery of the abdomen or pelvis or retroperitoneal structures in the last 6 months, appendectomy or cholecystectomy in the 60 days before screening, other major surgery in 30 days before screening, history of diverticulitis or any chronic condition associated with abdominal pain or discomfort (e.g. IBD, chronic pancreatitis, polycystic kidney disease, ovarian cysts, endometriosis, lactose intolerance), family history of a familial form of colorectal cancer, takincg constipating drugs such as narcotics (exception- TCAs if dose was stable). Women of childbearing potential were required to use contraceptives and have a negative serum pregnancy test. | Linaclotide 290 mcg orally once daily or placebo for treatment period  Withdrawal period: placebo group switched to linaclotide, linaclotide group were randomized to continue or switch to placebo  Screening period up to 21 days, baseline period 14-21 days, treatment period 12 weeks, withdrawal period 4 weeks  Could continue any fiber, bulk laxatives, stool softeners, or probiotics if the dose was stable  Rescue medication of bisacodyl 5mg orally or 10mg suppository was allowed if it had been 72 hours since last BM or symtpoms were intolerable | 803 patients: 397 placebo, 406 linaclotide  Average age 43, 90% female, 76-77% white  Baseline IBS-C severity 3.7-3.8 on a 5-point scale.  No significant differences in baseline characteristics except: linaclotide group had slightly higher abdominal fullness score (6.8 vs. 6.5, p=0.011), placebo group had slightly higher stool consistency score (2.4 vs. 2.3, p=0.046), and linaclotide group had slightly higher straining score (3.6 vs. 3.4, p=0.020) | Primary Endpoints:  ≥ 30% improvement in abdominal pain and ≥ 1 complete SBM increase in ≥ 6 of 12 weeks: 21.0% placebo vs. 33.6% linaclotide, OR 1.9 (95% CI 1.4-2.7), p <0.0001, NNT = 8  ≥ 30% improvement in abdominal pain for ≥ 9 of 12 weeks: 27.1% placebo vs. 34.3% linaclotide, OR 1.4 (95% CI 1.0-1.9), p=0.0262, NNT=13.8  ≥ 3 complete SBM and increase of ≥ 1 from baseline for ≥ 9 of 12 weeks: 6.3% placebo vs. 19.5% linaclotide, OR 3.7 (95% CI 2.3-5.9), p < 0.0001, NNT = 7.6  ≥ 30% improvement in abdominal pain, ≥ 3 complete SBM and increase of ≥ 1 from baseline for ≥ 9 of 12 weeks: 5.1% placebo vs. 12.1% linaclotide, OR 2.6 (95% CI 1.5-4.5) p=0.0004, NNT=14.2  Secondary endpoints:  IBS severity (≥ 1 point decrease from baseline on 5 point scale for ≥ 6 of 12 weeks) 37.5% placebo vs. 56.3% linaclotide, p<0.0001 NNT=5.3  Adequate relief of symptoms: 34.2% placebo vs. 48.9% linaclotide, p<0.0001, NNT 6.8 | No deaths  No evidence of rebound in the withdrawal period  Serious adverse events 0.5% in both groups  Any adverse event 53% placebo vs. 56.2% linaclotide, p=0.3949  Diarrhea 3.5% placebo vs. 19.5% linaclotide, p<0.0001  Abdominal pain 2.5% placebo vs. 5.4% linaclotide, p=0.0462  Flatulence 1.5% placebo vs. 4.9% linaclotide, p=0.0084 | More linaclotide patients achieved statistical and clinical improvement in IBS-C symptoms than placebo. Most patients experienced a BM within 24 hours. Improvement in bloating and abdominal discomfort began in the first week. Maximum improvement in IBS-C symptoms was reached after 6-8 weeks. There was no sign of rebound in the withdrawal period. Diarrhea was the most common side effect.  Jadad Quality Rating: 5 |
| Chey (2012)  Linaclotide for Irritable Bowel Syndrome With Constipation: A 26-Week, Randomized Double-blind, Placebo-Controlled Trial to Evaluate Efficacy and Safety  MC DB PC CO RCT  ITT  Outpatient clinics (USA)3 | Inclusion criteria:  At least 18 years old; met modified Rome II criteria for IBS-C, mean daily abdominal pain score of at least 3.0 (on 11-point scale)during 2 weeks baseline period, Mean of < 3 CSBMs and ≤ 5 SBMs per week during baseline period  Exclusion criteria: loose (mushy) or watery stools in the absence of laxatives > 25% of  BMs during the 12 weeks preceding the study, mushy stool (BSFS score of 6) for > 1 SBM or watery, liquid stool  (BSFS of 7) for any SBM during baseline period, history of surgery to remove a segment of the GI