August 21, 2017

Ironwood Pharmaceuticals Announces FDA Approval of DUZALLO® (lesinurad and allopurinol) for the Treatment of Hyperuricemia in Patients with Uncontrolled Gout

- Once-Daily DUZALLO Is the First FDA-Approved Fixed-Dose Combination Treatment That Addresses Both Causes of Hyperuricemia in Gout, Over-Production and Under-Excretion of Serum Uric Acid, In A Single Pill -

CAMBRIDGE, Mass.--(BUSINESS WIRE)-- Ironwood Pharmaceuticals, Inc. (NASDAQ: IRWD) today announced DUZALLO was approved by the U.S. Food and Drug Administration (FDA) as a once-daily oral treatment for hyperuricemia associated with gout in patients who have not achieved target serum uric acid (sUA) levels with a medically appropriate daily dose of allopurinol alone. DUZALLO is not recommended for the treatment of asymptomatic hyperuricemia. Ironwood expects DUZALLO to be commercially available early in the fourth quarter of 2017.

This Smart News Release features multimedia. View the full release here: http://www.businesswire.com/news/home/20170821005414/en/

DUZALLO(R) (lesinurad and allopurinol) (Photo: Business Wire)

DUZALLO is the first drug that combines the current standard of care for the treatment of hyperuricemia associated with gout, allopurinol, with the most recent FDA-approved treatment for this condition, lesinurad. This fixed-dose combination provides a dual mechanism of action in a single tablet that can address both underlying causes of hyperuricemia - overproduction and underexcretion of serum uric acid.

Gout is a highly symptomatic and painful form of inflammatory arthritis caused by hyperuricemia, or elevated sUA levels in the blood, which can lead to painful flares and serious potential long-term health consequences.

"The approval of DUZALLO provides a new fixed-dose and dual-mechanism treatment option to help patients with uncontrolled gout achieve target serum uric acid levels. This represents an important and needed new option in the treatment of hyperuricemia," said Michael A. Becker, M.D., professor emeritus of medicine, Department of Medicine, The University of Chicago, Chicago, IL. "Gout is a serious and potentially progressive and debilitating inflammatory disease. Getting patients with gout to serum urate goal, and keeping them at or below goal, are essential to success in treating these patients. DUZALLO will help reduce the significant unmet need among patients in the U.S. who fail to get their serum uric acid levels to goal despite taking allopurinol alone."

"With DUZALLO, nearly twice as many patients with uncontrolled gout may be able to achieve target serum uric acid levels compared to those patients taking allopurinol alone, which is important, considering the significant unmet need among uncontrolled gout patients to get to goal of under 6 mg/dL," said Tom McCourt, senior vice president of marketing and sales and chief commercial officer at Ironwood. "We believe DUZALLO will be the critical driver behind Ironwood's gout franchise, which is expected to exceed total annual U.S. peak sales of $300 million."

The FDA approval of DUZALLO was based on the clinical program supporting the ZURAMPIC® (lesinurad) new drug

application (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 lesinurad plus allopurinol were demonstrated in two pivotal Phase III clinical trials, CLEAR 1 (n=402) and CLEAR 2 (n=410), which supported the ZURAMPIC NDA. In clinical trials of adult patients with gout who failed to achieve target sUA levels on allopurinol alone, lesinurad in combination with allopurinol nearly doubled the number of patients who achieved sUA target of < 6 mg/dL at month 6, reduced the mean sUA level to < 6 mg/dL by month 1 and maintained that level through month 12. The most common adverse reactions in clinical trials were headache, influenza, higher levels of blood creatinine (a measure of kidney function), and heartburn (acid reflux). DUZALLO has a boxed warning regarding the risk of acute renal failure.

The DUZALLO NDA was submitted by Ardea Biosciences, Inc. on behalf of Ironwood.

About DUZALLO (lesinurad and allopurinol) Tablets
DUZALLO (lesinurad and allopurinol) is a once-daily oral therapy that contains lesinurad 200 mg plus allopurinol 300 mg; it is also available in a lesinurad 200 mg plus allopurinol 200 mg dosage. DUZALLO is approved by the FDA as a once-daily oral treatment for hyperuricemia associated with gout in patients who have not achieved target serum uric acid (sUA) levels with a medically appropriate daily dose of allopurinol alone. DUZALLO is not recommended for the treatment of asymptomatic hyperuricemia. Allopurinol is an XOI whose action differs from that of uricosuric agents such as lesinurad. Allopurinol reduces the production of uric acid (UA); lesinurad increases renal excretion of UA by selectively inhibiting the action of URAT1, the UA transporter responsible for the majority of renal UA reabsorption. The dual-mechanism combination of DUZALLO can address both inefficient excretion and overproduction of UA, thereby lowering sUA levels. DUZALLO should be taken in the morning with food and water, and patients should be advised to stay well hydrated when taking DUZALLO (about 2 liters of liquid a day).

For more information about DUZALLO, please visit www.duzallo.com.

About Hyperuricemia and Gout
Gout, the most common inflammatory arthritis in adults, is a highly symptomatic and painful form of inflammatory arthritis caused by hyperuricemia - high serum uric acid (sUA) levels in the blood. Some patients can lower sUA levels sufficiently by using a xanthine oxidase inhibitor (XOI), such as allopurinol. However, an estimated two million patients currently treated with an XOI in the U.S. suffer from uncontrolled gout, which means they are not achieving target sUA levels of less than 6 mg/dL, as recommended by the American College of Rheumatology. Long-term effects can be serious for patients with elevated sUA levels, which is why it is important for gout patients to reach target sUA levels.

