4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2021-N-0208]

Proposal to Refuse to Approve a New Drug Application for Sotagliflozin Oral Tablets, 200 Milligrams and 400 Milligrams; Opportunity for a Hearing

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Director of the Center for Drug Evaluation and Research (Center Director) of the Food and Drug Administration (FDA or Agency) is proposing to refuse to approve a new drug application (NDA) submitted by Lexicon Pharmaceuticals, Inc. (Lexicon) for sotagliflozin oral tablets, 200 milligrams (mg) and 400 mg, in its present form. This notice summarizes the grounds for the Center Director's proposal and offers Lexicon an opportunity to request a hearing on the matter.

DATES: Submit either electronic or written requests for a hearing by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]; submit data, information, and analyses in support of the hearing and any other comments by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit hearing requests, documents in support of the hearing, and any other comments as follows. Please note that late, untimely filed requests and documents will not be considered. Electronic requests for a hearing must be submitted on or before [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]; electronic documents in support of the hearing and any other comments must be submitted on or before [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The https://www.regulations.gov electronic filing system will accept hearing requests until 11:59 p.m. Eastern Time at the end of [INSERT DATE 30 DAYS AFTER DATE

OF PUBLICATION IN THE *FEDERAL REGISTER*], and will accept documents in support of the hearing and any other comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Documents received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before these dates.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2021-N-0208 for "Proposal to Refuse to Approve a New Drug Application for Sotagliflozin Oral Tablets, 200 Milligrams and 400 Milligrams; Opportunity for a Hearing." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Kevin Fain, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 6419, Silver Spring, MD 20993, 301-796-5842, Kevin.Fain@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Proposal to Refuse to Approve NDA 210934

Sanofi-aventis U.S. LLC (Sanofi), Lexicon's predecessor-in-interest, submitted NDA 210934 for sotagliflozin oral tablets in 200 and 400 mg strengths on March 22, 2018, pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b)(1)). Sanofi proposed that sotagliflozin tablets be indicated as an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus (T1DM).

On March 22, 2019, the Office of Drug Evaluation II (ODE II) in the Office of New Drugs (OND) in FDA's Center for Drug Evaluation and Research (CDER) issued a complete response letter to Sanofi under § 314.110(a) (21 CFR 314.110(a)) stating that NDA 210934 could not be approved in its present form, describing the specific deficiencies, and, where possible, recommending ways that Sanofi might remedy these deficiencies. The application in its present form is not approvable because the data submitted do not show that the drug is safe under the proposed conditions of use. The deficiencies, which are summarized below, include the following:

(1) The data demonstrated that the addition of sotagliflozin to insulin is associated with an increased risk of diabetic ketoacidosis (DKA), a serious and often life-threatening consequence of insulin insufficiency.

a. In particular, the submitted clinical trial data showed a nearly 8-fold excess risk of DKA associated with sotagliflozin. Based on an FDA analysis of all three trials, an overall estimated hazard ratio (95 percent confidence interval) for DKA associated with sotagliflozin was 7.9 (3.2, 19.9).

b. The majority of these cases required hospitalization and treatment in the intensive care unit, which underscores the seriousness of this risk.

c. Although DKA is an inherent risk in T1DM, the magnitude of excess risk, severity of the cases, and characteristics of DKA (e.g., euglycemic DKA) associated with sotagliflozin treatment raised significant safety concerns, particularly because they occurred in a clinical trial setting, where patients are carefully selected for enrollment and receive more intensive safety monitoring than in clinical practice.

d. Time-to-event analyses of the clinical trial data showed earlier development of DKA in sotagliflozin-treated patients than in patients assigned to placebo, without evidence that the risk stopped increasing over time.

e. The clinical trial data did not identify a patient group at lower risk of DKA, but instead showed the DKA risk was associated with sotagliflozin regardless of sex, age, duration of diabetes, method of insulin delivery, or body mass index.

f. Overall, risk mitigation strategies used in the clinical trials were not sufficient to address the excess DKA risk observed in the clinical trials, as evidenced by the nearly 8-fold excess risk.

g. Data analyses assessing the impact of risk mitigation strategies implemented during the course of the trials were inadequate to provide reassurance that these strategies would be successful in reducing DKA risk post-approval.

(2) The data demonstrated the significant DKA risk resulting from the addition of sotagliflozin to insulin was not justified by the drug's modest clinical benefits.

a. The data showed that sotagliflozin reduced HbA1c, a validated surrogate endpoint for clinical benefits expected due to improved glycemic control in the treatment of diabetes mellitus, including T1DM. However, the effect on HbA1c in the sotagliflozin clinical trials was modest.

b. In the three pivotal trials, addition of sotagliflozin to insulin resulted in statistically significant reductions in HbA1c at Week 24. The treatment difference relative to placebo was approximately -0.3 percent with sotagliflozin 200 mg and -0.4 percent with sotagliflozin 400 mg.

c. In the extension of two pivotal trials to 52 weeks, the effect of sotagliflozin on HbA1c was smaller (-0.23 percent and -0.33 percent HbA1c reductions with the 200 mg and 400 mg doses, respectively), and there are no longer term data to evaluate persistence of effect. The decrease in treatment effect from Week 24 to Week 52 is clinically relevant, as the major benefits to consider with sotagliflozin treatment are related to improved long-term glycemic control reducing the risk of microvascular complications.

