Approval of Linzess® Tablets 0.25 mg in Japan for Additional Indication of Chronic Constipation

August 21, 2018

TOKYO & CAMBRIDGE, Mass.--(BUSINESS WIRE)--Aug. 21, 2018-- Astellas Pharma Inc. (TSE: 4503, President and CEO: Kenji Yasukawa, Ph.D., "Astellas") and Ironwood Pharmaceuticals, Inc (Nasdaq: IRWD , "Ironwood") today announced that approval has been obtained in Japan for the guanylate cyclase-C receptor agonist "Linzess® Tablets 0.25 mg (generic name: linaclotide)" for the additional indication of chronic constipation (other than constipation associated with organic disorders[1]) ("chronic constipation").

Linzess® Tablets 0.25 mg were licensed from Ironwood and have been developed and commercialized in Japan by Astellas. It was approved in Japan in December 2016 for the indication of irritable bowel syndrome with constipation (IBS-C)[2], and has been on the Japanese market since March 2017.

This approval is based on the results of a Phase 3, double-blind, placebo-controlled, parallel group trial conducted to evaluate the efficacy and safety of linaclotide orally administered for 4 weeks in 186 Japanese patients with chronic constipation. The subjects were randomly assigned to either the linaclotide (0.5 mg) or placebo group in a 1:1 ratio. In the linaclotide group, the change in weekly mean frequency of spontaneous bowel movement (SBM)[3] at 1 week after the start of administration, which was the primary endpoint, represented a statistically significant improvement as compared to the placebo group. The most common adverse event was diarrhea, and its severity was mild to moderate in all cases.

Constipation is definedas the state in which feces cannot be excreted adequately and comfortably[4], and it is classified as chronic or transient condition depending on its duration[5]. The prevalence of constipation in Japan has been reported as 2.5% for men and 4.6% for women[6].

By providing a new therapy option with the additional chronic constipation indication, Astellas and Ironwood hope to be able to make a significant contribution to a large number of patients suffering from chronic constipation.

The impact of the approval of the additional chronic constipation indication has already been factored into Astellas' consolidated financial forecast for the fiscal year ending March 2019.

(1) **Organic disorders**: Disorders caused by the anatomical/pathological changes or abnormalities in the visceral, organic, nervous, or other tissues (detectable by examinations such as radiography and endoscopy).

(2) **Irritable bowel syndrome constipation (IBS-C)**: A condition associated with irritable bowel syndrome (IBS) in which hard or lumpy stool constitute 25% or more and soft (mushy) or watery stools constitute less than 25% of feces. IBS is a functional disorder characterized by the absence of organic disorders and by its main gastrointestinal manifestations of abdominal pain/discomfort and abnormal bowel movement (diarrhea, constipation) that persist for a long time or relapse over time. The abnormal bowel movement and the abdominal symptoms associated with IBS are induced by various factors, including stress, that excessively activate the enteric nerves and eventually cause gastrointestinal hypermotility.

(3) **Spontaneous bowel movement (SBM)**: A bowel movement occurring without treatments (the use of a laxative, suppository, or enema, disimpaction, etc.) on the same or the previous day.

(4) Clinical Guidelines for Chronic Constipation 2017: Edited by Japan Society of Gastroneterology-affiliated Study Group, Chronic Constipation Diagnosis and Treatment Study Group; Nankodo. p.2

(5) Clinical Guidelines for Pediatric Chronic Functional Constipation: Edited by Japanese Society for Pediatric Gastroenterology, Hepatology and Nutrition; Japan Pediatric Gastrointestinal Function Study Group; SHINDAN TO CHIRYO SHA (Diagnosis and Treatment Inc.). p. 14

(6) Ministry of Health, Labour and Welfare: Comprehensive Survey of Living Conditions (2016). p. 29

<Reference>

Revisions to the package insert with the approval of the additional indication are shown below.

After revision (addition underlined)	Before revision
[Indications]	[Indications]
Irritable bowel syndrome with constipation	Irritable bowel syndrome with
Chronic constipation (other than constipation associated with organic disorders)	constipation

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 nearly 2 million unique patients in the United States having filled nearly 11 million linaclotide prescriptions since launch, according to IQVIA. Linaclotide is marketed by Allergan for the treatment of adults with moderate to severe IBS-C in Europe under the brand name CONSTELLA®. Astellas has the exclusive rights to develop and commercialize linaclotide in Japan based on the license agreement with Ironwood from 2009. Ironwood also has partnered with AstraZeneca for development and commercialization of linaclotide in China, Hong Kong and Macau.

About Astellas
Astellas Pharma Inc., based in Tokyo, Japan, is a company dedicated to improving the health of people around the world through the provision of innovative and reliable pharmaceutical products. For more information, please visit our website at https://www.astellas.com/en

Astellas Cautionary Notes
In this press release, statements made with respect to current plans, estimates, strategies and beliefs and other statements that are not historical facts are forward-looking statements about the future performance of Astellas. These statements are based on management's current assumptions and beliefs in light of the information currently available to it and involve known and unknown risks and uncertainties. A number of factors could cause actual results to differ materially from those discussed in the forward-looking statements. Such factors include, but are not limited to: (i) changes in general economic conditions and in laws and regulations, relating to pharmaceutical markets, (ii) currency exchange rate fluctuations, (iii) delays in new product launches, (iv) the inability of Astellas to market existing and new products effectively, (v) the inability of Astellas to continue to effectively research and develop products accepted by customers in highly competitive markets, and (vi) infringements of Astellas' intellectual property rights by third parties.

Information about pharmaceutical products (including products currently in development) which is included in this press release is not intended to constitute an advertisement or medical advice.

About Ironwood
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 currently commercializing two innovative primary care products: linaclotide, the U.S. branded prescription market leader for adults with irritable bowel syndrome with constipation (IBS-C) or chronic idiopathic constipation (CIC), and lesinurad, which is approved to be taken with a xanthine oxidase inhibitor (XOI), or as a fixed-dose combination with allopurinol, for the treatment of hyperuricemia associated with gout. We are also advancing a pipeline of innovative product candidates in areas of significant unmet need, including persistent gastroesophageal reflux disease, diabetic nephropathy, heart failure with preserved ejection fraction, achalasia and sickle cell disease. Ironwood was founded in 1998 and is headquartered in Cambridge, Mass. For more information, please visitironwoodpharma.comor twitter.com/ironwoodpharma**;** information that may be important to investors will be routinely posted in both these locations.

Ironwood Cautionary Notes
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, commercial availability and commercial potential of linaclotide, the potential indications for, and benefits of, linaclotide; and the anticipated timing of preclinical, clinical and regulatory developments and the design, timing and results of clinical and preclinical studies. 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 preclinical and clinical development, manufacturing and formulation development; the effectiveness of development and commercialization efforts by us and our partners; 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 and judicial authorities; the risk that we or our partners may never get sufficient patent protection for linaclotide or that we or they are not able to successfully protect such patents; the outcomes in legal proceedings to protect or enforce the patents relating to linaclotide; developments in the intellectual property landscape; challenges from and rights of competitors or potential competitors; the risk that our planned investments do not have the anticipated effect on our company revenues, products or product candidates; the risk that we are unable to manage our operating expenses or cash use for operations, or are unable to commercialize our products, within the guided ranges or otherwise as expected; and the risks listed under the heading "Risk Factors" and elsewhere in Ironwood's Quarterly Report on Form 10-Q for the quarter ended June 30, 2018, 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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