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: PEDIATRIC RISK
See full prescribing information for complete boxed warning.

LINZESS is contraindicated in pediatric patients up to 6 years of age; linaclotide caused deaths due to dehydration in young juvenile mice. Avoid use of LINZESS in pediatric patients 6 through 17 years of age. The safety and efficacy of LINZESS has not been established in pediatric patients under 18 years of age (4, 5.1, 8.4, 13.2).

----------RECENT MAJOR CHANGES----------
Dosage and Administration (2.3) 11/2015

----------INDICATIONS AND USAGE----------

LINZESS is a guanylate cyclase-C agonist indicated in adults for treatment of:
- Irritable bowel syndrome with constipation (IBS-C) (1.1)
- Chronic idiopathic constipation (CIC) (1.2)

----------DOSAGE AND ADMINISTRATION----------

- IBS-C: Take 290 mcg orally once daily (2.1)
- CIC: Take 145 mcg orally once daily (2.2)
- Take on empty stomach at least 30 minutes prior to first meal of the day (2.1, 2.2)
- For patients who have difficulty swallowing capsules or those with a nasogastric or gastrostomy tube, see full prescribing information for instructions for opening the capsule and administering with applesauce or water.

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 145 mcg and 290 mcg (3)

----------CONTRAINDICATIONS----------

- Pediatric patients under 6 years of age (4)
- Patients with known or suspected mechanical gastrointestinal obstruction (4)

---------- WARNINGS AND PRECAUTIONS----------

- *Diarrhea:* Patients may experience severe diarrhea. Hold or stop LINZESS (5.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence of at least 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 1-800-433-8871 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2016

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FULL PRESCRIBING INFORMATION

WARNING: PEDIATRIC RISK

LINZESS is contraindicated in pediatric patients up to 6 years of age; in nonclinical studies, administration of a single, clinically relevant adult oral dose of linaclotide caused deaths due to dehydration in young juvenile mice. Avoid use of LINZESS in pediatric patients 6 through 17 years of age. The safety and efficacy of LINZESS has not been established in pediatric patients under 18 years of age *[see Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.4) and Nonclinical Toxicology (13.2)].*

1 INDICATIONS AND USAGE

1.1 Irritable Bowel Syndrome with Constipation (IBS-C)

LINZESS (linaclotide) is indicated in adults for the treatment of irritable bowel syndrome with constipation (IBS-C).

1.2 Chronic Idiopathic Constipation (CIC)

LINZESS is indicated in adults for the treatment of chronic idiopathic constipation (CIC).

2 DOSAGE AND ADMINISTRATION

2.1 Irritable Bowel Syndrome with Constipation (IBS-C)

The recommended dose of LINZESS is 290 mcg taken orally once daily on an empty stomach, at least 30 minutes prior to the first meal of the day.

2.2 Chronic Idiopathic Constipation (CIC)

The recommended dose of LINZESS is 145 mcg taken orally once daily on an empty stomach, at least 30 minutes prior to the first meal of the day.

2.3 Important Administration Instructions

Do not crush or chew capsule or capsule contents. Swallow LINZESS capsule whole, or for adult patients with swallowing difficulties, follow the instructions below for administration with applesauce or water. Sprinkling of LINZESS beads on other soft foods or in other liquids has not been tested.

For administration in applesauce:

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

For administration in water:

1. Pour approximately 1 ounce (30 mL) of bottled water at room-temperature into a clean cup.
2. Open the capsule
3. Sprinkle entire contents (beads) into the water
4. Gently swirl beads and water for at least 10 seconds.
5. Swallow the entire mixture of beads and water immediately.
6. Add another 1 ounce of water to any beads remaining in cup, swirl for 10 seconds, and swallow immediately.
7. Do not store the bead-water mixture for future 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.

For nasogastric or gastric feeding tube administration in water:

1. Open the capsule and empty the beads into a clean container with 1 ounce (30 mL) of room-temperature bottled water.
2. Mix by gently swirling beads for at least 10 seconds
3. Draw-up the beads and water mixture to 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. After administering the bead-water mixture, flush nasogastric/gastric 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.

After dosing of linaclotide in either applesauce or water, the first meal of the day can be consumed 30 minutes later.

3 DOSAGE FORMS AND STRENGTHS

- 145 mcg capsules are white to off-white opaque with gray imprint “FL 145”
- 290 mcg capsules are white to off-white opaque with gray imprint “FL 290”

4 CONTRAINDICATIONS

LINZESS is contraindicated in:

- Pediatric patients under 6 years of age *[see Warnings and Precautions (5.1), Use in Specific Populations (8.4) and Nonclinical Toxicology (13.2)]*
- Patients with known or suspected mechanical gastrointestinal obstruction

5 WARNINGS AND PRECAUTIONS

5.1 Pediatric Risk

LINZESS is contraindicated in children under 6 years of age. The safety and effectiveness of LINZESS in pediatric patients under 18 years of age have not been established. In neonatal mice, increased fluid secretion as a consequence of GC-C agonism resulted in mortality within the first 24 hours due to dehydration. Due to increased intestinal expression of GC-C, children under 6 years of age may be more likely than older children and adults to develop significant diarrhea and its potentially serious consequences.

