November 28, 2012

Constella® (linaclotide) Approved in Europe for the Treatment of Irritable Bowel Syndrome with Constipation (IBS-C) in Adults

- **Constella® (linaclotide) is the first and only medicine approved by the European Commission for the symptomatic treatment of moderate to severe IBS-C in adults, that improves abdominal pain/discomfort, bloating and constipation**
- **First launches in Europe are expected in the first half of 2013**
- **IBS-C is a functional gastrointestinal disorder affecting approximately 15 million adults across the European Union**[1]

BARCELONA, Spain & CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Almirall, S.A. (ALM:MC) and Ironwood Pharmaceuticals, Inc. (NASDAQ: IRWD) announced today that the European Commission has granted marketing authorization to Constella® (linaclotide 290mcg) for the symptomatic treatment of moderate to severe Irritable Bowel Syndrome with Constipation (IBS-C) in adults. This approval follows the positive recommendation received from the European Committee for Medicinal Products for Human Use (CHMP) in September.

Constella® is an oral, once-daily medication. Linaclotide, the active ingredient in Constella®, is a guanylate cyclase-C agonist (GCCA) with visceral analgesic and secretory activities, as stated in the product label for European use. In non-clinical studies, linaclotide has been shown to reduce visceral pain by decreasing pain-fiber activity and to accelerate gastrointestinal transit by increasing intestinal fluid secretion. Linaclotide acts locally in the intestine with minimal systemic exposure.

"Despite affecting more than 10% of the population in the EU there are few effective treatment options for IBS. Approximately one third of IBS patients suffer from the IBS-C form of the disease and the approval of Constella® provides physicians with an innovative medication, for improving the lives of patients whose quality of life is impaired," said Professor Jan Tack, Head of Clinic in the Department of Gastroenterology, and Professor in Internal Medicine at the University Hospital Gasthuisberg of the University of Leuven, Belgium.

IBS is a functional gastrointestinal disorder impacting over 10% of the European population, and it is estimated that one-third of IBS patients suffer from IBS-C[1], which means that approximately 15 million adults across the European Union might be affected. Symptoms associated with IBS-C include abdominal pain and discomfort, bloating, and constipation resulting in a significant impact on affected individuals. There are few prescription treatment options for this condition approved in the European Union. Constella® is the first and only prescription medicine approved by the European Commission for the symptomatic treatment of moderate to severe Irritable Bowel Syndrome with Constipation (IBS-C) in adults.

"Almirall is delighted with the approval of Constella®, the first prescription medicine approved by the European Commission for the treatment of IBS-C in adults. This new medicine has the potential to improve some of the hallmark symptoms of IBS-C patients who up until now have had few treatment options. Furthermore the approval of Constella® is an important growth opportunity for Almirall and will strengthen our gastrointestinal franchise," said Eduardo Sanchiz, Chief Executive Officer at Almirall.

Almirall expects to begin launching Constella® in Europe in the first half of 2013.

"Linaclotide was discovered by Ironwood scientists, and obtaining marketing authorization for Constella® in Europe is important progress towards our goal of translating knowledge into medicines that make a difference for patients," said Peter Hecht, Ironwood's Chief Executive Officer. "*We look forward to continuing to work closely with our partner Almirall in their efforts to bring Constella® to adult IBS-C patients in Europe, and we will continue collaborating with our global network of partners with the goal of bringing this medicine to appropriate patients worldwide."*

In April 2009, Almirall signed a license agreement with Ironwood, under which Almirall holds exclusive marketing rights for linaclotide in all European Union member states, plus Russia, the CIS (Commonwealth of Independent States of the former

USSR), Switzerland, Norway and Turkey, as well as other countries in Europe, including the countries of former Yugoslavia. In September 2012, Almirall also signed an agreement by which Forest Laboratories sublicensed its commercialization rights for linaclotide in Mexico to Almirall.

