



Ironwood and Forest Announce FDA Approval of LINZESS™ (Linaclotide) for the Treatment of Irritable Bowel Syndrome with Constipation and Chronic Idiopathic Constipation

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

IBS-C and CIC are chronic functional gastrointestinal disorders that affect as many as 13 million¹ and 35 million² adult Americans, respectively. Symptoms associated with IBS-C include abdominal pain and constipation; symptoms associated with CIC include constipation (infrequent stools, hard stools and incomplete evacuation). There are few treatment options for these conditions, particularly options that relieve abdominal pain associated with IBS-C.

"The symptoms experienced by patients with IBS-C and chronic idiopathic constipation can have a significant impact on affected individuals," said William D. Chey, M.D., professor of gastroenterology at the University of Michigan Health System. "The approval of LINZESS provides physicians with a new, evidence-based, effective treatment option for their adult patients with IBS-C and chronic idiopathic constipation."

Linaclotide, the active ingredient in LINZESS, is a first-in-class guanylate cyclase-C (GC-C) agonist and acts locally in the intestine with minimal systemic exposure. In nonclinical studies, linaclotide has been shown to reduce intestinal pain and accelerate gastrointestinal transit. Linaclotide-induced intestinal pain reduction is thought to result from an increase in cyclic guanosine monophosphate (cGMP), which has been shown to decrease the activity of pain-sensing nerves.

In placebo-controlled Phase III clinical trials of more than 2,800 adults, LINZESS was shown to significantly reduce abdominal pain in IBS-C patients and significantly increase bowel movement frequency in both IBS-C patients and CIC patients. Improvements were reported in the first week of treatment and maintained throughout the treatment period. 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 has not been studied in pediatric patients. 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.

Ironwood and Forest expect LINZESS to be available in the fourth quarter of 2012.

"The discovery of LINZESS by Ironwood scientists, and the development work done together by Ironwood and our partner Forest, has resulted in a new medicine with the potential to improve the lives of millions of highly symptomatic IBS-C and CIC patients," said Peter Hecht, Chief Executive Officer of Ironwood. "As Ironwood's first FDA-approved drug, LINZESS represents significant progress towards achieving our goals of delivering medicines to patients and value to shareholders."

Howard Solomon, Chairman, Chief Executive Officer and President of Forest Laboratories, said: "The approval of LINZESS validates Forest and Ironwood's commitment to bringing forth an effective treatment in disease categories that previously had limited treatment options. We look forward to making this treatment available to the millions of adults with IBS-C and CIC in the United States. This achievement is the result of our close working relationship with Ironwood over the past five years in the development of this exciting product."

Data Highlights: Irritable Bowel Syndrome with Constipation (IBS-C)

The safety and efficacy of LINZESS to treat IBS-C were evaluated in two double-blind, placebo-controlled Phase III clinical trials in which LINZESS met all four primary endpoints examining changes in abdominal pain and constipation in each trial. The trials involved 1,605 patients aged 18 to 87 years old, of which 807 were treated with LINZESS 290 mcg. The data from these trials is scheduled for publication in the October 2012 issue of the American Journal of Gastroenterology.

Combined Responder

In both trials, the proportion of LINZESS-treated patients who were combined responders was statistically significantly higher than placebo-treated patients. Two definitions of combined responder were used. A 9 of 12 week combined responder is a patient who reported at least a 30% reduction from baseline in abdominal pain, at least three CSBMS, and an increase of at least one CSBM from baseline, all in the same week for at least 9 out of 12 weeks. A 6 out of 12 week responder is a patient who reported at least a 30% reduction from baseline in abdominal pain and an increase of at least one CSBM from baseline, all in the same week for at least 6 out of 12 weeks. This second definition is consistent with the FDA guidance document on IBS and was one of the four pre-specified primary endpoints in the LINZESS Phase III IBS-C trials.

In 9 out of 12 weeks, 12% (Study 1) and 13% (Study 2) of LINZESS-treated patients were combined responders, versus 5% (Study 1) and 3% (Study 2) of placebo-treated patients. In 6 out of 12 weeks, 34% (Study 1) and 34% (Study 2) of LINZESS-treated patients were combined responders, versus 21% (Study 1) and 14% (Study 2) of placebo-treated patients. During a two-week pre-treatment period, these patients reported a mean abdominal pain score of at least 3 on a 0-to-10-point scale and less than three CSBMs per week.

Abdominal Pain

LINZESS 290 mcg was proven to significantly reduce abdominal pain; effects were seen within the first week of treatment and improvements were maintained throughout the treatment period. In the two trials, 34% (Study 1) and 39% (Study 2) of patients treated with LINZESS experienced at least a 30% reduction in abdominal pain from baseline for at least 9 out of 12 weeks versus 27% (Study 1) and 20% (Study 2) of placebo-treated patients. For at least 6 out of 12 weeks (a secondary endpoint), 50% (Study 1) and 49% (Study 2) of LINZESS-treated patients versus 38% (Study 1) and 35% (Study 2) of placebo-treated patients experienced at least a 30% reduction in abdominal pain from baseline.