Avoid use of LINZESS in pediatric patients 6 through 17 years of age. Although there were no deaths in older juvenile mice, given the deaths in young juvenile mice and the lack of clinical safety and efficacy data in pediatric patients, avoid the use of LINZESS in pediatric patients 6 through 17 years of age *[see Contraindications (4), Warnings and Precautions (5.2), Use in Specific Populations (8.4) and Nonclinical Toxicology (13.2)]*.

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. Severe diarrhea was reported in 2% of the LINZESS-treated patients. The incidence of diarrhea was similar between the IBS-C and CIC populations *[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 consider dose suspension and rehydration.

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.

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

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. Demographic characteristics were comparable between treatment groups *[see Clinical Studies (14.1)]*. **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: Adverse Reactions Reported in at least 2% of LINZESS-treated Patients and at an Incidence Greater than in Placebo Group Patients in the Two Phase 3 Placebo-controlled Trials (1 and 2) in IBS-C

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

a: “Abdominal pain” term includes abdominal pain, upper abdominal pain, and lower abdominal pain.

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. Fecal incontinence and

dehydration were each reported in less than or equal to 1% of patients in the LINZESS treatment group *[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 reactions were diarrhea (5%) and abdominal pain (1%). In comparison, less than 1% of patients in the placebo group withdrew due to diarrhea or abdominal pain.

Adverse Reactions Leading to Dose Reductions
In the open-label, long-term trials, 2147 patients with IBS-C received 290 mcg of LINZESS daily for up to 18 months. In these trials, 29% of patients had their dose reduced or suspended secondary to adverse reactions, the majority of which were diarrhea or other GI adverse reactions.

Other Adverse Reactions
Adverse reactions that were reported in at least 1% and less than 2% of IBS-C patients in the LINZESS treatment group and at an incidence greater than in the placebo treatment group are listed below by body system:

Gastrointestinal Disorders: gastroesophageal reflux disease, vomiting
General Disorders and Administration Site Conditions: fatigue

Other Adverse Events
In placebo-controlled trials in patients with IBS-C, less than 1% LINZESS-treated patients and no placebo-treated patients reported hematochezia; no patient in either treatment group reported melena. Less than 1% of LINZESS-treated and placebo-treated patients reported allergic reactions, urticaria, or hives as adverse events.

Chronic Idiopathic Constipation (CIC)

Most Common Adverse Reactions
The data described below reflect exposure to LINZESS in the two double-blind placebo-controlled clinical trials of 1275 adult patients with CIC (Trials 3 and 4). Patients were randomized to receive placebo or 145 mcg LINZESS or 290 mcg LINZESS once daily on an empty stomach, for at least 12 weeks. Demographic characteristics were comparable between both LINZESS treatment groups and placebo *[see Clinical Studies (14.2)]*. Only data for the recommended LINZESS 145 mcg dose and placebo are presented. **Table 2** provides the incidence of adverse reactions reported in at least 2% of CIC patients in the 145 mcg LINZESS treatment group and at an incidence that was greater than in the placebo treatment group.

Table 2: Adverse Reactions Reported in at least 2% of 145 mcg LINZESS-treated Patients and at an Incidence Greater than in Placebo Group Patients in the Two Phase 3 Placebo-controlled Trials (3 and 4) in CIC

Adverse Reactions	LINZESS 145 mcg [N=430] %	Placebo [N=423] %
Gastrointestinal		
Diarrhea	16	5
Abdominal pain[a]	7	6
Flatulence	6	5
Abdominal distension	3	2
Infections and Infestations		
Upper respiratory tract infection	5	4
Sinusitis	3	2

a: "Abdominal pain" term includes abdominal pain, upper abdominal pain, and lower abdominal pain.

Diarrhea

Diarrhea was the most commonly reported adverse reaction of the LINZESS-treated patients in the pooled CIC placebo-controlled trials. In these trials, 16% of LINZESS-treated patients reported diarrhea compared to 5% of placebo-treated patients. Severe diarrhea was reported in 2% of the 145 mcg 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. Fecal incontinence was reported in 1% of patients in the LINZESS treatment group, compared with less than 1% in the placebo group. Dehydration was reported in less than 1% of patients in the LINZESS treatment group *[see Warnings and Precautions (5.2)]*.

Adverse Reactions Leading to Discontinuation

In placebo-controlled trials in patients with CIC, 8% of patients treated with LINZESS and 4% of patients treated with placebo discontinued prematurely due to adverse reactions. In the 145 mcg LINZESS treatment group, the most common reasons for discontinuation due to adverse reactions were diarrhea (5%) and abdominal pain (1%). In comparison, less than 1% of patients in the placebo group withdrew due to diarrhea or abdominal pain.

Adverse Reactions Leading to Dose Reductions

In the open-label, long-term trials, 1129 patients with CIC received 290 mcg of LINZESS daily for up to 18 months. In these trials, 27% of patients had their dose reduced or suspended secondary to adverse reactions, the majority of which were diarrhea or other GI adverse reactions.

