January 8, 2017

Ironwood Pharmaceuticals Demonstrates Strong Execution on Strategy to Build Top-Performing Commercial Biotech

- Expect > 25% compound annual growth rate (CAGR) for Ironwood revenue between 2016 and 2020 -

- LINZESS® (linaclotide) 2016 U.S. net sales expected to be ~$625M with > 55% commercial margin; on track to exceed $1B by 2020 -

- Continued R&D innovation expected to deliver multiple catalysts in 2017 including ≥2 launches, ≥4 data readouts and ≥4 trial initiations -

- Presentation Monday, Jan. 9 at 12:00 p.m. PT during J.P. Morgan Healthcare Conference -

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Ironwood Pharmaceuticals, Inc. (NASDAQ:IRWD) today detailed strong execution against its strategy of building a top-performing commercial biotechnology company generating rapid, sustainable, high-margin growth. The company also outlined future goals and will provide further details during its presentation at the 35th Annual J.P. Morgan Healthcare Conference on Monday, January 9, 2017, at 12:00 p.m. Pacific Time / 3:00 p.m. Eastern Time at the Westin St. Francis Hotel in San Francisco.

"Ironwood discovered, developed and commercialized a market-leading product - which is rare in the biotech industry - and we have now translated innovation into strong revenue growth and continuing margin expansion, which is fueling further research and development of additional innovative product candidates," said Peter Hecht, chief executive officer of Ironwood. "This cycle of innovation and value creation is enabling us to build a top-performing commercial biotech company and realize our mission of bringing important medicines to patients and maximizing long-term, per-share cash flows for our fellow shareholders."

2016 Accomplishments and Recent Updates:

- LINZESS U.S. net sales, based on estimates provided by Allergan, are expected to be approximately $625 million for the full year 2016, representing estimated growth of more than 35% over 2015 with an estimated commercial margin of greater than 55%. Ironwood expected 2016 revenue from LINZESS represents an increase of more than 60% compared to the full year 2015. Final numbers will be provided during Ironwood's Fourth Quarter 2016 Investor Update.
- Reported topline Phase IIb data for linaclotide colonic release-1 (CR1) supporting advancement into Phase III for irritable bowel syndrome with constipation (IBS-C) and for linaclotide colonic release-2 (CR2) supporting further investigation for non-constipation subtypes of IBS.
- In-licensed U.S. rights to lesinurad and launched ZURAMPIC® (lesinurad) for the treatment of hyperuricemia in patients with uncontrolled gout who are already taking a xanthine oxidase inhibitor (XOI); filed for U.S. Food and Drug Administration (FDA) approval of DUZALLO™ (fixed-dose combination of lesinurad and allopurinol), which if approved would be the first fixed-dose, dual-mechanism treatment for patients with uncontrolled gout.
- Announced approval, with partner Astellas, of LINZESS as the first prescription treatment for adults with IBS-C in Japan.
- Initiated a Phase IIb clinical trial of IW-3718 for adults with uncontrolled gastroesophageal reflux disease (GERD).
- Advanced sGC stimulators IW-1973 and IW-1701 into Phase II trials in diabetic hypertension and achalasia, respectively.
- Used less than $30 million in cash for operations during 2016, as estimated based on Ironwood's preliminary calculations, a decrease from the less than $50 million previously guided; lowered cost of capital through debt refinancing. Final 2016 use of cash for operations will be provided during Ironwood's Fourth Quarter 2016 Investor Update.

2017 Goals:

- Continue strong LINZESS growth and margin expansion, and introduce a 72 mcg dose of linaclotide for adult chronic idiopathic constipation (CIC) patients, if approved, in early 2017.
- Launch at least two products, including LINZESS for adults with IBS-C in Japan, expected to be launched by Astellas in the first half of 2017, and DUZALLO, if approved for uncontrolled gout, expected to launch in late 2017.
- Generate data from at least four clinical trials, including the ongoing Phase IIb trial of IW-3718 for uncontrolled GERD, expected mid-year; the ongoing Phase III trial of LINZESS for CIC in Japan; and the ongoing Phase II trials of IW-1973 and IW-1701 in diabetic hypertension and achalasia, respectively.
- Initiate at least four clinical studies, including a Phase III trial of linaclotide CR1 for adults with IBS-C and Phase II trials of IW-1973 for diabetic nephropathy, resistant hypertension and heart failure (pEF).