tract or bariatric  surgery for obesity at any time, history of any chronic condition that could be associated with  abdominal pain or discomfort and could confound the trial assessments, abdominal surgery within 6 months prior to study, laxative abuse | Linaclotide 290 mcg orally once daily or placebo  Rescue medication (per protocol use) of bisacodyl 5 mg tablets or 10 mg suppositories | (Weeks 1-12) 804 patients: 403 placebo, 401 linaclotide  Average age 44, 90% female, 78% white  No significant differences in baseline characteristics except placebo group had higher percentage of men than linaclotide group (12.7% vs. 8.2% p = 0.0379) | Primary endpoints: Decrease of both ≥ 30% from baseline in average abdominal pain score and increase of ≥ 1 CSBM from baseline during same week for at least 6/12 or 13/26 weeks of treatment period. Weeks not have to be consecutive: (Weeks 1-12)13.9% placebo vs. 33.7% linaclotide(NNT = 5.1), (Weeks 1-26) 13.2% placebo vs. 32.4% linaclotide (NNT = 5.2)  Decrease of ≥ 30% from baseline in average abdominal pain score during particular week for at least 9/12 or 20/26 weeks of treatment period (Weeks 1-12) 19.6% placebo vs. 38.9% linaclotide(NNT = 5.2). (Weeks 1-26) 17.4% placebo vs. 36.9% linaclotide (NNT = 5.1)  ≥ 3 CSBMs and increase of ≥ 1 CSBM from baseline during  same week for at least 9/12 or 20/26 weeks of treatment period. Weeks not have to be consecutive. (Weeks 1-12) 5.0% placebo vs. 18.0% linaclotide (NNT = 7.7). (Weeks 1-26) 3.5% placebo vs. 15.7% linaclotide (NNT = 8.2).  Decrease of ≥ 30% from baseline in average abdominal pain score, ≥ 3 CSBMs and increase of ≥ 1 CSBM from baseline during particular week for at least 9/12 or 20/26 weeks of treatment period. (Weeks 1-12) 3.0% placebo vs. 12.7% linaclotide (NNT = 10.3). (Weeks 1-26) 2.5% vs. 12.0% linaclotide (NNT = 10.5)  Secondary endpoint: : SBM frequency after 12 weeks compared to baseline: 1.3 placebo vs. 4.0 linaclotide  Percentage of patients reporting adequate relief of IBS symptoms for at least 75% of the weeks (9/12 or 20/26): 17.6% placebo vs. 41.9% linaclotide | No deaths  Patients with at least 1 TEAE 56.6% placebo vs. 65.4 linaclotide  Diarrhea 2.5% placebo vs. 19.7% linaclotide  Flatulence 2.2% placebo vs. 3.7% linaclotide  Viral gastroenteritis 2.2% placebo vs. 3.7% linaclotide  Fatige 1% placebo vs. 2% linaclotide  Sinus congestion 1% placebo vs. 2% linaclotide | Linaclotide treatment resulted significantly greater percentages of patients who experienced improvements in abdominal and bowel symptoms compared with placebo treatment  Effects of linaclotide on abdominal and bowel symptoms appeared within first week of treatment and sustained over entire 26-week treatment period  90% of reported diarrhea events were mild or moderate in severity and only 4.5% of linaclotide-treated patients discontinued treatment due to diarrhea. 28% of patients reporting diarrhea experienced this AE on the first day of therapy and 76% within first 4 weeks of treatment.  Jadad Quality Rating: 5 |

1. Product Information: LINZESS(TM) oral capsules, linaclotide oral capsules. Forest Pharmaceuticals, Inc. (per FDA), St. Louis, MO, 2012. [↑](#endnote-ref-1)
2. Lembo A., et al. Two Randomized Trials of Linaclotide for Chronic Constipation. The New England Journal of Medicine 2011; 365: 527-536. [↑](#endnote-ref-2)
3. Chey W., et al. Linaclotide for Irritable Bowel Syndrome With Constipation: A 26-Week, Randomized Double-blind, Placebo-Controlled Trial to Evaluate Efficacy and Safety. The American Journal of Gastroenterology 2012; 107: 1702-1712. [↑](#endnote-ref-3)
4. Ford AC, Suares NC. Effect of laxatives and pharmacological therapies in chronic idiopathic constipation: systematic review and meta-analysis. Gut 2011;60:209-18. [↑](#endnote-ref-4)
5. Rao S, Lembo AJ, Shiff SJ, Lavins BJ, et al. 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;107:1714-24. [↑](#endnote-ref-5)
6. Amitiza [prescribing information]. Bethesda, MD: Sucampo Pharma Americas, Inc., and

   Deerfield, IL: Takeda Pharmaceuticals America 2011 February [↑](#endnote-ref-6)