Other Adverse Reactions

Adverse reactions that were reported in at least 1% of and less than 2% of CIC patients in the 145 mcg LINZESS treatment group and at an incidence greater than in the placebo treatment group are listed below by body system:

Gastrointestinal Disorders: dyspepsia, fecal incontinence
Infections and Infestations: viral gastroenteritis

Other Adverse Events

In placebo-controlled trials in patients with CIC, less than 1% of both LINZESS-treated and placebo-treated patients reported rectal hemorrhage, hematochezia or melena. Less than 1% of LINZESS-treated and placebo-treated patients reported allergic reactions, urticaria, or hives as adverse events.

7 DRUG INTERACTIONS

No drug-drug interaction studies have been conducted with LINZESS. Linaclotide and its active metabolite are not measurable in plasma following administration of the recommended clinical doses; hence, no systemic drug-drug interactions or drug interactions mediated by plasma protein binding of linaclotide or its metabolite are anticipated *[see Clinical Pharmacology (12.3)]*.

Linaclotide does not interact with the cytochrome P450 enzyme system based on the results of *in vitro* studies. In addition, linaclotide is neither a substrate nor an inhibitor of the efflux transporter P-glycoprotein (P-gp).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary
There are no adequate and well-controlled studies with LINZESS in pregnant women. In animal developmental studies, adverse fetal effects were observed only with maternal toxicity and at doses of linaclotide much higher than the maximum recommended human dose. LINZESS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data
The potential for linaclotide to cause teratogenic effects was studied in rats, rabbits and mice. Oral administration of up to 100,000 mcg/kg/day in rats and 40,000 mcg/kg/day in rabbits produced no maternal toxicity and no effects on embryo-fetal development. In mice, oral dose levels of at least 40,000 mcg/kg/day produced severe maternal toxicity including death, reduction of gravid uterine and fetal weights, and effects on fetal morphology. Oral doses of 5000 mcg/kg/day did not produce maternal toxicity or any adverse effects on embryo-fetal development in mice.

The maximum recommended human dose is approximately 5 mcg/kg/day, based on a 60-kg body weight. Limited systemic exposure to linaclotide was achieved at the tested dose levels in animals (AUC = 40, 640, and 25 ng•hr/mL in rats, rabbits, and mice, respectively, at the highest dose levels), whereas no detectable exposure occurred in humans. Therefore, animal and human doses should not be compared directly for evaluating relative exposure.

8.3 Nursing Mothers

It is not known whether linaclotide is excreted in human milk; however, linaclotide and its active metabolite are not measurable in plasma following administration of the recommended clinical doses *[see Clinical Pharmacology (12.3)]*.

Caution should be exercised when LINZESS is administered to nursing women *[see Contraindications (4), Warnings and Precautions (5.1) and Use in Specific Populations (8.4)].*

8.4 Pediatric Use

LINZESS is contraindicated in children under 6 years of age. The safety and effectiveness of LINZESS in pediatric patients under 18 years of age have not been established. In neonatal mice, increased fluid secretion as a consequence of GC-C agonism resulted in mortality due to dehydration. Due to increased intestinal expression of GC-C, children under 6 years of age may be more likely than older children and adults to develop diarrhea and its potentially serious consequences.

Avoid use of LINZESS in pediatric patients 6 through 17 years of age. Although there were no deaths in older juvenile mice, given the deaths in young juvenile mice and the lack of clinical safety and efficacy

data in pediatric patients, avoid the use of LINZESS in pediatric patients 6 through 17 years of age *[see Contraindications (4), Warnings and Precautions (5.1, 5.2) and Nonclinical Toxicology (13.2)]*.

8.5 Geriatric Use

Irritable Bowel Syndrome with Constipation (IBS-C)
Of 1605 IBS-C patients in the placebo-controlled clinical studies of LINZESS, 85 (5%) were at least 65 years of age, while 20 (1%) were at least 75 years old. Clinical studies of LINZESS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Chronic Idiopathic Constipation (CIC)
Of 1275 CIC patients in the placebo-controlled clinical studies of LINZESS, 155 (12%) were at least 65 years of age, while 30 (2%) were at least 75 years old. Clinical trials of LINZESS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.6 Hepatic or Renal Impairment

No dose adjustment is necessary based on hepatic or renal function *[see Clinical Pharmacology (12.3)]*.

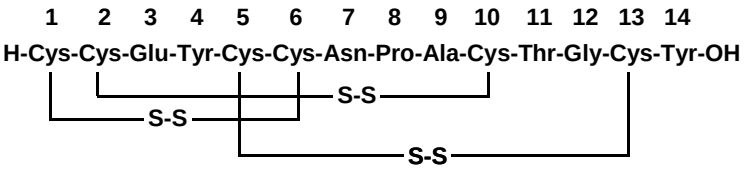
10 OVERDOSAGE

There is limited experience with overdose of LINZESS. During the clinical development program of LINZESS, single doses of 2897 mcg were administered to 22 healthy volunteers; the safety profile in these subjects was consistent with that in the overall LINZESS-treated population, with diarrhea being the most commonly reported adverse reaction.