2020 Goals:

- Greater than 25% Ironwood revenue CAGR between 2016 and 2020, excluding any current or future revenue recognized in the period related to milestone payments to Ironwood, including approximately $39 million expected to be recognized in 2016.
- Greater than $1 billion in LINZESS annual U.S. net sales; greater than 70% LINZESS commercial margin .
- ZURAMPIC/DUZALLO cash flow accretive in 2019 and rapidly expanding commercial margins.
- At least two new product launches.
- At least five Phase III clinical programs ongoing.
- Rapid growth in cash flows; expect to achieve positive cash flow during 2018.

Ironwood will provide further details during its presentation at the 35th Annual J.P. Morgan Healthcare Conference on Monday, January 9, 2017, at 12:00 p.m. Pacific Time / 3:00 p.m. Eastern Time at the Westin St. Francis Hotel in San Francisco. The presentation will be followed by a question and answer session that will begin at 1:30 p.m. Pacific Time / 4:30 p.m. Eastern Time. Additional details are expected to be provided during the company's Fourth Quarter 2016 Investor Update in February and its Investor Day on Thursday, March 9, 2017, in Cambridge, Mass.

A live webcast of Ironwood's presentation and the question and answer session at the J.P. Morgan Healthcare Conference will be accessible through the Investors section of the company's website at www.ironwoodpharma.com. To access the webcast, please log on to the Ironwood website approximately 15 minutes prior to the start time to ensure adequate time for any software downloads that may be required. A replay of the webcast will be available on Ironwood's website for 14 days following the conference.

About IBS-C and CIC

Irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) are functional gastrointestinal disorders. While estimates vary, as many as 13 million adults in the U.S. may suffer from IBS-C and as many as 35 million adults in the U.S. may suffer from CIC. IBS-C is generally characterized by hallmark symptoms of abdominal pain and infrequent bowel movements (less than three times per week); CIC is generally characterized by infrequent bowel movements (less than three times per week), but symptoms vary across this broad and heterogeneous patient population and may also include recurrent straining, lumpy or hard stools, and/or a sensation that the bowels are not fully empty. Results derived from responses to a web based survey commissioned by Forest Pharmaceuticals and Ironwood Pharmaceuticals suggest that only about half of adult IBS-C sufferers and only 12 percent of CIC sufferers are medically diagnosed. There are few available prescription treatment options for these conditions.

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 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). Linaclotide is marketed by Allergan for the treatment of adults with moderate to severe IBS-C in Europe under the brand name CONSTELLA®. 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.

LINZESS 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 Hyperuricemia and Gout

Gout is a highly symptomatic and painful form of inflammatory arthritis affecting more than nine million people in the U.S. It is caused by an underlying metabolic disorder, hyperuricemia - high levels of uric acid in the blood - and can lead to painful flares, characterized by excruciating pain, inflammation, swelling and tenderness in one or more joints. Gout has a hereditary component and is not only a lifestyle disease. While diet and lifestyle changes are important in managing gout and its comorbidities, they are often not enough to get patient serum uric acid (sUA) levels to target.

More than four million patients are treated with a xanthine oxidase inhibitor (XOI), either allopurinol or febuxostat, for gout in the U.S. Of these, an estimated two million patients are uncontrolled and are not achieving target serum uric acid (sUA) levels < 6 mg/dL as recommended by the American College of Rheumatology (ACR), despite treatment with an XOI alone. These patients continue to suffer from flares, and may face serious long-term consequences that can result from having

uncontrolled sUA levels. ACR guidelines recommend adding a uricosuric agent, like ZURAMPIC, to an XOI in patients who are not achieving target sUA levels.