Gout is often hereditary and not only a lifestyle disease. While diet and lifestyle changes are important considerations in the management of gout and its comorbidities, they're often not enough to get these patients' sUA levels to target. There are two mechanisms of the disease that can lead to high serum uric acid levels: overproduction and underexcretion of uric acid. It's important for patients to know their serum uric acid levels, and for those patients with levels above 6 mg/dL to talk to their doctor about possible treatment options.

DUZALLO Important Safety Information

WARNING: RISK OF ACUTE RENAL FAILURE

• Acute renal failure has occurred with lesinurad, one of the components of DUZALLO

Contraindications:

- Severe renal impairment (estimated creatinine clearance [eCLcr] < 30 mL/min), end-stage renal disease, kidney transplant recipients, or patients on dialysis
- Tumor lysis syndrome or Lesch-Nyhan syndrome
- Known hypersensitivity to allopurinol, including previous occurrence of skin rash

Warnings and Precautions:

- **Renal events:** Adverse reactions related to renal function, including acute renal failure, can occur after initiating DUZALLO. Renal function should be evaluated prior to initiation of DUZALLO and periodically thereafter, as clinically indicated. More frequent renal function monitoring is recommended in patients with eCLcr < 60 mL/min or with serum creatinine elevations 1.5 to 2 times the value when lesinurad treatment was initiated. DUZALLO should not be initiated in patients with an eCLcr < 45 mL/min. Interrupt treatment with DUZALLO if serum creatinine is elevated to > 2 times the pretreatment value or if there are symptoms that may indicate acute uric acid nephropathy, including flank pain, nausea, or vomiting. DUZALLO should not be restarted without another explanation for the serum creatinine abnormalities
- **Skin rash and hypersensitivity:** Skin rash is a frequently reported adverse event in patients taking allopurinol. In

some instances, a skin rash may be followed by more severe hypersensitivity reactions associated with exfoliation, fever, lymphadenopathy, arthralgia, and/or eosinophilia including Stevens-Johnson syndrome and toxic epidermal necrolysis. Associated vasculitis and tissue response may be manifested in various ways including hepatitis, renal impairment, seizures, and on rare occasions, death. Hypersensitivity reactions to allopurinol may be increased in patients with decreased renal function who are receiving thiazide diuretics and DUZALLO concurrently. DUZALLO should be discontinued immediately at the first appearance of skin rash or other signs that may indicate an allergic reaction, and additional medical care should be provided as needed

- **Hepatotoxicity:** A few cases of reversible clinical hepatotoxicity have been reported in patients taking allopurinol and, in some patients, asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed. If anorexia, weight loss, or pruritus develops in patients taking DUZALLO, evaluation of liver function should be performed. In patients with preexisting liver disease, periodic liver function tests are recommended
- **Cardiovascular events:** In clinical trials, major adverse cardiovascular events (defined as cardiovascular deaths, nonfatal myocardial infarctions, and nonfatal strokes) were observed with DUZALLO. A causal relationship has not been established
- **Bone marrow depression:** Bone marrow depression has been reported in patients receiving allopurinol, most of whom received concomitant drugs with the potential for causing this reaction. This has occurred as early as 6 weeks to as long as 6 years after the initiation of allopurinol therapy. Rarely, a patient may develop varying degrees of bone marrow depression, affecting one or more cell lines, while receiving allopurinol alone. Patients taking allopurinol and mercaptopurine or azathioprine require a reduction in dose to approximately one-third to one-fourth of the usual dose of mercaptopurine or azathioprine
- **Increase in prothrombin time:** It has been reported that allopurinol prolongs the half-life of dicumarol, a coumarin anticoagulant. The prothrombin time should be reassessed periodically in patients receiving coumarin anticoagulants (dicumarol, warfarin) concomitantly with DUZALLO
- **Drowsiness:** Occasional occurrence of drowsiness was reported in patients taking allopurinol. Patients should be alerted to the need for caution when engaging in activities where alertness is mandatory

Adverse Reactions:

- The most common adverse reactions in controlled studies (occurring in 2% or more of patients on lesinurad in combination with allopurinol and at least 1% greater than observed in patients on allopurinol alone) were headache, influenza, blood creatinine increased, and gastroesophageal reflux disease
- The most common adverse reactions identified during post-approval use of allopurinol are skin rash, nausea, and diarrhea

Indication and Limitations of Use:

DUZALLO, a combination of lesinurad, a URAT1 inhibitor, and allopurinol, a xanthine oxidase inhibitor, is indicated for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a medically appropriate daily dose of allopurinol alone.

- DUZALLO is not recommended for the treatment of asymptomatic hyperuricemia

Please see full Prescribing Information, including Boxed Warning:
https://www.irwdpi.com/duzallo/DuzalloPIandMedguide2017.pdf#page=1

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 commercial availability of DUZALLO and the timing thereof, the potential benefits of DUZALLO, prevalence and unmet need, and market size, growth and opportunity, including peak sales

and potential demand for DUZALLO and Ironwood's gout franchise in the U.S. 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; developments in the intellectual property landscape; and those risks listed under the heading "Risk Factors" and elsewhere in Ironwood's Quarterly Report on Form 10-Q for the quarter ended June 30, 2017, 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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