11 DESCRIPTION

LINZESS (linaclotide) is a guanylate cyclase-C agonist. Linaclotide is a 14-amino acid peptide with the following chemical name: L-cysteinyl-L-cysteinyl-L-glutamyl-L-tyrosyl-L-cysteinyl-L-cysteinyl-L-asparaginyl-L-prolyl-L-alanyl-L-cysteinyl-L-threonyl-glycyl-L-cysteinyl-L-tyrosine, cyclic (1-6), (2-10), (5-13)-tris (disulfide).

The molecular formula of linaclotide is $C_{59}H_{79}N_{15}O_{21}S_6$ and its molecular weight is 1526.8. The amino acid sequence for linaclotide is shown below:



Linaclotide is an amorphous, white to off-white powder. It is slightly soluble in water and aqueous sodium chloride (0.9%). LINZESS contains linaclotide-coated beads in hard gelatin capsules. LINZESS is available as 145 mcg and 290 mcg capsules for oral administration.

The inactive ingredients of LINZESS capsules include: calcium chloride dihydrate, L-leucine, hypromellose, microcrystalline cellulose, gelatin, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Linaclotide is a guanylate cyclase-C (GC-C) agonist. Both linaclotide and its active metabolite bind to GC-C and act locally on the luminal surface of the intestinal epithelium. Activation of GC-C results in an increase in both intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP). Elevation in intracellular cGMP stimulates secretion of chloride and bicarbonate into the intestinal lumen, mainly through activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel, resulting in increased intestinal fluid and accelerated transit. In animal models, linaclotide has been shown to both accelerate GI transit and reduce intestinal pain. The linaclotide-induced reduction in visceral pain in animals is thought to be mediated by increased extracellular cGMP, which was shown to decrease the activity of pain-sensing nerves.

12.2 Pharmacodynamics

Although the pharmacologic effects of LINZESS in humans have not been fully evaluated, in clinical studies, LINZESS has been shown to change stool consistency as measured by the Bristol Stool Form Scale (BSFS) and increase stool frequency.

12.3 Pharmacokinetics

Absorption
LINZESS is minimally absorbed with low systemic availability following oral administration. Concentrations of linaclotide and its active metabolite in plasma are below the limit of quantitation after oral doses of 145 mcg or 290 mcg were administered. Therefore, standard pharmacokinetic parameters such as area under the curve (AUC), maximum concentration (C_{max}), and half-life ($t_{½}$) cannot be calculated.

Distribution
Given that linaclotide plasma concentrations following therapeutic oral doses are not measurable, linaclotide is expected to be minimally distributed to tissues.

Metabolism
Linaclotide is metabolized within the gastrointestinal tract to its principal, active metabolite by loss of the terminal tyrosine moiety. Both linaclotide and the metabolite are proteolytically degraded within the intestinal lumen to smaller peptides and naturally occurring amino acids.

Elimination
Active peptide recovery in the stool samples of fed and fasted subjects following the daily administration of 290 mcg of LINZESS for seven days averaged about 5% (fasted) and about 3% (fed) and virtually all as the active metabolite.

Food Effect
In a cross-over study, 18 healthy subjects were given LINZESS 290 mcg for 7 days both in the non-fed and fed state. Neither linaclotide nor its active metabolite was detected in the plasma. Taking LINZESS immediately after the high fat breakfast resulted in looser stools and a higher stool frequency compared with taking it in the fasted state *[see Dosage and Administration (2.1, 2.2)].* In clinical trials, LINZESS was administered on an empty stomach, at least 30 minutes before breakfast.

Specific Populations

Age and Gender
Clinical studies to determine the impact of age and gender on the pharmacokinetics of LINZESS have not been conducted. See *Use in Specific Populations (8.5)* for information regarding patients aged 65 years and older.

Hepatic Impairment
LINZESS has not been specifically studied in patients who have hepatic impairment. Hepatic impairment is not expected to affect the metabolism or clearance of the parent drug or its metabolite because linaclotide is metabolized within the gastrointestinal tract *[see Use in Specific Populations (8.6)]*.

Renal Impairment
LINZESS has not been specifically studied in patients who have renal impairment. Renal impairment is not expected to affect clearance of the parent drug or its metabolite because linaclotide has low systemic availability following oral administration and is metabolized within the gastrointestinal tract *[see Use in Specific Populations (8.6)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis
In 2-year carcinogenicity studies, linaclotide was not tumorigenic in rats at doses up to 3500 mcg/kg/day or in mice at doses up to 6000 mcg/kg/day. The maximum recommended human dose is approximately 5 mcg/kg/day based on a 60-kg bodyweight. Limited systemic exposure to linaclotide was achieved at the tested dose levels in animals, whereas no detectable exposure occurred in humans. Therefore, animal and human doses should not be compared directly for evaluating relative exposure.

Mutagenesis
Linaclotide was not genotoxic in an *in vitro* bacterial reverse mutation (Ames) assay or in the *in vitro* chromosomal aberration assay in cultured human peripheral blood lymphocytes.

Impairment of Fertility
Linaclotide had no effect on fertility or reproductive function in male and female rats at oral doses of up to 100,000 mcg/kg/day.

