



## Ironwood and Forest Announce U.S. Availability of LINZESS™ (Linaclotide)

*- New Treatment for Adults with Irritable Bowel Syndrome with Constipation or Chronic Idiopathic Constipation Now in Pharmacies Across the U.S.-*

CAMBRIDGE, Mass. & NEW YORK--(BUSINESS WIRE)-- [Ironwood Pharmaceuticals, Inc.](#) (NASDAQ: IRWD) and [Forest Laboratories, Inc.](#) (NYSE: FRX) announced today that LINZESS™ (linaclotide) is now available in pharmacies throughout the United States. The U.S. Food and Drug Administration (FDA) recently approved LINZESS as a once-daily oral capsule for adult men and women suffering from irritable bowel syndrome with constipation (IBS-C) or chronic idiopathic constipation (CIC).

LINZESS is the first and only FDA-approved guanylate cyclase-C (GC-C) agonist and acts locally in the intestine. For the first time in over six years, a new prescription option is available for adults with these disorders.

Visit [www.linzess.com](http://www.linzess.com) for more information about LINZESS.

### About LINZESS

LINZESS is the first and only guanylate cyclase-C (GC-C) agonist approved by the FDA for the treatment of both irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) in adults. LINZESS is a once-daily capsule that helps relieve the abdominal pain and constipation associated with IBS-C and constipation and hard stools associated with CIC. The recommended dose is 290 mcg for IBS-C patients and 145 mcg for CIC patients. LINZESS should be taken at least 30 minutes before the first meal of the day.

LINZESS is thought to work in two ways based on nonclinical studies. LINZESS binds to the GC-C receptor locally, within the intestinal epithelium. Activation of GC-C results in increased intestinal fluid secretion and transit and a reduction in visceral pain, which is thought to be mediated by decreased activity of pain-sensing nerves. The clinical relevance of the effect on pain fibers in nonclinical studies has not been established.

In placebo-controlled Phase III clinical trials of more than 2,800 adults, LINZESS was shown to reduce abdominal pain in IBS-C patients and increase bowel movement frequency in both IBS-C patients and CIC patients. Improvement in abdominal pain and constipation occurred in the first week of treatment and was maintained throughout the 12-week treatment period. Maximum effect on abdominal pain was seen at weeks 6-9 and maximum effect on constipation occurred during the first week. When a subset of LINZESS-treated patients in the trials were switched to placebo, they reported their symptoms returned toward pretreatment levels within one week, while placebo-treated patients switched to LINZESS reported symptom improvements. LINZESS is contraindicated in pediatric patients up to 6 years of age. The use of LINZESS in pediatric patients 6 through 17 years of age should be avoided. In nonclinical studies, administration of a single, clinically relevant adult oral dose of linaclotide caused deaths in young juvenile mice. LINZESS has not been studied in pediatric patients. In adults with IBS-C or CIC treated with LINZESS, the most commonly reported adverse event was diarrhea.

Ironwood and Forest are co-promoting LINZESS in the United States. Linaclotide was also approved recently by the European Commission for the treatment of adults in the European Union with IBS-C and will be marketed under the brand name Constella® through a license agreement between Ironwood and Ammirall, S.A. Ironwood also has partnered linaclotide with Astellas Pharma Inc. for development and commercialization in Japan and certain other Asian countries and with AstraZeneca for development and commercialization in China.

### About Irritable Bowel Syndrome with Constipation

Irritable bowel syndrome with constipation (IBS-C) is a chronic functional gastrointestinal disorder that affects as many as 13 million people in the United States. IBS-C can have a negative impact on daily living; patients often experience recurring abdominal pain or discomfort, constipation, and bowel symptoms including hard or lumpy stools in more than 25% of bowel movements, and soft or watery stools in less than 25% of bowel movements. There are currently few available therapies approved to treat this disorder.

