November 13, 2016

Ironwood Highlights ZURAMPIC® (lesinurad) Phase III Extension Study Data at the American College of Rheumatology 2016 Annual Meeting

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Ironwood Pharmaceuticals, Inc. (NASDAQ: IRWD) today presented efficacy and safety data from two Phase III extension studies of ZURAMPIC (lesinurad), as well as pooled analyses from the two extension studies and from the three pivotal Phase III ZURAMPIC clinical trials, in four poster presentations at the American College of Rheumatology (ACR) Annual Meeting in Washington, D.C.

ZURAMPIC is FDA-approved as a once-daily oral tablet to be taken 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. ZURAMPIC is not recommended for the treatment of asymptomatic hyperuricemia and should not be used as monotherapy.

The FDA approval of lesinurad was based upon three pivotal Phase III trials: the CLEAR 1 and CLEAR 2 trials, in which patients were randomized to receive either 200 mg lesinurad plus the XOI allopurinol, 400 mg lesinurad plus allopurinol, or placebo plus allopurinol for 12 months, and the CRYSTAL trial, in which patients were randomized to receive 200 mg lesinurad plus the XOI febuxostat, 400 mg lesinurad plus febuxostat, or placebo plus febuxostat for 12 months. The two lesinurad extension studies, which were open-label, further evaluated the safety and efficacy of lesinurad plus an XOI over a 12-month extension period. The CLEAR extension study enrolled patients from the CLEAR 1 and CLEAR 2 trials, with patients who received lesinurad plus allopurinol in those trials continuing their treatment, while patients who previously received placebo were randomized to a lesinurad plus allopurinol treatment arm. The CRYSTAL extension study enrolled patients from the CRYSTAL trial, with patients who received lesinurad plus febuxostat in that trial continuing their treatment, while patients who previously received placebo were randomized to a lesinurad plus febuxostat treatment arm.

Data are to be presented on Sunday, November 13, from 9:00 a.m. to 11:00 a.m. Eastern Time as follows:

- ***Examination of Serum Uric Acid (sUA) Lowering and Safety With Extended Lesinurad + Allopurinol Treatment in Subjects With Gout*** (abstract #208), to be presented by Kenneth G. Saag, M.D., M.Sc., University of Alabama at Birmingham, during the Metabolic and Crystal Arthropathies Poster Session I: Clinical Practice. This analysis found that patients treated with lesinurad plus allopurinol in the CLEAR 1 and CLEAR 2 trials who continued treatment in the CLEAR extension study maintained target sUA levels over the full two years. Additionally, an increased proportion of patients who received placebo in CLEAR 1 and CLEAR 2 reached target sUA levels after crossing into the CLEAR extension study and receiving treatment with lesinurad plus allopurinol. The data from this extension study identified no new safety signals in patients continuing lesinurad plus allopurinol treatment in the CLEAR extension study relative to the safety profile observed for those receiving lesinurad plus allopurinol in CLEAR 1 and CLEAR 2.
- ***Clinical Response of Tophus and Flares to Extended Use of Lesinurad in Combination With a Xanthine Oxidase Inhibitor in Patients With Gout*** (abstract #209), to be presented by Thomas Bardin, M.D., Lariboisière Hospital, Paris, France, during the Metabolic and Crystal Arthropathies Poster Session I: Clinical Practice. This analysis of pooled data from patients receiving lesinurad plus XOI in the CLEAR 1, CLEAR 2 or CRYSTAL trials who continued treatment in the CLEAR and CRYSTAL extension studies examined the impact of treatment of lesinurad plus XOI on tophi and flares. The pooled analysis found that patients treated with lesinurad plus an XOI for up to two years exhibited continued increases in the rate of complete resolution of tophi and reduction in tophus area, as well as decreased rates of gout flares.
- ***Renal Safety of Lesinurad: A Pooled Analysis of Phase III and Extension Studies*** (abstract #206), to be presented by Robert Terkeltaub, M.D., University of California, San Diego, during the Metabolic and Crystal Arthropathies Poster Session I: Clinical Practice. In this study, renal-related and kidney stone safety data were pooled from patients enrolled in the CLEAR 1, CLEAR 2 and CRYSTAL trials taking either lesinurad 200 mg plus XOI or lesinurad 400 mg plus XOI as well as patients enrolled in the CLEAR and CRYSTAL extension studies. These pooled safety data were compared against patients taking XOI alone in the three pivotal Phase III trials, to evaluate the impact on renal safety of extended lesinurad plus XOI treatment. The study concluded that, except for a higher rate of serum creatinine elevations, the majority of which resolved during the study period, lesinurad at the approved dose of 200 mg once-daily combined with an XOI demonstrated a comparable rate of renal adverse events to XOI alone. There was no clinically relevant increase in these adverse events with the extension of treatment beyond one year.

- ***Integrated Safety of Lesinurad, A Novel Uric Acid Reabsorption Inhibitor for the Treatment of Gout*** (abstract #207), to be presented by Michael A. Becker, M.D., University of Chicago, during the Metabolic and Crystal Arthropathies Poster Session I: Clinical Practice. This study integrated safety data for lesinurad based on patients who completed the CLEAR 1, CLEAR 2 and CRYSTAL trials taking either lesinurad 200 mg plus XOI or lesinurad 400 mg plus XOI, as well as the CLEAR and CRYSTAL extension studies. The integrated study concluded that lesinurad at the FDA-approved dose of 200 mg once-daily combined with an XOI demonstrated a consistent, acceptable safety profile, with rates of treatment-emergent adverse events comparable to XOI alone and lower than with lesinurad 400 mg once-daily plus XOI. There were no new safety concerns identified in the extension studies.

About Hyperuricemia and Gout
Gout is a highly symptomatic and painful form of inflammatory arthritis affecting an estimated eight 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 is commonly hereditary and 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.

Approximately 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 ZURAMPIC® (lesinurad) 200 mg tablets
ZURAMPIC® (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. ZURAMPIC is not recommended for the treatment of asymptomatic hyperuricemia and should not be used as a monotherapy. XOIs reduce the production of uric acid; ZURAMPIC 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 ZURAMPIC plus an XOI (allopurinol or febuxostat) can address both inefficient excretion and overproduction of UA, thereby lowering sUA levels. The safety and efficacy of ZURAMPIC were established in three Phase III clinical trials that evaluated a once-daily dose of ZURAMPIC in combination with the XOI allopurinol or febuxostat compared to XOI alone. Visit www.zurampic.com for more information about 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.

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