13.2 Animal Toxicology and/or Pharmacology

In toxicology studies in neonatal mice, linaclotide caused deaths at 10 mcg/kg/day after oral administration of 1 or 2 daily doses on post-natal day 7. These deaths were due to rapid and severe dehydration produced by significant fluid shifts into the intestinal lumen resulting from GC-C agonism in neonatal mice. Supplemental subcutaneous fluid administration prevented death after linaclotide administration in neonatal mice *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

In studies conducted without supplemental fluid administration, tolerability to linaclotide increases with age in juvenile mice. In 2-week-old mice, linaclotide was well tolerated at a dose of 50 mcg/kg/day, but deaths occurred after a single oral dose of 100 mcg/kg. In 3-week-old mice, linaclotide was well tolerated at 100 mcg/kg/day, but deaths occurred after a single oral dose of 600 mcg/kg. Linaclotide was well tolerated and did not cause death in 4-week-old juvenile mice at a dose of 1,000 mcg/kg/day for 7 days and in 6-week-old juvenile mice at a dose of 20,000 mcg/kg/day for 28 days

Linaclotide did not cause death in adult mice, rats, rabbits and monkeys at dose levels up to 5,000 mcg/kg/day. The maximum recommended dose in adults is approximately 5 mcg/kg/day, based on a 60-kg body weight. Animal and human doses of linaclotide should not be compared directly for evaluating relative exposure *[see Nonclinical Toxicology (13.1)].*

14 CLINICAL STUDIES

14.1 Irritable Bowel Syndrome with Constipation (IBS-C)

The efficacy of LINZESS for the management of symptoms of IBS-C was established in two double-blind, placebo-controlled, randomized, multicenter trials in adult patients (Trials 1 and 2). A total of 800 patients in Trial 1 and 804 patients in Trial 2 [overall mean age of 44 years (range 18 - 87 years with 5% at least 65 years of age), 90% female, 77% white, 19% black, and 12% Hispanic] received treatment with LINZESS 290 mcg or placebo once daily and were evaluated for efficacy. All patients met Rome II criteria for IBS and were required, during the 2-week baseline period, to meet the following criteria:

- a mean abdominal pain score of at least 3 on a 0-to-10-point numeric rating scale
- less than 3 complete spontaneous bowel movements (CSBMs) per week [a CSBM is a spontaneous bowel movement (SBM) that is associated with a sense of complete evacuation; a SBM is a bowel movement occurring in the absence of laxative use], and
- less than or equal to 5 SBMs per week.

The trial designs were identical through the first 12 weeks, and thereafter differed only in that Trial 1 included a 4-week randomized withdrawal (RW) period, and Trial 2 continued for 14 additional weeks (total of 26 weeks) of double-blind treatment. During the trials, patients were allowed to continue stable doses of bulk laxatives or stool softeners but were not allowed to take laxatives, bismuth, prokinetic agents, or other drugs to treat IBS-C or chronic constipation.

Efficacy of LINZESS was assessed using overall responder analyses and change-from-baseline endpoints. Results for endpoints were based on information provided daily by patients in diaries.

The 4 primary efficacy responder endpoints were based on a patient being a weekly responder for either at least 9 out of the first 12 weeks of treatment or at least 6 out of the first 12 weeks of treatment. For the 9 out of 12 weeks combined primary responder endpoint, a patient had to have at least a 30% reduction from baseline in mean abdominal pain, at least 3 CSBMs and an increase of at least 1 CSBM from baseline, all in the same week, for at least 9 out of the first 12 weeks of treatment. Each of the 2 components of the 9 out of 12 weeks combined responder endpoint, abdominal pain and CSBMs, was also a primary endpoint.

For the 6 out of 12 weeks combined primary responder endpoint, a patient had to have at least a 30% reduction from baseline in mean abdominal pain and an increase of at least 1 CSBM from baseline, all in the same week, for at least 6 out of the first 12 weeks of treatment. To be considered a responder for this analysis, patients did not have to have at least 3 CSBMs per week.

The efficacy results for the 9 out of 12 weeks and the 6 out of 12 weeks responder endpoints are shown in **Tables 3 and 4**, respectively. In both trials, the proportion of patients who were responders to LINZESS 290 mcg was statistically significantly higher than with placebo.

Table 3: Efficacy Responder Rates in the Two Placebo-controlled IBS-C Trials: at Least 9 Out of 12 Weeks

	Trial 1			Trial 2		
	LINZESS 290 mcg (N=405)	**Placebo (N=395)**	**Treatment Difference [95% CI]**	**LINZESS 290 mcg (N=401)**	**Placebo (N=403)**	**Treatment Difference [95% CI]**
Combined Responder* (Abdominal Pain and CSBM Responder)	12.1%	5.1%	7.0% [3.2%, 10.9%]	12.7%	3.0%	9.7% [6.1%, 13.4%]
Abdominal Pain Responder* (≥ 30% Abdominal Pain Reduction)	34.3%	27.1%	7.2% [0.9%, 13.6%]	38.9%	19.6%	19.3% [13.2%, 25.4%]
CSBM Responder* (≥ 3 CSBMs and Increase ≥1 CSBM from Baseline)	19.5%	6.3%	13.2% [8.6%, 17.7%]	18.0%	5.0%	13.0% [8.7%, 17.3%]

