Recorlev® (levoketoconazole) – New orphan drug approval

- On December 30, 2021, Xeris Biopharma announced the 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.

    — Recorlev is not approved for the treatment of fungal infections. The safety and effectiveness of Recorlev for the treatment of fungal infections have not been established.

- Recorlev is a cortisol synthesis inhibitor and an enantiomer of ketoconazole.

- The efficacy of Recorlev was established in two studies in patients with Cushing's syndrome. Study 1 (N = 84) consisted of an open-label dose titration and maintenance phase of up to 19 weeks duration, followed by an 8-week double-blind, placebo-controlled, randomized withdrawal phase. Patients who achieved a stable therapeutic dose for at least 4 weeks and achieved a normal mean urinary free cortisol (mUFC) at the end of the dose titration and maintenance phase were eligible for the randomized withdrawal phase. Forty-four patients entered the randomized withdrawal phase where they were randomized to either continue Recorlev or receive placebo for approximately 2 months or until early rescue was necessary (ie, for mUFC > 1.5 x upper limit of normal).

    — The number and percent of patients who had normal mUFC at the end of the randomized withdrawal phase was 11/21 (52.4%) in Recorlev group and 1/18 (5.6%) in placebo group (treatment difference 46.8, 95% CI: 16.5, 70.2).

- Supportive evidence of efficacy was obtained from Study 2 (N = 94) which was a single-arm, open-label study that consisted of three study phases (dose titration, maintenance, and extended evaluation) for a total estimated treatment duration of up to 73 weeks. The primary efficacy endpoint of the study was the proportion of patients with normalization of mUFC at the end of the 6-month maintenance phase.

    — At the end of the maintenance phase, 29 of 94 patients (30.9%, 95% CI: 21.7, 41.2) met the primary endpoint.

- Recorlev carries a boxed warning for hepatotoxicity and QT prolongation.

- Recorlev is contraindicated in patients:

    — With cirrhosis, acute liver disease or poorly controlled chronic liver disease, baseline AST or ALT greater than 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 arrhythmias, including torsades de pointes
    — With a prolonged QTcF interval of greater than 470 msec at baseline, history of torsades de pointes, ventricular tachycardia, ventricular fibrillation, or long QT syndrome (including first-degree family history)
    — With known hypersensitivity to levoketoconazole, ketoconazole or any excipient in Recorlev
    — Taking certain drugs that are sensitive substrates of CYP3A4 or CYP3A4 and P-gP.

- Additional warnings and precautions for Recorlev include hypocortisolism, hypersensitivity reactions, and risks related to decreased testosterone.

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- The most common adverse reactions (> 20%) with Recorlev use were 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.

- The recommended initial dose of Recorlev is 150 mg orally twice daily. The dosage should be titrated by 150 mg daily, no more frequently than every 2 to 3 weeks based on 24-hour urine free cortisol levels and patient tolerability. Cortisol levels should be monitored from at least two 24-hour urine free cortisol collections every 2 to 3 weeks until an adequate clinical response is achieved.

    - The maximum recommended dosage is 1200 mg per day.
    - The dosage may be reduced to 150 mg once daily if needed for reasons of tolerability.
    - Once the maintenance dosage is achieved, cortisol levels should be monitored from at least two 24-hour urine free cortisol collections at least every 1 to 2 months or as indicated.
    - If 24-hour urine free cortisol levels remain above the upper normal limit after treatment with the maximum recommended dosage of 1200 mg per day, or the patient cannot tolerate treatment with Recorlev, discontinuing Recorlev should be considered and switching patient to another therapy.

- Xeris Biopharma plans to launch Recorlev for first quarter 2022. Recorlev will be available as a 150 mg tablet.