Center for Drug Evaluation and Research
Division of Diabetes Lipid Disorders and Obesity

BLA 208471/S-004; 208673/S-011, PMR fulfilment report and Transitional BLA labeling changes

BLA: 208471 /S-004 and 208673 -S-011
Name of Drug: Adlyxin (Lixisenatide) and Soliqua (insulin glargine and lixisenatide)
Formulation: injection- subcutaneous in a pre-filled device.
Indication: Treatment of Type 2 diabetes mellitus (T2DM)
Applicant: Sanofi.
Reviewer: Suchitra Balakrishnan, MD, Ph.D.
Team Leader: Patrick Archdeacon, MD

Background:
Adlyxin (lixisenatide) is a once-daily injectable glucagon-like peptide-1 (GLP-1) receptor agonist approved on July 27, 2016 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) with an initiation dose of 10 µg for 2 weeks and a maintenance dose of 20 µg. Soliqua (insulin glargine/lixisenatide). Soliqua (insulin glargine and lixisenatide fixed-ration combination) was approved for the treatment of T2DM on November 2016.

On November 25, 2020 Sanofi submitted supplements to BLA 208471 and 208673 proposing supplements to the lixisenatide labeling. This included changes to (b) (4) based on results from the study conducted to address PREA PMR 3102-1 (Conduct a repeat dose, pharmacokinetic/pharmacodynamics (PK/PD) study evaluating Adlyxin (lixisenatide) in patients with type 2 diabetes ages 10 to 17 years (inclusive) that are insufficiently controlled with metformin and/or basal insulin. Subjects will be randomized to lixisenatide or placebo. Titration will occur every 2 weeks increasing the dose from 5 mcg to 10 mcg then to 20 mcg). They also included transitional BLA labeling changes for the Package Insert, MedGuide, and Carton/Container labeling.

The sponsor had initially conducted a single dose, six-sequence cross-over PK/PD study (PKD11475) evaluating lixisenatide doses of 5 µg, 10 µg and placebo in 12 pediatric patients and adults as part of the original clinical program. The dose of 20 µg (maintenance dose in adults) was not evaluated in this study. Therefore, the sponsor proposed to conduct a repeated dose study (TDR14311) to further evaluate safety and PK in pediatric patients at a dose of 10µg and 20µg before conducting a safety and efficacy study with the expected therapeutic dose and this study was included in the product approval as PMR 3102-1[1]

[1] Pediatric Study Plan- Initial Agreement, IND 62724, May 29, 2015, Reference ID:3767817

Based on review of data available from clinical trials conducted in patients with pediatric T2DM, and the status update provided by the sponsor for TDR14311 on June 18, 2019, the Agency allowed the Sponsor to stop the study and to submit the final study report for review. In addition, the sponsor was also released from PMR 3102-2 (dedicated Efficacy and Safety study in pediatric patients with T2DM) on July 1, 2019, based on the rationale that lixisenatide would not offer meaningful benefit over liraglutide, which was newly approved for pediatric patients with T2DM. For Soliqua, a full waiver for all pediatric studies (age 0-17 years) was requested. This was granted based on the rationale that the insulin/lixisenatide fixed-ratio combination did not represent a foreseeable therapeutic benefit over the flexibility associated with the individual components or existing therapies in pediatric patients.

On July 17, 2020, Sanofi submitted the final report for study TDR14311. On July 24, 2020, the Agency requested submission of this final report as a labeling supplement by July 31, 2020, to the NDA in order to address PREA. On July 31, 2020 the sponsor submitted a deferral extension request for this study (b) (4).On September 1, 2020, based on PeRC recommendations, the Division granted a deferral extension of 60 days.

Submission Review- Study TDR 14311:
For details regarding the PK/PD and Pharmacometrics assessments, please refer to the Clinical Pharmacology review in DARRTs[2]

This was a randomized, double-blind, placebo-controlled, dose escalation study evaluating safety, pharmacokinetics (PK) and pharmacodynamics (PD) of lixisenatide in pediatric patients (13-17 years of age) with T2DM not adequately controlled with metformin and/or basal insulin. The treatment duration was 6 weeks and the dosing regimen included incremental (5 μg, 10 μg and 20 μg) sequential steps of 2 weeks for the lixisenatide dose escalation or matching placebo. The primary endpoint was assessment of the safety of 14-day repeated lixisenatide doses of 5 μg, 10 μg and 20 μg as compared to placebo in pediatric patients with T2DM.

Twenty-three patients were randomized and treated in the study: 5 received placebo and 18 received lixisenatide. 16 patients were female (69.6%) and 16 patients (69.6%) were white with mean baseline BMI of 34.9 kg/m^2. The baseline mean HbA1c values were similar between the placebo group (8.14%) and the lixisenatide group (8.16 %). One patient in the lixisenatide group did not complete the study treatment period due to poor compliance to the protocol. One patient in the lixisenatide group reported an SAE of viral gastroenteritis at the 20 μg dose level. No allergic reactions, pancreatitis or symptomatic hypoglycemia were reported in the study. The most common treatment-emergent adverse events were gastrointestinal events: nausea (1 patient [20%] in the placebo group reported 1 event and 2 patients [11.1%] in the lixisenatide group reported 8 events), and vomiting (no event in the placebo group and 2 patients [11.1%] in the lixisenatide group reported

[2] NDA 208471 Clinical Pharmacology review by Dr. Harisudhan Thanukrishnan and Hezhen Wang dated 6/14/2021, DARRTs ID 4811281

11 events). One patient in the lixisenatide group reported an TEAE of injection site pain at the 20 µg dose level.

Mean lixisenatide concentrations and inter-subject variability both tended to be higher for patients with positive anti-drug antibody (ADA) status. Mean lixisenatide concentrations generally increased with each increase in dose irrespective of ADA status. At 20 µg lixisenatide, the median t_{max} was 1.24 hours and 2.00 hours for ADA-negative and ADA-positive patients, respectively, while mean C_{max} and $AUC_{0-4.5}$ were approximately 6- to 9-fold higher for ADA-positive patients compared to ADA-negative patients.

Exploratory analyses were conducted for PD parameters. The estimated treatment difference (lixisenatide versus placebo) was -4.20 mmol/L for the change from baseline to Day 42 in fasting plasma glucose (FPG) and -31.18 mmol/L for the change from baseline to Day 42 in glucose $AUC_{0-4.5}$. A dose-dependent decrease in mean 1H-post-prandial glucose (PPG) and 2H-PPG was observed in the lixisenatide group, with the maximum decrease observed at the 20 µg lixisenatide dose. The estimated treatment difference (lixisenatide versus placebo) for the change from baseline to Day 42 was -3.71 mmol/L for 1H-PPG and -3.85 mmol/L for 2H-PPG

Reviewer's Assessment: There are no new safety concerns for lixisenatide identified in this study. The most common TEAEs were gastrointestinal events and overall, safety findings were consistent with the established safety profile of lixisenatide in adults.

Clinical Recommendation

The sponsor proposed the following changes to the PI:

(b) (4)

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(b) (4)

I do not recommend any changes to the PI given the limited study duration and sample size to adequately inform pediatric safety. In the absence of adequate efficacy or safety information to support pediatric use, it is not useful to inform prescribers (b) (4) . The sponsor has fulfilled the PMR.

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/s/

SUCHITRA M BALAKRISHNAN
06/29/2021 01:51:15 PM

PATRICK ARCHDEACON
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