* Primary Endpoints
Note: Analyses based on first 12 weeks of treatment for both Trials 1 and 2
CI =Confidence Interval

Table 4: Efficacy Responder Rates in the Two Placebo-controlled IBS-C Trials: at Least 6 Out of 12 Weeks

	Trial 1			Trial 2		
	LINZESS 290 mcg (N=405)	**Placebo (N=395)**	**Treatment Difference [95% CI]**	**LINZESS 290 mcg (N=401)**	**Placebo (N=403)**	**Treatment Difference [95% CI]**
Combined Responder* (Abdominal Pain and CSBM Responder)	33.6%	21.0%	12.6% [6.5%, 18.7%]	33.7%	13.9%	19.8% [14.0%, 25.5%]
Abdominal Pain Responder** (≥ 30% Abdominal Pain Reduction)	50.1%	37.5%	12.7% [5.8%, 19.5%]	48.9%	34.5%	14.4% [7.6%, 21.1%]
CSBM Responder** (Increase ≥ 1 CSBM from Baseline)	48.6%	29.6%	19.0% [12.4%, 25.7%]	47.6%	22.6%	25.1% [18.7%, 31.4%]

* Primary Endpoint, ** Secondary Endpoints
Note: Analyses based on first 12 weeks of treatment for both Trials 1 and 2
CI =Confidence Interval

In each trial, improvement from baseline in abdominal pain and CSBM frequency was seen over the first 12-weeks of the treatment periods. For change from baseline in the 11-point abdominal pain scale, LINZESS 290 mcg began to separate from placebo in the first week. Maximum effects were seen at weeks 6 - 9 and were maintained until the end of the study. The mean treatment difference from placebo at week 12 was a decrease in pain score of approximately 1.0 point in both trials (using an 11-point scale). Maximum effect on CSBM frequency occurred within the first week, and for change from baseline in CSBM frequency at week 12, the difference between placebo and LINZESS was approximately 1.5 CSBMs per week in both trials.

In each trial, in addition to improvements in abdominal pain and CSBM frequency over the first 12 weeks of the treatment period, improvements were observed in the following when LINZESS was compared to placebo: SBM frequency [SBMs/week], stool consistency [as measured by the Bristol Stool Form Scale (BSFS)], and amount of straining with bowel movements [amount of time pushing or physical effort to pass stool].

During the 4-week randomized withdrawal period in Trial 1, patients who received LINZESS during the 12-week treatment period were re-randomized to receive placebo or continue treatment on LINZESS 290 mcg. In LINZESS-treated patients re-randomized to placebo, CSBM frequency and abdominal-pain severity returned toward baseline within 1 week and did not result in worsening compared to baseline. Patients who continued on LINZESS maintained their response to therapy over the additional 4 weeks. Patients on placebo who were allocated to LINZESS had an increase in CSBM frequency and a decrease in abdominal pain levels that were similar to the levels observed in patients taking LINZESS during the treatment period.

14.2 Chronic Idiopathic Constipation (CIC)

The efficacy of LINZESS for the management of symptoms of CIC was established in two double-blind, placebo-controlled, randomized, multicenter clinical trials in adult patients (Trials 3 and 4). A total of 642 patients in Trial 3 and 630 patients in Trial 4 [overall mean age of 48 years (range 18 - 85 years with 12% at least 65 years of age), 89% female, 76% white, 22% black, 10% Hispanic] received treatment with LINZESS 145 mcg, 290 mcg, or placebo once daily and were evaluated for efficacy. All patients met modified Rome II criteria for functional constipation. Modified Rome II criteria were less than 3 Spontaneous Bowel Movements (SBMs) per week and 1 of the following symptoms for at least 12 weeks, which need not be consecutive, in the preceding 12 months:

- Straining during greater than 25% of bowel movements
- Lumpy or hard stools during greater than 25% of bowel movements
- Sensation of incomplete evacuation during greater than 25% of bowel movements

Patients were also required to have less than 3 CSBMs per week and less than or equal to 6 SBMs per week during a 2-week baseline period. Patients were excluded if they met criteria for IBS-C or had fecal impaction that required emergency room treatment.

The trial designs were identical through the first 12 weeks. Trial 3 also included an additional 4-week randomized withdrawal (RW) period. During the trials, patients were allowed to continue stable doses of bulk laxatives or stool softeners but were not allowed to take laxatives, bismuth, prokinetic agents, or other drugs to treat chronic constipation.

Efficacy of LINZESS was assessed using overall responder analysis and change-from-baseline endpoints. Results for endpoints were based on information provided daily by patients in diaries.

A CSBM overall responder in the CIC trials was defined as a patient who had at least 3 CSBMs and an increase of at least 1 CSBM from baseline in a given week for at least 9 weeks out of the 12-week treatment period. The CSBM responder rates are shown in **Table 5**. During the individual double-blind placebo-controlled trials, LINZESS 290 mcg did not consistently offer additional clinically meaningful treatment benefit over placebo than that observed with the LINZESS 145 mcg dose. Therefore, the 145 mcg dose is the recommended dose. Only the data for the approved 145 mcg dose of LINZESS are presented in **Table 5**.

