4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2021-N-0874]

Proposal To Refuse To Approve a New Drug Application for ITCA 650 (Exenatide in DUROS Device); 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) at the Food and Drug Administration (FDA or Agency) is proposing to refuse to approve a new drug application (NDA) submitted by Intarcia Therapeutics, Inc. (Intarcia), for ITCA 650 (exenatide in DUROS device) in its present form. This notice summarizes the grounds for the Center Director's proposal and offers Intarcia 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-0874 for "Proposal To Refuse To Approve a New Drug Application for ITCA 650 (Exenatide in DUROS Device); 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 209053

Intarcia submitted NDA 209053 for ITCA 650 (exenatide in DUROS device), a drug-device combination product intended to deliver the active ingredient exenatide, a GLP-1 receptor agonist (RA), on November 21, 2016, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b)(1)). Intarcia proposed that ITCA 650 be indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

On September 21, 2017, the former Division of Metabolism and Endocrinology Products (DMEP), Office of Drug Evaluation II (now the Division of Diabetes, Lipid Disorders, and Obesity, within the Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)) in the Office of New Drugs (OND) in FDA's Center for Drug Evaluation and Research (CDER), issued a complete response letter to Intarcia under § 314.110(a) (21 CFR 314.110(a)) stating that NDA 209053 could not be approved in its present form, describing the specific deficiencies and, where possible, recommending ways that Intarcia might remedy these deficiencies. On September 9, 2019, Intarcia resubmitted the NDA under section 505(b)(1) of the FD&C Act. On March 9, 2020, the former DMEP issued a second complete response letter stating that NDA 209053 could not be approved in its present form, describing the specific

deficiencies and, where possible, recommending ways that Intarcia might remedy these deficiencies. These deficiencies, which are summarized below, include the following:

1. The clinical trial data demonstrated that ITCA 650 causes acute kidney injury (AKI).
    a. A signal of AKI was evident in the pivotal phase 3 trials of the ITCA 650 clinical development program. A standardized Medical Dictionary for Regulatory Activities query for acute renal failure identified reports of AKI serious adverse events in 14 subjects (0.6 percent) who received ITCA 650 versus 4 subjects (0.2 percent) who received placebo.
    b. The magnitude of the AKI risk was greater for ITCA 650 than for the marketed exenatide products or for other members of the GLP-1 RA class. Although other drugs in the GLP-1 RA class have a risk of AKI, this information is based on spontaneous postmarketing adverse event reports. The risk of AKI was not detected in the clinical trials that supported the approval of these drugs. In contrast, the risk of AKI was clearly identified in the ITCA 650 clinical trial data. This AKI risk for ITCA 650, compared to other members of the GLP-1 RA class, is particularly concerning because it was identified from these adequate and well-controlled clinical trials, which constitute stronger evidence for assessing a drug's safety than spontaneous postmarketing adverse event reports.
    c. AKI events experienced by participants who received ITCA 650 sometimes resulted in prolonged hospitalization; complications observed in association with AKI events included dialysis and death.
    d. A majority of the serious AKI events in participants randomized to ITCA 650 appeared to be associated with vomiting, diarrhea, and dehydration, which are known adverse reactions associated with exenatide therapy, supporting a causal relationship between ITCA 650 and AKI.
    e. Intarcia's proposed risk mitigation measures were inadequate and sufficient risk mitigation approaches could not be identified for the AKI risk identified in the clinical

trial data, particularly because serious AKI events occurred in participants who received ITCA 650 who did not have known risk factors (moderate to severe renal impairment or use of concomitant medications that increase the risk of AKI) and serious AKI events were observed with use of both the nominal initial/reduced dose ITCA 650, 20 micrograms (mcg)/day, and the nominal maintenance dose ITCA 650, 60 mcg/day.

2. The cardiovascular risk assessment failed to provide sufficient assurance that ITCA 650 is not associated with excess cardiovascular (CV) risk. Rather, the clinical trial data suggested that ITCA 650 may be associated with an increased risk for major adverse cardiovascular events (MACE), defined as myocardial infarction, nonfatal stroke, and cardiovascular death.

a. A prespecified meta-analysis incorporated the data from clinical trials CLP-103, CLP-105, and CLP-107, and included 181 MACE and unstable angina (UA) events. An unfavorable point estimate of 1.12 was observed [hazard ratio (HR) for MACE + UA; 1.12 (95 percent confidence interval (CI): 0.83, 1.51)].

b. Furthermore, estimates of CV risk from the meta-analysis were notably higher and nominally statistically significant in the subgroup of participants 65 years of age or older [HR for MACE + UA; 1.67 (95 percent CI: 1.02, 2.71)]. Subgroup analyses also suggested an interaction between CV risk and baseline renal function, where the HR estimates trended higher with worse renal function.

c. The CV risk analyses from trial CLP-107 augmented the concern that the drug is associated with a higher risk for MACE. CLP-107 was a randomized, double-blind, placebo-controlled cardiovascular outcomes trial (CVOT) conducted in a patient population at high risk of MACE. CLP-107 contributed 174 of the 181 total MACE + UA events observed in the CV risk meta-analysis. In CLP-107, the assessment of product-related CV risk yielded an HR for MACE of 1.24 (95 percent CI: 0.90, 1.70).

d. This CV risk resulting from ITCA 650 use is particularly concerning when compared to the beneficial effect of other drugs in this class on CV outcomes. In contrast to the

unfavorable CVOT results for ITCA 650, some other GLP-1 RA products carry indications for MACE risk reduction in patients with T2DM based on favorable results of CVOTs. The MACE HR observed in a CVOT conducted for another formulation of exenatide was 0.91 (95 percent CI: 0.83, 1.0). The lower bound of the CLP-107 confidence interval (0.90) nearly excludes the point estimate for MACE risk observed with this other product (0.91), suggesting a true difference in MACE risk between the products.