About lesinurad

Lesinurad is a URAT1 inhibitor approved by the FDA for use in combination with a xanthine oxidase inhibitor (XOI) for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid (sUA) levels with an XOI alone. Lesinurad is not recommended for the treatment of asymptomatic hyperuricemia and should not be used as a monotherapy. XOIs reduce the production of uric acid; lesinurad increases renal excretion of uric acid by selectively inhibiting the action of URAT1, the UA transporter responsible for the majority of renal UA reabsorption. The dual-mechanism combination of lesinurad plus an XOI (allopurinol or febuxostat) can address both inefficient excretion and overproduction of UA, thereby lowering sUA levels. The safety profile and efficacy of lesinurad were established in three Phase III clinical trials that evaluated a once-daily dose of lesinurad in combination with the XOI allopurinol or febuxostat compared to XOI alone. Lesinurad is marketed by Ironwood in the U.S. as ZURAMPIC®; see the important safety information below for more information.

About allopurinol

Allopurinol is a xanthine oxidase inhibitor. Allopurinol's action differs from that of uricosuric agents such as lesinurad. Allopurinol reduces both the serum and urinary uric acid levels by inhibiting the formation of uric acid. The most frequent adverse reaction to allopurinol is skin rash. Skin reactions can be severe and sometimes fatal. The incidence of skin rash may be increased in the presence of renal insufficiency.

ZURAMPIC Important Safety Information

WARNING: RISK OF ACUTE RENAL FAILURE MORE COMMON WHEN USED WITHOUT A XANTHINE OXIDASE INHIBITOR (XOI)

- **Acute renal failure has occurred with ZURAMPIC and was more common when ZURAMPIC was given alone**
- **ZURAMPIC should be used in combination with an XOI**

Contraindications:

- Severe renal impairment (eCLcr less than 30 mL/min), end-stage renal disease, kidney transplant recipients, or patients on dialysis
- Tumor lysis syndrome or Lesch-Nyhan syndrome

Warnings and Precautions:

- **Renal events:** Adverse reactions related to renal function have occurred after initiating ZURAMPIC. A higher incidence was observed at the 400-mg dose, with the highest incidence occurring with monotherapy use. Monitor renal function at initiation and during therapy with ZURAMPIC, particularly in patients with eCLcr below 60 mL/min or with serum creatinine elevations 1.5 to 2 times the pre-treatment value, and evaluate for signs and symptoms of acute uric acid nephropathy. Interrupt treatment with ZURAMPIC if serum creatinine is elevated to greater than 2 times the pre-treatment value or if there are symptoms that may indicate acute uric acid nephropathy. ZURAMPIC should not be restarted without another explanation for the serum creatinine abnormalities. ZURAMPIC should not be initiated in patients with an eCLcr less than 45 mL/min.

- **Cardiovascular events:** In clinical trials, major adverse cardiovascular events (defined as cardiovascular deaths, non-fatal myocardial infarctions, or non-fatal strokes) were observed with ZURAMPIC. A causal relationship has not been established.

Adverse Reactions:

- Most common adverse reactions with ZURAMPIC (in combination with an XOI and more frequently than on an XOI alone) were headache, influenza, blood creatinine increased, and gastroesophageal reflux disease.

Indication and Limitations of Use for ZURAMPIC:

ZURAMPIC is a URAT1 inhibitor indicated in combination with an XOI for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with an XOI alone.

- ZURAMPIC is not recommended for the treatment of asymptomatic hyperuricemia
- ZURAMPIC should not be used as monotherapy

Please see full Prescribing Information, including Boxed WARNING,
http://www.azpicentral.com/zurampic/zurampic.pdf

About Uncontrolled Gastroesophageal Reflux Disease

An estimated 45 million Americans have gastroesophageal reflux disease (GERD), an estimated 10 million of whom are thought to suffer from the uncontrolled form of the condition, meaning they continue to experience symptoms such as heartburn and regurgitation despite receiving the current standard of care treatment with a proton pump inhibitor (PPI). While PPIs suppress production of stomach acid, research suggests reflux of bile from the intestine into the stomach and esophagus may play a role in the ongoing symptoms of uncontrolled GERD. There are few FDA-approved treatment options for these patients. If left untreated, uncontrolled GERD can lead to serious complications including Barrett's esophagus and, in rare instances, esophageal cancer.