In Trials 3 and 4, the proportion of patients who were CSBM responders was statistically significantly greater with the LINZESS 145 mcg dose than with placebo.

Table 5: Efficacy Responder Rates in the Two Placebo-controlled CIC Trials: at Least 9 Out of 12 Weeks

	Trial 3			Trial 4		
	LINZESS 145 mcg (N=217)	**Placebo (N=209)**	**Treatment Difference [95% CI]**	**LINZESS 145 mcg (N=213)**	**Placebo (N=215)**	**Treatment Difference [95% CI]**
CSBM Overall Responder* (≥ 3 CSBMs and Increase ≥ 1 CSBM from Baseline)	20.3%	3.3%	16.9% [11.0%, 22.8%]	15.5%	5.6%	9.9% [4.2%, 15.7%]
*Primary Endpoint CI=Confidence Interval						

CSBM frequency reached maximum level during week 1 and was also demonstrated over the remainder of the 12-week treatment period in Trial 3 and Trial 4. For the mean change from baseline in CSBM frequency at week 12, the difference between placebo and LINZESS was approximately 1.5 CSBMs.

On average, patients who received LINZESS across the 2 trials had significantly greater improvements compared with patients receiving placebo in stool frequency (CSBMs/week and SBMs/week), and stool consistency (as measured by the BSFS).

In each trial, in addition to improvements in CSBM frequency over the first 12 weeks of the treatment period, improvements were observed in each of the following when LINZESS was compared to placebo: SBM frequency [SBMs/week], stool consistency [as measured by the BSFS], and amount of straining with bowel movements [amount of time pushing or physical effort to pass stool].

During the 4-week randomized withdrawal period in Trial 3, patients who received LINZESS during the 12-week treatment period were re-randomized to receive placebo or continue treatment on the same dose of LINZESS taken during the treatment period. In LINZESS-treated patients re-randomized to placebo, CSBM and SBM frequency returned toward baseline within 1 week and did not result in worsening compared to baseline. Patients who continued on LINZESS maintained their response to therapy over the additional 4 weeks. Patients on placebo who were allocated to LINZESS had an increase in CSBM and SBM frequency similar to the levels observed in patients taking LINZESS during the treatment period.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

- **145 mcg Capsules**: White to off-white opaque hard gelatin capsules with gray imprint "FL 145" Bottle of 30: NDC 0456-1201-30

- **290 mcg Capsules**: White to off-white opaque hard gelatin capsules with gray imprint "FL 290" Bottle of 30: NDC 0456-1202-30

Storage
Store at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

Keep LINZESS in the original container. Do not subdivide or repackage. Protect from moisture. Do not remove desiccant from the container. Keep bottles tightly closed in a dry place.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Patients should be instructed as follows:

- **Do not give LINZESS to children who are under 6 years of age. It may harm them. You should not give LINZESS to children 6 to 17 years of age. It may harm them** *[see Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.4) and Nonclinical Toxicology (13.2)].*

- Keep LINZESS in the original container. Do not subdivide or repackage. Protect from moisture. Do not remove desiccant from the container. Keep bottles closed tightly in a dry place *[see How Supplied/Storage and Handling (16)]***.**

- Take LINZESS once daily on an empty stomach as prescribed. The first meal of the day can be consumed 30 minutes after taking LINZESS*. [see Dosage and Administration (2.1 and 2.2)].*
- If you miss a dose, skip the missed dose. Just take the next dose at your regular time. Do not take 2 doses at the same time.

- Do not crush or chew capsules or capsule contents. Swallow the capsule whole or, for adult patients with swallowing difficulties, the contents of LINZESS capsules, may be given with applesauce or in water. Sprinkling of LINZESS beads on other soft foods or in other liquids has not been tested.

For administration in applesauce:

1. Place one teaspoonful of applesauce at room temperature into a clean container.
2. Open the capsule
3. Sprinkle entire contents (beads) onto applesauce.
4. Consume all of the beads and applesauce immediately. Do not chew the beads.
5. Do not store the mixture of beads and applesauce for future use.

For administration in water:

1. Pour approximately 1 ounce (or 30 mL) of room-temperature bottled water into a clean cup.
2. Open the capsule
3. Sprinkle entire contents (beads) into the water
4. Gently swirl beads and water for at least 10 seconds.
5. Swallow the entire mixture of beads and water immediately.
6. Add another 1 ounce of water to any beads remaining in cup, swirl for 10 seconds, and swallow immediately.
7. Do not store the bead-water mixture for future use.

For nasogastric or gastric feeding tube administration:

1. Open the capsule and empty the beads into a clean container with 1 ounce (30 mL) of room-temperature bottled water.
2. Mix by gently swirling beads for at least 10 seconds
3. Draw-up the mixture of beads and water to 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. After administering the bead-water mixture, flush nasogastric/gastric tube with a minimum of 10 mL of water.

- Stop LINZESS and contact your physician if you experience severe diarrhea *[see Warnings and Precautions (5.2)]*.

- Seek immediate medical attention if you develop unusual or severe abdominal pain, and /or severe diarrhea, especially if in combination with hematochezia or melena *[see Adverse Reactions (6.1)]*.