d. The improved HbA1c associated with sotagliflozin was not accompanied by an increased rate of hypoglycemia (defined as glucose ≤ 55 mg/dL) in the clinical trials, an adverse clinical effect that occurs with insulin therapy; however, this observation does not outweigh the increased rate of DKA. The data did not show sotagliflozin was associated with an overall decrease in the rate of severe hypoglycemia.

e. In addition to improved glycemic control, other clinical benefits associated with sotagliflozin, small reductions in body weight and blood pressure, were not sufficient to outweigh the serious risk of DKA.

f. The data did not show that sotagliflozin was associated with an effect on glycemic variability and time-in-range that provided benefits distinct from reduced HbA1c.

g. Patient reported outcome measures were not adequate in directly reflecting important aspects of the patient's experience with T1DM and how sotagliflozin treatment affected these important aspects.

The complete response letter stated that Sanofi is required either to resubmit the application, fully addressing all deficiencies listed in the letter, or take other actions available under § 314.110 (i.e., withdraw the application or request an opportunity for a hearing). Applicable regulations, including 21 CFR 10.75, also provide a mechanism for applicants to obtain formal review of one or more decisions reflected in a complete response letter (see FDA's guidance for industry and review staff "Formal Dispute Resolution: Sponsor Appeals Above the Division Level" (May 2019)).[1]

Sanofi submitted a formal dispute resolution request (FDRR) on September 3, 2019, concerning the complete response letter issued by ODE II. Peter Stein, Director of CDER's OND, denied the FDRR by correspondence dated November 29, 2019, based on his determination that the drug's immediate, sustained, and substantial increase in DKA risk outweighed the modest benefit on glycemic control and any potential additional benefits (e.g., reductions in body weight and blood pressure). Sanofi submitted another FDRR on December 19, 2019, for review of the OND denial. On January 30, 2020, FDA was notified that NDA 210934 had been transferred from Sanofi to Lexicon. Robert Temple, Deputy Director for Clinical Science, CDER, denied the second FDRR on behalf of CDER by correspondence dated March 11, 2020, based on his determination that the drug's DKA risk outweighed its benefits, reaffirming the reasoning in OND's denial of the prior FDRR.

On November 10, 2020, Lexicon submitted a request for an opportunity for a hearing under § 314.110(b)(3) on whether there are grounds under section 505(d) of the FD&C Act for denying approval of NDA 210934.

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[1] Available at https://www.fda.gov/media/126910/download. FDA updates guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs.

II. Notice of Opportunity for a Hearing

For the reasons stated above and as explained in further detail in the complete response letter and the November 29, 2019, and March 11, 2020, FDRR denials, notice is given to Lexicon and all other interested persons that the Center Director proposes to issue an order refusing to approve NDA 210934 on the grounds that the application fails to meet the criteria for approval under section 505(d)(2) of the FD&C Act because data submitted in the application do not show that the product would be safe under the proposed conditions of use.[2]

Lexicon may request a hearing before the Commissioner of Food and Drugs (the Commissioner) on the Center Director's proposal to refuse to approve NDA 210934. If Lexicon decides to seek a hearing, it must file: (1) a written notice of participation and request for a hearing (see the DATES section) and (2) the studies, data, information, and analyses relied upon to justify a hearing (see the DATES section), as specified in § 314.200 (21 CFR 314.200).

As stated in § 314.200(g), a request for a hearing may not rest upon allegations or denials, but must present specific facts showing that there is a genuine and substantial issue of fact that requires a hearing to resolve. We note in this regard that because CDER proposes to refuse to approve NDA 210934 based on the multiple deficiencies summarized above, any hearing request from Lexicon must address all of those deficiencies. Failure to request a hearing within the time provided and in the manner required by § 314.200 constitutes a waiver of the opportunity to request a hearing. If a hearing request is not properly submitted, FDA will issue a notice refusing to approve NDA 210934.

The Commissioner will grant a hearing if there exists a genuine and substantial issue of fact or if the Commissioner concludes that a hearing would otherwise be in the public interest

[2] Section 505(d)(2) of the FD&C Act provides that FDA shall refuse to approve an NDA if "the results of … tests show that such drug is unsafe for use under [the] conditions [prescribed, recommended, or suggested in the proposed labeling] or do not show that such drug is safe for use under such conditions[.]" For the reasons explained in this notice, CDER has concluded that the data and information submitted in the NDA do not show that the drug is safe for use under the proposed conditions of use.

(§ 314.200(g)(6)). If a hearing is granted, it will be conducted according to the procedures provided in 21 CFR parts 10 through 16 (21 CFR 314.201).

Paper submissions under this notice of opportunity for a hearing should be filed in one copy. Except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, submissions may be seen in the Dockets Management Staff Office between 9 a.m. and 4 p.m., Monday through Friday, and on the internet at https://www.regulations.gov. This notice is issued under section 505(c)(1)(B) of the FD&C Act and §§ 314.110(b)(3) and 314.200.

Dated: February 25, 2021.

Patrizia Cavazzoni,

Acting Director,

Center for Drug Evaluation and Research.

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