Xeris Biopharma Announces U.S. FDA Approval of Recorlev® (levoketoconazole) for the Treatment of Endogenous Hypercortisolemia in Adult Patients With Cushing's Syndrome

December 30, 2021

FDA approval supported by positive results from the pivotal Phase 3 SONICS and LOGICS studies demonstrating Recorlev to be a safe and effective therapeutic option in the treatment of Cushing's syndrome

FDA decision follows successful completion of acquisition of Strongbridge Biopharma on October 5, 2021

Post-acquisition, the Company is well-positioned to address the needs of Cushing's syndrome patients in the U.S. who are treated with prescription therapy

Commercial launch of Recorlev is planned for Q1 2022

CHICAGO--(BUSINESS WIRE)--Dec. 30, 2021-- Xeris Biopharma Holdings, Inc. (Nasdaq: XERS), a biopharmaceutical company developing and commercializing unique therapies for patient populations in endocrinology, neurology, and gastroenterology, today announced the U.S. Food and Drug Administration (FDA) approval of Recorlev® (levoketoconazole) for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome for whom surgery is not an option or has not been curative.[1]

"We are thrilled with the FDA's approval of Recorlev as a safe and effective treatment option for patients with endogenous Cushing's syndrome. With this approval, Xeris' experienced endocrinology-focused commercial organization can begin rapidly working to help address the needs of Cushing's syndrome patients in the U.S. who are treated with prescription therapy," said Paul R. Edick, Chairman and CEO of Xeris Biopharma. "Today's announcement also reinforces the value that we saw in acquiring Strongbridge Biopharma's attractive rare disease portfolio, which we believe will deliver compelling long-term value to our shareholders. We look forward to making Recorlev commercially available in the first quarter."

The approval of Recorlev was based upon safety and efficacy data from two positive Phase 3 studies that evaluated a combined study population of 166 patients, which was representative of the adult drug-treated U.S. population with Cushing's syndrome. [1] The SONICS study met its primary and key secondary endpoints, significantly reducing and normalizing mean urinary free cortisol concentrations without a dose increase (detailed results **here**).[1,2] LOGICS, a double-blind, placebo-controlled randomized-withdrawal study that met its primary and key secondary endpoints, confirmed the efficacy and safety of Recorlev in normalizing and maintaining therapeutic response compared with placebo (detailed results **here**).[1]

"Levoketoconazole (Recorlev) is an important and welcome new therapeutic option for clinicians to help manage patients with endogenous Cushing's syndrome, a severe, potentially life-threatening rare disease, if not appropriately treated, with multisystem signs and symptoms," said Maria Fleseriu, M.D., FACE, professor of Medicine and Neurological Surgery and director of the Pituitary Center at Oregon Health Sciences University. "In prospective clinical studies, treatment with levoketoconazole was shown to be effective for reducing and normalizing cortisol."

"Cushing's syndrome is a rare disease that can be physically and emotionally devastating to the patient. Most patients endure years of symptoms prior to obtaining a diagnosis and are then faced with limited effective treatment options," said Leslie Edwin, president of the Cushing's Support & Research Foundation. "Today we are excited to see that the long and complicated path of rare drug development has reached FDA approval on a new therapeutic option for our underserved Cushing's community. We are grateful that the researchers worked so diligently for so long to establish the safety and efficacy of this drug. Rare disease patients know the importance of sharing their complicated experiences as 'expert witnesses', and we thank Xeris for being an early adherent to this concept. We especially want to thank the clinical trial patients who made this progress possible."

Xeris is committed to ensuring everyone who needs access to their therapies will receive it. Xeris has created Xeris CareConnection™ to provide a comprehensive program for patients and their caregivers throughout the treatment journey, including financial assistance, one-on-one support, and educational resources. Xeris CareConnection also supports healthcare professionals and their teams through education on access and reimbursement. To get started with Recorlev, reach out to Xeris CareConnection (available Monday–Friday from 8 a.m–7 p.m ET) at 1-844-444-RCLV (7258).