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Irvine, CA 92612

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MEDICATION GUIDE
LINZESS® (lin-ZESS)
(linaclotide) capsules

Read this Medication Guide before you start taking LINZESS and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is the most important information I should know about LINZESS?

- **Do not give LINZESS to children who are under 6 years of age. It may harm them.**
- **You should not give LINZESS to children 6 to 17 years of age. It may harm them.**

See the section "**What are the possible side effects of LINZESS?"** for more information about side effects.

What is LINZESS?

LINZESS is a prescription medication used in adults to treat

- irritable bowel syndrome with constipation (IBS-C)
- a type of constipation called chronic idiopathic constipation (CIC). "Idiopathic" means the cause of the constipation is unknown.

It is not known if LINZESS is safe and effective in children.

Who should not take LINZESS?

- **Do not give LINZESS to children who are under 6 years of age.**
- Do not take LINZESS if a doctor has told you that you have a bowel blockage (intestinal obstruction).

What should I tell my doctor before taking LINZESS?

Before you take LINZESS, tell your doctor if you:

- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if LINZESS will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if LINZESS passes into your breast milk. Talk with your doctor about the best way to feed your baby, if you take LINZESS.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

How should I take LINZESS?

- Take LINZESS exactly as your doctor tells you to take it.
- Take LINZESS 1 time each day on an empty stomach, at least 30 minutes before your first meal of the day. You should also wait 30 minutes before eating a meal if you take LINZESS with applesauce or mixed with water.
- If you miss a dose, skip the missed dose. Just take the next dose at your regular time. Do not take 2 doses at the same time.
- LINZESS capsule should be swallowed whole. Do not crush or chew LINZESS.
  - Adults who cannot swallow LINZESS capsules whole may open the LINZESS capsule and sprinkle over applesauce or mix LINZESS with bottled water before swallowing.

It is not known if LINZESS is safe and effective when sprinkled on other foods or mixed with other liquids.

Taking LINZESS in applesauce:

- Open the LINZESS capsule and sprinkle all of the LINZESS beads onto 1 teaspoon of room temperature applesauce.
- Swallow all of the LINZESS beads and applesauce right away. Do not keep the applesauce for future use.
- Do not chew the LINZESS beads.

Taking LINZESS in water:

- Open the LINZESS capsule and pour all of the LINZESS beads into a cup with 1 ounce (30 mL) of room temperature bottled water.
- Gently swirl the beads and water for at least 10 seconds.
- Swallow all of the LINZESS beads and water mixture right away. Do not keep the mixture for future use.
- If you see any LINZESS beads left in the cup, add another 1 ounce (30mL) of water to the beads in the cup, swirl for at least 10 seconds, and swallow right away.

Taking LINZESS in a nasogastric or gastric feeding tube:

Gather the supplies you will need to take your LINZESS dose. Your doctor should tell you what size catheter tipped syringe you will need for your dose. Ask your doctor if you have any questions about how to give LINZESS the right way.

- Open the LINZESS capsule and pour all the LINZESS beads into a cup with 1 ounce (30 mL) room temperature bottled water.
- Gently swirl the beads and water for at least 10 seconds.
- Remove the plunger from the catheter tipped syringe, and then pour the LINZESS bead and water mixture into the syringe and replace the plunger.
- Remove the cap from the syringe, insert the tip of the syringe into the nasogastric or gastric feeding tube and push the plunger all the way in to give the dose.

After giving the LINZESS dose, flush the nasogastric or gastric tube with at least 10 mL of water.

What are the possible side effects of LINZESS?

LINZESS can cause serious side effects, including:

- **See "What is the most important information I should know about LINZESS?"**
- **Diarrhea is the most common side effect of LINZESS, and it can sometimes be severe.**
  - Diarrhea often begins within the first 2 weeks of LINZESS treatment.
  - **Stop taking LINZESS and call your doctor right away if you get severe diarrhea during treatment with LINZESS.**

Other common side effects of LINZESS include:

- gas

- stomach-area (abdomen) pain
- swelling, or a feeling of fullness or pressure in your abdomen (distention)

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of LINZESS. For more information, ask your doctor or pharmacist.

In addition, **call your doctor or go to the nearest hospital emergency room right away, if you develop unusual or severe stomach-area (abdomen) pain, especially if you also have bright red, bloody stools or black stools that look like tar**.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LINZESS?

- Store LINZESS at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep LINZESS in the bottle that it comes in.
- The LINZESS bottle contains a desiccant packet to help keep your medicine dry (protect it from moisture). Do not remove the desiccant packet from the bottle.
- Keep the container of LINZESS tightly closed and in a dry place.

Keep LINZESS and all medicines out of the reach of children.

General information about LINZESS

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LINZESS for a condition for which it was not prescribed. Do not give LINZESS to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about LINZESS. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about LINZESS that is written for health professionals. For more information, go to www.LINZESS.com or call 1-800-678-1605.

What are the ingredients in LINZESS?

Active ingredient: linaclotide

Inactive ingredients: calcium chloride dihydrate, L-leucine, hypromellose, microcrystalline cellulose, gelatin, and titanium dioxide

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