HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LINZESS safely and effectively. See full prescribing information for LINZESS.

LINZESS® (linaclotide) capsules, for oral use
Initial U.S. Approval: 2012

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS LESS THAN 2 YEARS OF AGE
See full prescribing information for complete boxed warning.

- **LINZESS is contraindicated in patients less than 2 years of age; in neonatal mice, linaclotide caused deaths due to dehydration. (4, 5.1, 8.4)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	8/2021
Contraindications (4)	8/2021
Warnings and Precautions (5.1)	8/2021

----------INDICATIONS AND USAGE----------
LINZESS is a guanylate cyclase-C agonist indicated in adults for treatment of:
- Irritable bowel syndrome with constipation. (IBS-C) (1)
- Chronic idiopathic constipation. (CIC) (1)

----------DOSAGE AND ADMINISTRATION----------
The recommended dosage in adults is:
- IBS-C: 290 mcg orally once daily. (2.1)
- CIC: 145 mcg orally once daily or 72 mcg orally once daily based on individual presentation or tolerability. (2.1)

Administration Instructions (2.2):
- Take on empty stomach at least 30 minutes prior to first meal of the day.
- Do not crush or chew LINZESS capsule or capsule contents.
- For patients who have difficulty swallowing capsules whole or those with a nasogastric or gastrostomy tube, see full prescr bing information for instructions for opening the capsule and administering with applesauce or water.

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 72 mcg, 145 mcg and 290 mcg (3)

----------CONTRAINDICATIONS----------
Patients with known or suspected mechanical gastrointestinal obstruction. (4)

----------WARNINGS AND PRECAUTIONS----------
Diarrhea: Patients may experience severe diarrhea. If severe diarrhea occurs, suspend dosing and rehydrate the patient. (5.2)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥2%) reported in IBS-C or CIC patients are: diarrhea, abdominal pain, flatulence and abdominal distension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS LESS THAN 2 YEARS OF AGE

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS LESS THAN 2 YEARS OF AGE

- **LINZESS is contraindicated in patients less than 2 years of age; in nonclinical studies in neonatal mice, administration of a single, clinically relevant adult oral dose of linaclotide caused deaths due to dehydration *[see Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.4)]*.**

1 INDICATIONS AND USAGE

LINZESS is indicated in adults for the treatment of:

- irritable bowel syndrome with constipation (IBS-C)
- chronic idiopathic constipation (CIC)

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Irritable Bowel Syndrome with Constipation (IBS-C)

The recommended dosage of LINZESS is 290 mcg orally once daily.

Chronic Idiopathic Constipation (CIC)

The recommended dosage of LINZESS is 145 mcg orally once daily. A dosage of 72 mcg once daily may be used based on individual presentation or tolerability.

2.2 Preparation and Administration Instructions

- Take LINZESS on an empty stomach, at least 30 minutes prior to the first meal of the day.
- If a dose is missed, skip the missed dose and take the next dose at the regular time. Do not take 2 doses at the same time.
- Do not crush or chew LINZESS capsule or capsule contents.
- Swallow LINZESS capsule whole.
- For adult patients with swallowing difficulties, LINZESS capsules can be opened and administered orally in either applesauce or with water or administered with water via a nasogastric or gastrostomy tube. Sprinkling of LINZESS beads on other soft foods or in other liquids has not been tested.

Oral Administration in Applesauce:

1. Place one teaspoonful of room-temperature applesauce into a clean container.
2. Open the capsule.
3. Sprinkle the entire contents (beads) on applesauce.
4. Consume the entire contents immediately. Do not chew the beads. Do not store the bead-applesauce mixture for later use.

Oral Administration in Water:

1. Pour approximately 30 mL of room-temperature bottled water into a clean cup.
2. Open the capsule.
3. Sprinkle the entire contents (beads) into the water.
4. Gently swirl beads and water for at least 20 seconds.
5. Swallow the entire mixture of beads and water immediately.
6. Add another 30 mL of water to any beads remaining in cup, swirl for 20 seconds, and swallow immediately.
7. Do not store the bead-water mixture for later use.

Note: The drug is coated on the surface of the beads and will dissolve off the beads into the water. The beads will remain visible and will not dissolve. Therefore, it is not necessary to consume all the beads to deliver the complete dose.

Administration with Water via a Nasogastric or Gastrostomy Tube:

1. Open the capsule and empty the beads into a clean container with 30 mL of room-temperature bottled water.
2. Mix by gently swirling beads for at least 20 seconds.
3. Draw-up the beads and water mixture into an appropriately sized catheter-tipped syringe and apply rapid and steady pressure (10 mL/10 seconds) to dispense the syringe contents into the tube.
4. Add another 30 mL of water to any beads remaining in the container and repeat the process.
5. After administering the bead-water mixture, flush nasogastric/ gastrostomy tube with a minimum of 10 mL of water.

