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Ironwood Pharmaceuticals Announces Approval of LINZESS® (linaclotide) in Japan for the Treatment of Adults with IBS-C

-Approval Triggers $15 Million Milestone Payment to Ironwood from Astellas-

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Ironwood Pharmaceuticals, Inc. (NASDAQ:IRWD) today announced that its partner, Astellas Pharma Inc., secured marketing approval from the Japanese Ministry of Health, Labor and Welfare for LINZESS as the first prescription treatment for adults with irritable bowel syndrome with constipation (IBS-C) in Japan. Ironwood anticipates that Astellas will launch the drug in the first half of 2017.

Linaclotide is a guanylate cyclase-C (GC-C) receptor agonist currently approved and available for the treatment of adults with IBS-C or chronic idiopathic constipation (CIC) in the United States and more than 30 other countries.

"Today's regulatory approval of LINZESS in Japan by our partner Astellas represents important progress toward Ironwood's goal of bringing innovative medicines to appropriate patients around the world," said Mark Currie, Ph.D., chief scientific officer and president of research and development at Ironwood. "In Japan, nearly three percent of adults are estimated to suffer from IBS-C. Today's news is particularly significant for these patients who, until now, did not have a prescription medicine approved to treat the recurring symptoms associated with IBS-C."

Data from the Phase III trial in Japan indicate that patients treated with 500 mcg of linaclotide showed statistically significant improvement compared to placebo-treated patients for both co-primary endpoints. Regarding the first primary endpoint, 34% of linaclotide-treated patients were Global Assessment of Relief of IBS Symptoms Responders, compared to 18% of placebo-treated patients ($p < 0.001$). Regarding the second primary endpoint, 35% of linaclotide-treated patients were Complete Spontaneous Bowel Movement (CSBM) Overall Responders, compared to 19% of placebo-treated patients ($p < 0.001$). Additionally, improvements were achieved in pre-specified secondary endpoints in this trial covering abdominal and constipation symptoms, including bloating and abdominal pain/discomfort. Diarrhea rates in this trial were 9.6% for linaclotide vs. 0.4% for placebo; all cases of diarrhea were characterized as mild or moderate in severity. The discontinuation rate for diarrhea in the linaclotide 500 mcg group was 1.6% vs. 0% for placebo.

The double-blind, placebo-controlled Phase III clinical trial randomized 500 adults with IBS-C in Japan. Patients were randomized 1:1 to receive either 500 mcg of linaclotide or placebo for 12 weeks. The co-primary endpoints of the trial were (i) Global Assessment of Relief of IBS Symptoms Responder Rate, in which patients rated their improvement in IBS-C symptoms over each week compared to the baseline period and achieved significant or moderate relief for at least six out of 12 weeks, and (ii) CSBM Overall Responder Rate, in which patients reported experiencing at least three CSBMs per week and an increase of at least one CSBM from baseline in the same week, and achieved both of these measures for at least six out of 12 weeks. The trial also included an additional 40-week, open-label follow-on study period.

Ironwood and Astellas entered into a licensing agreement in 2009 to develop and commercialize linaclotide in Japan for the treatment of IBS-C, chronic constipation and other gastrointestinal conditions. Per the agreement, Astellas paid Ironwood a $30 million upfront licensing fee, a $15 million development milestone payment upon enrollment of the first patient in the Phase III IBS-C trial, and a $15 million milestone payment upon the IBS-C new drug application submission. The agreement also includes an additional $15 million milestone payment for Ironwood as a result of today's approval of linaclotide by the Japanese regulatory authority, and provides for Ironwood to receive royalties, which escalate based on sales volume. Additionally, a Phase III trial of linaclotide in patients with chronic constipation is ongoing in Japan, with top-line data expected in 2017.

About Linaclotide

Linaclotide is a guanylate cyclase-C (GC-C) agonist that is thought to work in two ways based on nonclinical studies. Linaclotide binds to the GC-C receptor locally, within the intestinal epithelium. Activation of GC-C results in increased intestinal fluid secretion and accelerated transit and a decrease in the activity of pain-sensing nerves in the intestine. The clinical relevance of the effect on pain fibers, which is based on nonclinical studies, has not been established. Linaclotide is

marketed by Ironwood and Allergan plc in the United States as LINZESS® and is indicated for the treatment of adults with irritable bowel syndrome with constipation (IBS-C) or chronic idiopathic constipation (CIC), with more than 1 million unique patients in the United States having filled more than 5.5 million linaclotide prescriptions since launch, according to IMS Health. Linaclotide is marketed by Allergan for the treatment of adults with moderate to severe IBS-C in Europe under the brand name CONSTELLA®, and Ironwood's partner Astellas received approval of linaclotide in Japan under the brand name LINZESS® for the treatment of adults with IBS-C. Ironwood also has partnered with AstraZeneca for development and commercialization of linaclotide in China, Hong Kong and Macau.

Important Safety Information

WARNING: PEDIATRIC RISK

LINZESS is contraindicated in pediatric patients under 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. Use of LINZESS should be avoided 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.

Contraindications

- LINZESS is contraindicated in pediatric patients under 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 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.
- Use of LINZESS should be avoided 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, 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. The healthcare provider should consider dose suspension and rehydration.

Adverse Reactions

- In IBS-C clinical trials, the most common adverse reactions in LINZESS-treated patients (incidence ≥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 ≥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%).

Please see full Prescribing Information including Boxed Warning: http://www.allergan.com/assets/pdf/linzess_pi

About Ironwood Pharmaceuticals
Ironwood Pharmaceuticals (NASDAQ: IRWD) is a commercial biotechnology company focused on creating medicines that make a difference for patients, building value for our fellow shareholders, and empowering our passionate team. We are advancing a pipeline of innovative medicines in areas of significant unmet need, including irritable bowel syndrome with

constipation (IBS-C)/chronic idiopathic constipation (CIC), uncontrolled gout, refractory gastroesophageal reflux disease, and vascular and fibrotic diseases. We discovered, developed and are commercializing linaclotide, the U.S. branded prescription market leader in the IBS-C/CIC category, and we are applying our proven R&D and commercial capabilities to advance multiple internally-developed and externally-accessed product opportunities. Ironwood was founded in 1998 and is headquartered in Cambridge, Mass. For more information, please visit www.ironwoodpharma.com or www.twitter.com/ironwoodpharma; information that may be important to investors will be routinely posted in both these locations.

This press release contains forward-looking statements. Investors are cautioned not to place undue reliance on these forward-looking statements, including statements about the development, launch and commercial potential of linaclotide; market size, growth and opportunity, including the potential demand for linaclotide; the anticipated timing of preclinical, clinical and regulatory developments and the design, timing and results of clinical and preclinical studies; and milestone and royalty payments. Each forward-looking statement is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied in such statement. Applicable risks and uncertainties include those related to the effectiveness of commercialization efforts by us and our partners; preclinical and clinical development, manufacturing and formulation development; the risk that findings from our completed nonclinical and clinical studies may not be replicated in later studies; efficacy, safety and tolerability of linaclotide; decisions by regulatory authorities; the risk that we may never get sufficient patent protection for linaclotide or that we are not able to successfully protect such patents; developments in the intellectual property landscape; challenges from and rights of competitors or potential competitors; and the risks listed under the heading "Risk Factors" and elsewhere in Ironwood's Quarterly Report on Form 10-Q for the quarter ended September 30, 2016, and in our subsequent SEC filings. These forward-looking statements (except as otherwise noted) speak only as of the date of this press release, and Ironwood undertakes no obligation to update these forward-looking statements.

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