3. The data provided to validate the limits of the in vitro dose delivery specifications did not support the safe and effective use of the device constituent of ITCA 650.

   a. The device design validation data did not support the proposed daily, weekly, and biweekly in vitro drug-release specifications as appropriate for the intended use.

   b. The in vitro device performance data demonstrated inconsistent day-to-day drug delivery and did not support that weekly and biweekly in vitro drug-release testing is adequate to ensure controlled in vivo drug release by the device constituent of ITCA 650.

4. The data provided, inclusive of delivery performance data and failure analyses, did not demonstrate adequate device reliability associated with in vitro dose delivery to support safety and effectiveness for the intended use.

   a. Variability in the daily in vitro drug-release data did not support the use of weekly and biweekly averages to calculate device failure rates.

   b. The failure rate data was inadequate to support the safety and effectiveness of the device constituent of ITCA 650.

   c. The sponsor provided inadequate mitigation strategies to reduce device failures.

5. The information provided, including the following, was inadequate in support of sterility assurance for ITCA 650:

   a. The container-closure integrity test data provided to support integrity of a container-closure system used for sterile intermediate storage of sterile components of ITCA 650.

b. Information regarding the product-contact filling equipment used for commercial manufacturing of ITCA 650.

c. Information provided to support the routine depyrogenation process for components of the primary container-closure system for ITCA 650.

d. The method suitability data provided to support the proposed routine endotoxins test method with ITCA 650.

6. An FDA inspection of the Intarcia manufacturing facility identified deficiencies with the manufacturing practices for ITCA 650 that were not adequately addressed.

a. Controls were inadequate to ensure empty devices would not be included in the final release of ITCA 650.

b. Qualification of the filling line with an original or new manifold was not performed.

c. The results and reports of the process simulation test, used to demonstrate the effectiveness of preventing microbiological contamination of ITCA 650, were not provided.

The complete response letters issued on September 21, 2017, and March 9, 2020, both stated that to address the clinical deficiencies, Intarcia should address all the specific device and product quality-related deficiencies and provide additional clinical data that adequately address the clinical risks and establish that ITCA 650 is safe and effective for the intended use. The complete response letters stated that Intarcia 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" (November 2017)).[1]

Intarcia submitted a formal dispute resolution request (FDRR) on June 5, 2020, concerning the complete response letter issued on March 9, 2020, by the former DMEP. Ellis Unger, Director of OND's OCHEN, denied the FDRR by correspondence dated July 30, 2020, based on his determination that the drug's unexpected numeric imbalance in cases of serious AKI, the MACE observed in the CVOT, and device-related deficiencies regarding exenatide release rates over the life of the product outweighed the benefit in reductions in Hemoglobin A1c. Intarcia submitted another FDRR on August 14, 2020, for review of the OCHEN denial. Robert Temple, Senior Advisor to OND, denied the second FDRR on behalf of OND by correspondence dated October 30, 2020, based on his determination that the drug's clinical risks, device-related deficiencies, and product quality and manufacturing deficiencies had not been satisfactorily resolved, reaffirming the reasoning in OCHEN's denial of the prior FDRR. Intarcia submitted a third FDRR on November 27, 2020, for review of the OND denial and requested an advisory committee meeting. Douglas Throckmorton, Deputy Director for Regulatory Programs, CDER, denied the third FDRR and the request for an advisory committee meeting on behalf of CDER by correspondence dated February 12, 2021, based on his determination that the drug's clinical risks and device-related deficiencies had not been satisfactorily resolved, reaffirming the reasoning in OND's denial of the prior FDRR, and determined that an advisory committee would be premature because of these unresolved safety issues.

On March 16, 2021, Intarcia 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 209053.

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[1] Available at https://www.fda.gov/media/126910/download. FDA updates guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

II. Notice of Opportunity for a Hearing

For the reasons stated above and as explained in further detail in the March 9, 2020, complete response letter and the February 12, 2021, November 27, 2020, and July 30, 2020, FDRR denials, notice is given to Intarcia and all other interested persons that the Center Director proposes to issue an order refusing to approve NDA 209053 on the grounds that the application fails to meet the criteria for approval under section 505(d) of the FD&C Act, including the following: (1) data submitted in the application do not show that the product would be safe under the proposed conditions of use (section 505(d)(2) of the FD&C Act) and (2) the methods used in, and the facilities and controls used for, the manufacture, processing, or packing of the product are not shown to be adequate to preserve its identity, strength, quality, and purity (section 505(d)(3) of the FD&C Act).

Intarcia may request a hearing before the Commissioner of Food and Drugs (the Commissioner) on the Center Director's proposal to refuse to approve NDA 209053. If Intarcia 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 mere 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 209053 based on the multiple deficiencies summarized above, any hearing request from Intarcia 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 209053.

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

(§ 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 those submitted as "Confidential Submissions" (see "Written/Paper Submissions" and "Instructions"). 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: August 27, 2021.

Jacqueline Corrigan-Curay,

Principal Deputy Center Director,

Center for Drug Evaluation and Research.

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