About IW-3718

IW-3718 is a novel, investigational gastric retentive formulation of a bile acid sequestrant, developed by Ironwood using the proprietary Acuform® drug delivery technology licensed from Depomed, Inc. IW-3718 is designed to remain in the stomach and duodenum (upper small intestine) over an extended period of time and to work in combination with a PPI to reduce the detrimental effects of bile and acid on the esophagus.

About Ironwood's sGC Program

Soluble guanylate cyclase (sGC), a central component of the nitric oxide (NO)-sGC-cGMP pathway, plays an important role in regulating diverse physiological processes such as blood flow, inflammation, fibrosis, and metabolism. Dysregulation of sGC may play a role in multiple vascular and fibrotic diseases with high unmet need such as diabetic nephropathy, resistant hypertension, heart failure, achalasia, sickle cell disease and vascular dementia. Ironwood established its expertise in this signaling pathway through the discovery and development of linaclotide, a guanylate cyclase C (GC-C) agonist. Stimulation of sGC is a clinically validated approach, and Ironwood leveraged its GC-C expertise to discover and develop multiple sGC stimulators. IW-1973 is currently being studied in diabetic hypertension and IW-1701 is being studied in achalasia.

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 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) for the treatment of hyperuricemia associated with uncontrolled gout. We are also advancing a pipeline of internally and externally generated innovative product candidates in areas of significant unmet need, including uncontrolled gastroesophageal reflux disease and vascular and fibrotic diseases. 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, introduction and commercial potential of linaclotide, lesinurad, our product candidates (including expectations related to the introduction of LINZESS 72 mcg dose and launch of DUZALLO) and the other products that we promote and the drivers, timing, impact and results thereof; expectations concerning the timing of when we will become cash flow positive; market size, growth and opportunity, including peak sales and the potential demand for linaclotide, lesinurad and our product candidates, as well as their potential impact on applicable markets; the potential indications for, and benefits of, linaclotide, lesinurad and our product candidates; the anticipated timing of preclinical, clinical and regulatory developments and the design, timing and results of clinical and preclinical studies; the potential for, and timing of, regulatory submissions and approvals for linaclotide, lesinurad and our product candidates; expected periods of patent exclusivity; the strength of the intellectual property protection for linaclotide, lesinurad and our product candidates and our intentions and efforts to protect such intellectual property; our potential for rapid, sustainable, high-margin growth and shareholder returns; expectations related to driving productive, high-margin business; and our financial performance and results, and guidance and expectations related thereto, including expectations related to net product sales, Ironwood revenue CAGR, Ironwood revenue from LINZESS and cash used for operations, milestone revenue, LINZESS U.S. net sales, commercial margin and commercial costs, cash flow accretion and margin expansion. 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 risk that we are unable to successfully integrate lesinurad into our existing business, commercialize lesinurad or realize the anticipated benefits of the lesinurad transaction; those related to the effectiveness of commercialization efforts by us and our partners; preclinical and clinical development, manufacturing and formulation development; our reliance on AstraZeneca to provide critical support services related to lesinurad; the risk that findings from our completed nonclinical and clinical studies may not be replicated in later studies; efficacy, safety and tolerability of linaclotide, lesinurad and our product candidates; decisions by regulatory authorities; the risk that we may never get sufficient patent protection for linaclotide and our product candidates 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; the risk that our planned investments do not have the anticipated effect on our company revenues, linaclotide, lesinurad or our 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 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.

The 2016 LINZESS U.S. net sales and commercial margin, as well as the 2016 Ironwood revenue from LINZESS, milestone revenue, and cash used for operations information is preliminary and based on estimates, and may change as we receive final 2016 data from Allergan, and as we and Allergan complete the preparation of our respective 2016 financial statements. LINZESS U.S. net sales are reported by Allergan and LINZESS commercial costs incurred by each of us and Allergan are reported in our respective financial statements. Further, LINZESS U.S. commercial margin is defined as commercial profit on sales of LINZESS as a percent of total LINZESS U.S. net sales. Commercial profit on sales of LINZESS is equal to LINZESS U.S. net sales less (a) cost of goods sold incurred by Allergan and (b) selling, general and administrative expenses incurred by us and Allergan that are attributable to the cost-sharing arrangement between us. The 2016 LINZESS U.S. commercial margin presented assumes commercial costs within our previously guided range.

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