Notes to editors

About Constella® (linaclotide)[1]

Linaclotide is a Guanylate Cyclase-C receptor agonist (GCCA) with visceral analgesic and secretory activities.

Linaclotide is a 14-amino acid synthetic peptide structurally related to the endogenous guanylin peptide family. Both linaclotide and its active metabolite bind to the GC-C receptor, on the luminal surface of the intestinal epithelium. Through its action at GC-C, linaclotide has been shown to reduce visceral pain and increase GI transit in animal models and increase colonic transit in humans. Activation of GC-C results in an increase in concentrations of cyclic guanosine monophosphate (cGMP), both extracellularly and intracellularly. Extracellular cGMP decreases pain-fiber activity, resulting in reduced visceral pain in animal models. Intracellular cGMP causes secretion of chloride and bicarbonate into the intestinal lumen, through activation of the cystic fibrosis transmembrane conductance regulator (CFTR), which results in increased intestinal fluid and accelerated transit.

Constella® is a trademark owned by Ironwood Pharmaceuticals, Inc.

Clinical efficacy and safety[1]

The efficacy of linaclotide was established in two randomised, double-blind, placebo-controlled Phase 3 clinical studies in patients with IBS-C. In one clinical study (study 1), 802 patients were treated with Constella® 290 micrograms or placebo once daily for 26 weeks. In the second clinical study (study 2), 800 patients were treated for 12 weeks, and then re-randomised for an additional 4 weeks treatment period. During the 2-weeks pre-treatment baseline period, patients had a mean abdominal pain score of 5.6 (0-10 scale) with 2.2% of abdominal pain-free days, a mean bloating score of 6.6 (0-10 scale), and an average of 1.8 spontaneous bowel movements (SBM)/week.

The characteristics of the patient population included in Phase 3 clinical trials were as follows: mean age of 43.9 years [range 18 - 87 years with 5.3% ≥ 65 years of age], 90.1% female. All patients met Rome II criteria for IBS-C and were required to report a mean abdominal pain score of ≥ 3 on a 0-to-10-point numeric rating scale (criteria that correspond to a moderate to severe IBS population), < 3 complete spontaneous bowel movements and ≤ 5 SBMs per week during a 2-week baseline period.

The co-primary endpoints in both clinical studies were 12-week IBS degree of relief responder rate and 12 week abdominal pain/discomfort responder rate. An IBS degree of relief responder was a patient that was considerably or completely relieved for at least 50% of the treatment period; an abdominal pain/discomfort responder was a patient that had an improvement of 30% or more for at least 50% of the treatment period.

For the 12 weeks data, study 1 shows that 39% of the patients treated with linaclotide compared with 17% of the patients treated with placebo showed response to IBS degree of relief ($p < 0.0001$) and 54% of the patients treated with linaclotide compared with 39% of the patients treated with placebo showed response to abdominal pain/discomfort ($p < 0.0001$). Study 2 shows that 37% of the patients treated with linaclotide compared with 19% of the patients treated with placebo showed response to IBS degree of relief ($p < 0.0001$) and 55% of the patients treated with linaclotide compared with 42% of the patients treated with placebo showed response to abdominal pain/discomfort ($p=0.0002$).

For the 26 weeks data, study 1 shows that 37% and 54% of the patients treated with linaclotide compared with 17% and 36% of the patients treated with placebo showed response to IBS degree of relief ($p < 0.0001$) and abdominal pain/discomfort ($p < 0.0001$) respectively.

In both studies, these improvements were seen by week 1 and sustained over the entire treatment periods. Linaclotide has been shown not to cause rebound effect when the treatment was stopped after 3 months continuous treatment.

Other signs and symptoms of IBS-C including bloating, complete spontaneous bowel movement (CSBM) frequency, straining, stool consistency, were improved in linaclotide treated patients vs. placebo ($p < 0.0001$). These effects were reached at 1 week and sustained over the entire treatment periods.