Note: It is not necessary to flush all the beads through to deliver the complete dose.

3 DOSAGE FORMS AND STRENGTHS

LINZESS capsules are white to off-white opaque:

- 72 mcg; gray imprint “FL 72”
- 145 mcg; gray imprint “FL 145”
- 290 mcg; gray imprint “FL 290”

4 CONTRAINDICATIONS

LINZESS is contraindicated in:

- Patients less than 2 years of age due to the risk of serious dehydration *[see Warnings and Precautions (5.1), Use in Specific Populations (8.4)].*
- Patients with known or suspected mechanical gastrointestinal obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Dehydration in Pediatric Patients Less Than 2 Years of Age

LINZESS is contraindicated in patients less than 2 years of age. In neonatal mice (human age equivalent of approximately 0 to 28 days), linaclotide increased fluid secretion as a

consequence of age-dependent elevated GC-C agonism which was associated with increased mortality within the first 24 hours due to dehydration. There was no age-dependent trend in GC-C intestinal expression in a clinical study of children 2 to less than 18 years of age; however, there are insufficient data available on GC-C intestinal expression in children less than 2 years of age to assess the risk of developing diarrhea and its potentially serious consequences in these patients *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.4)*.

The safety and effectiveness of LINZESS in patients less than 18 years of age have not been established.

5.2 Diarrhea

Diarrhea was the most common adverse reaction of LINZESS-treated patients in the pooled IBS-C and CIC double-blind placebo-controlled trials. The incidence of diarrhea was similar between the IBS-C and CIC populations. Severe diarrhea was reported in 2% of 145 mcg and 290 mcg LINZESS-treated patients, and in <1% of 72 mcg LINZESS-treated CIC patients *[see Adverse Reactions (6.1)]*.

In post-marketing experience, severe diarrhea associated with dizziness, syncope, hypotension and electrolyte abnormalities (hypokalemia and hyponatremia) requiring hospitalization or intravenous fluid administration have been reported in patients treated with LINZESS.

If severe diarrhea occurs, suspend dosing and rehydrate the patient.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Exposure in clinical development included approximately 2570, 2040, and 1220 patients with either IBS-C or CIC treated with LINZESS for 6 months or longer, 1 year or longer, and 18 months or longer, respectively (not mutually exclusive).

Demographic characteristics were comparable between treatment groups in all studies *[see Clinical Studies (14)]*.

Irritable Bowel Syndrome with Constipation (IBS-C)

Most Common Adverse Reactions

The data described below reflect exposure to LINZESS in the two placebo-controlled clinical trials involving 1605 adult patients with IBS-C (Trials 1 and 2). Patients were randomized to receive placebo or 290 mcg LINZESS once daily on an empty stomach for up to 26 weeks. Table 1 provides the incidence of adverse reactions reported in at least 2% of IBS-C patients in the LINZESS treatment group and at an incidence that was greater than in the placebo group.

Table 1: Most Common Adverse Reactions[a] in Two Placebo-Controlled Trials (1 and 2) in Patients with IBS-C

Adverse Reactions	LINZESS 290 mcg [N=807] %	Placebo [N=798] %
Gastrointestinal		
Diarrhea	20	3
Abdominal pain[b]	7	5
Flatulence	4	2
Abdominal distension	2	1
Infections and Infestations		
Viral Gastroenteritis	3	1
Nervous System Disorders		
Headache	4	3

[a]: Reported in at least 2% of LINZESS-treated patients and at an incidence greater than placebo

[b]: "Abdominal pain" term includes abdominal pain, upper abdominal pain, and lower abdominal pain.

Adverse reactions in an additional placebo-controlled trial in 614 IBS-C patients randomized to placebo or LINZESS 290 mcg once daily on an empty stomach for 12 weeks (Trial 6) were similar to those in Table 1.

Diarrhea

Diarrhea was the most commonly reported adverse reaction of the LINZESS-treated patients in the pooled IBS-C pivotal placebo-controlled trials. In these trials, 20% of LINZESS-treated patients reported diarrhea compared to 3% of placebo-treated patients. Severe diarrhea was reported in 2% of the LINZESS-treated patients versus less than 1% of the placebo-treated patients, and 5% of LINZESS-treated patients discontinued due to diarrhea vs less than 1% of placebo-treated patients. The majority of reported cases of diarrhea started within the first 2 weeks of LINZESS treatment *[see Warnings and Precautions (5.2)]*.

Adverse Reactions Leading to Discontinuation

In placebo-controlled trials in patients with IBS-C, 9% of patients treated with LINZESS and 3% of patients treated with placebo discontinued prematurely due to adverse reactions. In the LINZESS-treatment group, the most common reasons for discontinuation due to adverse

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