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Ironwood Announces New Drug Application for DUZALLO™ (Fixed-Dose Combination of Lesinurad and Allopurinol) Has Been Accepted for FDA Review

If approved, DUZALLO would be first dual-mechanism treatment for patients with uncontrolled gout

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Ironwood Pharmaceuticals, Inc. (NASDAQ: IRWD) today announced the U.S. Food and Drug Administration (FDA) accepted for review a New Drug Application (NDA) for DUZALLO™ (fixed-dose combination of lesinurad and allopurinol) for the treatment of hyperuricemia in patients with uncontrolled gout. The FDA Prescription Drug User Fee Act (PDUFA) target action date is expected to occur in the second half of 2017 and, if approved, DUZALLO is expected to be commercially available in late 2017.

It is estimated that approximately half of the four million gout patients in the U.S. treated with a xanthine oxidase inhibitor (XOI), either allopurinol or febuxostat, are uncontrolled and are not achieving target serum uric acid (sUA) levels < 6 mg/dL as recommended by the American College of Rheumatology. Lesinurad is currently approved by the FDA under the brand name ZURAMPIC® to be taken in combination with an XOI for the treatment of hyperuricemia - high levels of uric acid in the blood - associated with gout in patients who have not achieved target sUA levels with an XOI alone. ZURAMPIC is not recommended for the treatment of asymptomatic hyperuricemia and should not be used as monotherapy.

Lesinurad is a once-daily oral tablet that lowers sUA by reducing reabsorption of uric acid, thereby increasing renal excretion of uric acid. The mechanism of lesinurad is distinct from and complementary to that of an XOI, which reduces production of uric acid. Together, the dual-mechanism combination of lesinurad plus an XOI can address both inefficient excretion and overproduction of uric acid. Currently, patients with uncontrolled gout are often treated with higher doses of XOIs that may require multiple pills daily in an attempt to reach their sUA target. If approved, DUZALLO would be the first treatment to offer this dual-mechanism of action in a single pill to be taken once per day.

The NDA for DUZALLO is based on the extensive clinical program supporting the ZURAMPIC NDA and a pharmacokinetic study that evaluated the bioequivalence of the fixed-dose combination of lesinurad and allopurinol compared to co-administration of separate lesinurad and allopurinol tablets. The efficacy and safety of the two drugs co-administered separately was demonstrated in two pivotal Phase III clinical trials, CLEAR 1 and CLEAR 2, which supported the ZURAMPIC NDA. In these clinical trials in adult patients with gout who failed to achieve target sUA levels on allopurinol alone, the addition of ZURAMPIC nearly doubled the number of patients who achieved sUA target of < 6 mg/dL at month 6, reduced the mean sUA to < 6 mg/dL by month 1 and maintained that level through month 12. Acute renal failure has occurred with ZURAMPIC and was more common when ZURAMPIC was given alone. The most common adverse reactions with ZURAMPIC in the clinical trials were headache, influenza, blood creatinine increased, and gastroesophageal reflux disease. The DUZALLO NDA was submitted by Ardea BioSciences on behalf of Ironwood.

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 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 FDA approval of, and the PDUFA target action date for, DUZALLO, the commercial availability of DUZALLO and the timing thereof, the potential benefits of DUZALLO and prevalence and unmet need. 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 Ironwood; efficacy, safety and tolerability of lesinurad; decisions by regulatory authorities; challenges from and rights of competitors or potential competitors; and those 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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