About Cushing's Syndrome

Endogenous Cushing's syndrome is a rare, serious, and potentially fatal endocrine disease caused by chronic elevated cortisol exposure–often the result of a benign tumor of the pituitary gland. This benign tumor tells the body to overproduce high levels of cortisol for a sustained period of time, which often results in characteristic physical signs and symptoms that are distressing to patients. The disease is most common among adults between the ages of 30–50, and it affects women three times more often than men. Women with Cushing's syndrome may experience a variety of health issues including menstrual problems, difficulty becoming pregnant, excess male hormones (androgens), primarily testosterone, which can cause hirsutism (growth of coarse body hair in a male pattern), oily skin, and acne.[3]

Additionally, the multisystem complications of the disease are potentially life threatening. These include metabolic changes such as high blood sugar or diabetes, high blood pressure, high cholesterol, fragility of various tissues including blood vessels, skin, muscle, and bone, and psychological disturbances such as depression, anxiety, and insomnia.[3] Untreated, the five-year survival rate is only approximately 50%.[4]

About Recorlev

Recorlev® (levoketoconazole) is a cortisol synthesis inhibitor for the treatment of endogenous hypercortisolemia in adult patients with Cushing's

syndrome for whom surgery is not an option or has not been curative.[1] Endogenous Cushing's syndrome is a rare but serious and potentially lethal endocrine disease caused by chronic elevated cortisol exposure.[2] Recorlev is the pure 2S,4R enantiomer of ketoconazole, a steroidogenesis inhibitor.[1] Recorlev has demonstrated in two successful Phase 3 studies to significantly reduce mean urine free cortisol.[1]

The Phase 3 program for Recorlev included SONICS and LOGICS, two multinational studies designed to evaluate the safety and efficacy of Recorlev when used to treat endogenous Cushing's syndrome. The SONICS study met its primary and secondary endpoints, significantly reducing and normalizing mean urinary free cortisol concentrations without a dose increase.[1,2] The LOGICS study, which met its primary endpoint and key secondary endpoint, was a double-blind, placebo-controlled randomized-withdrawal study of Recorlev that was designed to supplement the efficacy and safety information provided by SONICS.[1] The ongoing open-label OPTICS study will gather further useful information related to the long-term use of Recorlev.

Recorlev received orphan drug designation from the FDA and the European Medicines Agency for the treatment of endogenous Cushing's syndrome.

Indication & Important Safety Information for Recorlev®

BOXED WARNING: HEPATOTOXICITY AND QT PROLONGATION

HEPATOTOXICITY

Cases of hepatotoxicity with fatal outcome or requiring liver transplantation have been reported with oral ketoconazole. Some patients had no obvious risk factors for liver disease. Recorlev is associated with serious hepatotoxicity. Evaluate liver enzymes prior to and during treatment.

QT PROLONGATION

Recorlev is associated with dose-related QT interval prolongation. QT interval prolongation may result in life-threatening ventricular dysrhythmias such as torsades de pointes. Perform ECG and correct hypokalemia and hypomagnesemia prior to and during treatment.

INDICATION

Recorlev is a cortisol synthesis inhibitor indicated for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome for whom surgery is not an option or has not been curative.

Limitations of Use

Recorlev is not approved for the treatment of fungal infections.

CONTRAINDICATIONS

- Cirrhosis, acute liver disease or poorly controlled chronic liver disease, baseline AST or ALT > 3 times the upper limit of normal, recurrent symptomatic cholelithiasis, a prior history of drug induced liver injury due to ketoconazole or any azole antifungal therapy that required discontinuation of treatment, or extensive metastatic liver disease.
- Taking drugs that cause QT prolongation associated with ventricular arrythmias, including torsades de pointes.
- Prolonged QTcF interval > 470 msec at baseline, history of torsades de pointes, ventricular tachycardia, ventricular fibrillation, or prolonged QT syndrome.
- Known hypersensitivity to levoketoconazole, ketoconazole or any excipient in Recorlev.
- Taking certain drugs that are sensitive substrates of CYP3A4 or CYP3A4 and P-gp.