### About Chronic Idiopathic Constipation

Chronic idiopathic constipation (CIC) is a functional gastrointestinal disorder in which individuals experience infrequent bowel movements (less than three times per week) for at least three months. Patients who suffer from CIC may also experience a sensation of incomplete evacuation and hard stools. As many as 35 million Americans may suffer from symptoms associated with CIC.

## Important Safety Information

### **WARNING: PEDIATRIC RISK**

**LINZESS is contraindicated in pediatric patients up to 6 years of age. Use should be avoided in pediatric patients 6 through 17 years of age. In nonclinical studies, administration of a single, clinically relevant adult oral dose of linaclotide caused deaths in young juvenile mice.**

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## Contraindications

- LINZESS is contraindicated in pediatric patients up to 6 years of age.
- LINZESS is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

## Warnings and Precautions

### *Pediatric Risk*

- LINZESS is contraindicated in pediatric patients up to 6 years of age. In nonclinical studies, deaths occurred within 24 hours in young juvenile mice (1 to 3 week-old mice; approximately equivalent to human pediatric patients less than 2 years of age) following administration of one or two daily oral doses of linaclotide.
- Use of LINZESS should be avoided in pediatric patients 6 through 17 years of age. Linaclotide did not cause deaths in older juvenile mice (approximately equivalent to humans age 12 to 17 years). 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, use of LINZESS should be avoided in pediatric patients 6 through 17 years of age.

### *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 LINZESS-treated patients. The incidence of diarrhea was similar in the IBS-C and CIC populations.
- Patients should be instructed to stop LINZESS if severe diarrhea occurs and to contact their healthcare provider, who should consider dose suspension.

## Adverse Reactions

- In IBS-C clinical trials, the most common adverse reactions in LINZESS-treated patients (incidence  $\geq 2\%$  and greater than placebo) were diarrhea (20% vs 3% placebo), abdominal pain (7% vs 5%), flatulence (4% vs 2%), headache (4% vs 3%), viral gastroenteritis (3% vs 1%) and abdominal distension (2% vs 1%).
- In CIC clinical trials, the most common adverse reactions in LINZESS-treated patients (incidence  $\geq 2\%$  and greater than placebo) were diarrhea (16% vs 5% placebo), abdominal pain (7% vs 6%), flatulence (6% vs 5%), upper respiratory tract infection (5% vs 4%), sinusitis (3% vs 2%) and abdominal distension (3% vs 2%).

## 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.

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).

## About Ironwood Pharmaceuticals

Ironwood Pharmaceuticals (NASDAQ: IRWD) is an entrepreneurial pharmaceutical company dedicated to the art and science of great drugmaking. Ironwood is located in Cambridge, Mass. To learn more, visit [www.ironwoodpharma.com](http://www.ironwoodpharma.com).

## About Forest Laboratories, Inc.

Forest Laboratories' (NYSE: FRX) longstanding global partnerships and track record developing and marketing pharmaceutical products in the United States have yielded its well-established central nervous system and cardiovascular franchises and innovations in anti-infective and respiratory, gastrointestinal, and pain management medicine. The Company's pipeline, the most robust in its history, includes product candidates in all stages of development across a wide range of therapeutic areas. The Company is headquartered in New York, NY. To learn more, visit [www.FRX.com](http://www.FRX.com).

*Except for the historical information contained herein, this release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. These statements involve a number of risks and uncertainties, including the potential sales of LINZESS in the United States and of Constella in the European Union, the target patient populations in the United States for LINZESS, the potential reimbursement for LINZESS in the United States, the post approval development strategy for LINZESS, the acceptance and demand for new pharmaceutical products, the impact of competitive products and pricing, the timely development and launch of new products, and the risk factors listed from time to time in each of Forest's and Ironwood's Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, and other SEC filings. Neither Forest nor Ironwood undertakes any obligation to update these forward-looking statements to reflect events or circumstances occurring after this press release. These forward-looking statements speak only as of the date of this press release. All forward-looking statements are qualified in their entirety by this cautionary statement.*

Photos/Multimedia Gallery Available: <http://www.businesswire.com/multimedia/home/20121217005366/en/>

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