Treatment with linaclotide also resulted in significant improvements in validated and disease-specific Quality of Life (QoL) measure (IBS-QoL; $p < 0.0001$), and EuroQoL ($p = 0.001$). Clinically meaningful response in overall IBS-QoL (> 14 points difference) was achieved in 54% of linaclotide treated patients vs. 39% in placebo treated patients.

The most frequently reported adverse reaction associated with linaclotide therapy was diarrhoea, mainly mild to moderate in

intensity, occurring in less than 20% of patients. Other common adverse reactions (> 1%) were abdominal pain, abdominal distension and flatulence.

About Irritable Bowel Syndrome with Constipation (IBS-C)

IBS is defined as a functional bowel disorder in which abdominal pain or discomfort is associated with defecation or a change in bowel function and with features of disordered defecation.[2] IBS-C is one of four clinically different subtypes of IBS. One-third of patients with IBS are thought to have IBS-C[3] and suffer chronically from both abdominal pain and constipation.

The Rome III Diagnostic Criteria for Functional Gastrointestinal Disorders includes criterion for the diagnosis of IBS[3] as:

- Recurrent abdominal pain or discomfort at least three days/month, in the last three months with symptom onset at least 6 months prior to diagnosis, associated with two or more of the following:
  - improvement with defecation
  - onset associated with a change of frequency of stool
  - onset associated with a change in form (or appearance) of stool

The estimated prevalence of IBS at 10-15% of the European population puts it in line with conditions such as migraine (12%) and asthma (11%)[1]. IBS can have a negative impact on daily living with considerable socio-economic and psychological consequences, and represents a major proportion of gastrointestinal workload in both primary and secondary care. Due to the complex, multimodal nature of the condition there is no cure for IBS and there are minimal therapeutic options.[4]

About Almirall

Almirall is an international pharmaceutical company based on innovation and committed to health. Headquartered in Barcelona, it researches, develops, manufactures and commercialises its own R&D and licensed drugs with the aim of improving people's health and wellbeing. Almirall focuses its research resources on respiratory, gastrointestinal, dermatology and pain. Almirall's products are currently present in over 70 countries in the five continents. With the opening of the Canadian affiliate, Almirall has now direct presence in Europe, Mexico and Canada through 13 affiliates.

For further information please visit: www.almirall.com

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.

This press release contains forward looking statements. Investors are cautioned not to place undue reliance on these forward-looking statements, including, but not limited to, the potential for Constella as a treatment option for the symptomatic treatment of moderate to severe IBS-C in adult men and women, the anticipated launch timing of Constella, and the potential for linaclotide to achieve marketing authorization approval in countries outside of the European Union. 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 the risks that Constella is priced at a point lower than anticipated, Almirall is unable to secure sufficient reimbursement for Constella in any of the major E.U. countries, physicians do not view Constella as an effective or safe treatment option for adult men or women who suffer from moderate to severe IBS-C, or Almirall is unable to produce an adequate commercial supply of Constella, as well as risks related to the difficulty of predicting regulatory approvals, the acceptance of and demand for new pharmaceutical products, the potential prescribing habits of doctors, the impact of competitive products and pricing, and whether linaclotide will ever be commercialized successfully in a given country. Applicable risks also include those that are listed in Ironwood Pharmaceuticals' Quarterly Report on Form 10-Q for the quarter ended September 30, 2012, in addition to the risk factors that are listed from time to time in Ironwood Pharmaceuticals' Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q and any subsequent SEC filings. We undertake no 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.

References

[1] P. S. Hungin et al - The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000

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[3] American College of Gastroenterology Task Force on Irritable Bowel Syndrome. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol* 2009; 104 Suppl 1:S1-35

[4] Camilleri M, Chang L. - Challenges to the therapeutic pipeline for irritable bowel syndrome: end points and regulatory hurdles. *Gastroenterology* 2008;135:1877—1891

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