WARNINGS AND PRECAUTIONS

Hepatotoxicity

Serious hepatotoxicity has been reported in patients receiving Recorlev, irrespective of the dosages used or the treatment duration. Drug-induced liver injury (peak ALT or AST greater than 3 times upper limit of normal) occurred in patients using Recorlev. Avoid concomitant use of Recorlev with hepatotoxic drugs. Advise patient to avoid excessive alcohol consumption while on treatment with Recorlev. Routinely monitor liver enzymes and bilirubin during treatment.

QT Prolongation

Use Recorlev with caution in patients with other risk factors for QT prolongation, such as congestive heart failure, bradyarrythmias, and uncorrected electrolyte abnormalities, with more frequent ECG monitoring considered. Routinely monitor ECG and blood potassium and magnesium levels during treatment.

Hypocortisolism

Recorlev lowers cortisol levels and may lead to hypocortisolism with a potential for life-threatening adrenal insufficiency. Lowering of cortisol levels can cause nausea, vomiting, fatigue, abdominal pain, loss of appetite, and dizziness. Significant lowering of serum cortisol levels may result in adrenal insufficiency that can be manifested by hypotension, abnormal electrolyte levels, and hypoglycemia. Routinely monitor 24-hour urine free cortisol, morning serum or plasma cortisol, and patient's signs and symptoms for hypocortisolism during treatment.

Hypersensitivity Reactions

Hypersensitivity to Recorlev has been reported. Anaphylaxis and other hypersensitivity reactions including urticaria have been reported with oral ketoconazole.

Risks Related to Decreased Testosterone

Recorlev may lower serum testosterone in men and women. Potential clinical manifestations of decreased testosterone concentrations in men may include gynecomastia, impotence and oligospermia. Potential clinical manifestations of decreased testosterone concentrations in women include decreased libido and mood changes.

ADVERSE REACTIONS

Most common adverse reactions (incidence > 20%) are nausea/vomiting, hypokalemia, hemorrhage/contusion, systemic hypertension, headache, hepatic injury, abnormal uterine bleeding, erythema, fatigue, abdominal pain/dyspepsia, arthritis, upper respiratory infection, myalgia, arrhythmia, back pain, insomnia/sleep disturbances, and peripheral edema.

DRUG INTERACTIONS

- Consult approved product labeling for drugs that are substrates of CYP3A4, P-gp, OCT2, and MATE prior to initiating Recorlev.
- Sensitive CYP3A4 or CYP3A4 and P-gp Substrates: Concomitant use of Recorlev with these substrates is contraindicated or not recommended.
- Atorvastatin: Use lowest atorvastatin dose possible and monitor for adverse reactions for dosages exceeding 20 mg daily.
- Metformin: Monitor glycemia, kidney function, and vitamin B12 and adjust metformin dosage as needed.
- Strong CYP3A4 Inhibitors or Inducers: Avoid use of these drugs 2 weeks before and during Recorlev treatment.
- Gastric Acid Modulators: See Full Prescribing Information for recommendations regarding concomitant use with Recorlev.

USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed during treatment and for one day after final dose.

To report SUSPECTED ADVERSE REACTIONS, contact Xeris Pharmaceuticals, Inc. at 1-877-937-4737 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Full Prescribing Information including Boxed Warning.

About Xeris Biopharma

Xeris (Nasdaq: XERS) is a biopharmaceutical company developing and commercializing unique therapies for patient populations in endocrinology, neurology, and gastroenterology. Xeris has two commercially available products; Gvoke®, a ready-to-use liquid glucagon for the treatment of severe hypoglycemia, and Keveyis®, the first and only FDA-approved therapy for primary periodic paralysis. In addition to Recorlev® for the treatment of endogenous Cushing's syndrome, Xeris also has a robust pipeline of development programs to extend the current marketed products into important new indications and uses and bring new products forward using its proprietary formulation technology platforms, XeriSol™ and XeriJect™, supporting long-term product development and commercial success.