Constipation Symptoms

LINZESS significantly increased the frequency of complete spontaneous bowel movements (CSBMs), with 20% (Study 1) and 18% (Study 2) of patients treated with LINZESS experiencing an increase of at least one CSBM from baseline for at least 9 out of 12 weeks versus 6% (Study 1) and 5% (Study 2) of placebo-treated patients. For at least 6 out of 12 weeks (secondary endpoint), 49% (Study 1) and 48% (Study 2) of LINZESS-treated patients versus 30% (Study 1) and 23% (Study 2) of placebo-treated patients experienced at least three CSBMs and an increase of at least one CSBM from baseline. In each trial, the drug reached maximum effectiveness within the first week of treatment, and improvements were maintained throughout the treatment period.

Data Highlights: Chronic Idiopathic Constipation (CIC)

The efficacy of LINZESS for the management of CIC was established in two double-blind, placebo-controlled Phase III clinical trials in which LINZESS met the primary endpoint in both trials. The primary endpoint in these trials examined changes in bowel function. The trials involved 1,275 patients aged 18 to 85 years old, of which 430 received LINZESS 145 mcg and 422 received LINZESS 290 mcg. During a two-week pretreatment period at the beginning of the trials, these patients reported less than three CSBMs per week. The data were published in the August 11, 2011 issue of the New England Journal of Medicine⁴.

Constipation Symptoms

LINZESS significantly increased the frequency of CSBMs in treated patients. At the 145 mcg dose, 20% (Study 3) and 16% (Study 4) of LINZESS-treated patients experienced at least 3 CSBMs and an increase of at least one CSBM from baseline in the same week for at least 9 of the 12 weeks (CSBM responder) versus 3% (Study 3) and 6% (Study 4) of placebo patients. In each trial, the drug reached maximum effectiveness within the first week of treatment, and improvements were maintained throughout the treatment period. Patients taking LINZESS experienced significant improvement in stool frequency and hardness of stool compared to placebo.

Safety

The most common adverse reactions in IBS-C or CIC patients were diarrhea, abdominal pain, flatulence and abdominal distension.

Post Approval Pediatric Requirements

As part of the post approval requirements for LINZESS, Ironwood and Forest have agreed to a pediatric development program which will initially consist of additional nonclinical studies to characterize deaths previously observed in neonatal and young juvenile mice during nonclinical toxicology studies. Linaclotide did not cause deaths in older juvenile mice (approximately equivalent to humans age 12 to 17 years). In nonclinical toxicology studies with adult models, LINZESS was safely dosed up to 5,000 mcg/kg/day (the maximum recommended dose for an average adult person is 5 mcg/kg/day). To date, there have been no studies of LINZESS in pediatric patients, and until such nonclinical results are available and pediatric studies are conducted,

children should not be exposed to LINZESS. A boxed warning in the labeling informs physicians and patients that LINZESS is contraindicated in pediatric patients up to 6 years of age and use of LINZESS should be avoided in pediatric patients 6 through 17 years of age.

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 chronic 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 binds to the GC-C receptor locally in the intestine, with no measurable blood plasma concentrations, resulting in an increase in both intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP). Elevations in intracellular cGMP are believed to stimulate secretion of intestinal fluid and accelerate gastrointestinal transit resulting in increased frequency of bowel movements. Elevations in extracellular cGMP are believed to decrease activity of pain-sensing nerves, which is thought to be responsible for a reduction in intestinal pain, according to nonclinical models.

An issued composition of matter patent for linaclotide provides protection to 2025 in the United States. Ironwood and Forest will co-promote LINZESS in the United States. Ironwood has out-licensed linaclotide to Almirall, S.A. for European development and commercialization and to Astellas Pharma Inc. for development and commercialization in Japan, Indonesia, Korea, the Philippines, Taiwan, and Thailand.

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 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.

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. LINZESS (linaclotide), Ironwood's guanylate cyclase-C (GC-C) agonist, is an FDA-approved drug for the treatment of adults with irritable bowel syndrome with constipation (IBS-C) or chronic idiopathic constipation (CIC). Ironwood also has a growing pipeline of additional drug candidates in earlier stages of development. Ironwood is located in Cambridge, Mass. To learn more, visit 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.

References

1. Source: Chey, W. et al "Frequency and Bothersomeness of Symptoms, Health Care Seeking Behavior and Satisfaction with Therapy in IBS-C Patients Meeting ROME II Criteria: Results of a Population Based Survey". Poster presented at UEGW 2010. <http://uegw10.uegf.org/> (poster # P1275)
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3. Lembo, A., et al. *N Engl J Med* 2011; 365:527-536.

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 anticipated availability of LINZESS in the retail channels, the target patient populations in the United States for LINZESS, 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.

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Source: Forest Laboratories, Inc. & Ironwood Pharmaceuticals, Inc.

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