Xeris Biopharma Holdings is headquartered in Chicago, IL. For more information, visit www.xerispharma.com or follow us on Twitter, LinkedIn, or Instagram.

Forward-Looking Statements

Any statements in this press release about future expectations, plans and prospects for Xeris Biopharma Holdings, Inc. including statements regarding the market and therapeutic potential of its products and product candidates, expectations regarding the timing of the commercial launch of Recorlev, estimates and projections about the potential benefits of the Strongbridge Biopharma acquisition, the future performance of the combined company and estimated synergies, the timing or likelihood of expansion into additional markets and other statements containing the words "will," "would," "continue," and similar expressions, constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. These forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those indicated in the forward-looking statements. Such risks and uncertainties include, but are not limited to, reliance on third-party suppliers for Gvoke®, Ogluo®, Keveyis®, and Recorlev® the regulatory approval of its product candidates, its ability to market and sell its products, failure to realize the expected benefits of the acquisition, failure to promptly and effectively integrate Strongbridge's businesses, general economic and business conditions that affect the combined company following the consummation of the acquisition, the impact of the COVID-19 pandemic on the combined company following the consummation of the transaction, changes in global, political, economic, business, competitive, market and regulatory forces, future exchange and interest rates, changes in tax laws, regulations, rates and policies, future business acquisitions or disposals and competitive developments and the other risks described in our Quarterly Report on Form 10-Q and other reports we file from time to time with the SEC. These forward-looking statements are based on numerous assumptions and assessments made in light of Xeris' experience and perception of historical trends, current conditions, business strategies, operating environment, future developments, and other factors it believes appropriate. By their nature, forward-looking statements involve known and unknown risks and uncertainties because they relate to events and depend on circumstances that will occur in the future. The factors described in the context of such forward-looking statements in this communication could cause Xeris' plans with respect to Strongbridge, Xeris' plans with respect to its products and product candidates, Xeris' actual results, performance or achievements, industry results and developments to differ materially from those expressed in or implied by such forward-looking statements. Although it is believed that the expectations reflected in such forward-looking statements are reasonable, no assurance can be given that such expectations will prove to have been correct and persons reading this communication are therefore cautioned not to place undue reliance on these forward-looking statements which speak only as at the date of this communication. Additional information about economic, competitive, governmental, technological, and other factors that may affect Xeris is set forth in Item 1A, "Risk Factors," in Xeris' 2020 Annual Report on Form 10-K, which has been filed with the SEC and other important factors in Xeris' subsequent filings with the SEC, the contents of which are not incorporated by reference into, nor do they form part of, this communication. Additional information about economic, competitive, governmental, technological, and other factors that may affect Strongbridge is set forth in Item 1A, "Risk Factors," in Strongbridge's 2020 Annual Report on Form 10-K, which has been filed with the SEC, the contents of which are not incorporated by reference into, nor do they form part of, this communication. Any forward-looking statements in this communication are based upon

information available to Xeris, as of the date of this communication and, while believed to be true when made, may ultimately prove to be incorrect. Subject to any obligations under applicable law, Xeris does not undertake any obligation to update any forward-looking statement whether as a result of new information, future developments or otherwise, or to conform any forward-looking statement to actual results, future events, or to changes in expectations. All subsequent written and oral forward-looking statements attributable to Xeris or any person acting on behalf of any of them are expressly qualified in their entirety by this paragraph.

1. Recorlev [prescribing information]. Chicago, IL: Xeris Pharmaceuticals, Inc.; 2021. 2. Fleseriu M, et al. *Lancet Diabetes Endocrinol*. 2019;7(11):855-865. 3. Pivonello R et al. *Lancet Diabetes Endocrinol.* 2016; 4: 611-29. 4. Plotz CM, et al. *Am J Med.* 1952 November;13(5):597-614.

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