CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213224Orig1s000

OTHER ACTION LETTERS

NDA 213224

COMPLETE RESPONSE

Sun Pharmaceutical Industries, Inc.
U.S. Agent for Sun Pharmaceutical Industries Limited
Attention: Neha Rana
Director, Drug Safety
2 Independence Way
Princeton, NJ 08540

Dear Ms. Rana:

Please refer to your new drug application (NDA) dated and received March 28, 2019, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Bynfezia Pen (octreotide acetate) injection, 2.5 mg/mL.

We also refer to FDA's action letter dated January 28, 2020, informing you that this application was approved. Further, we refer to our May 19, 2021, letter informing you that we are rescinding our January 28, 2020, approval of NDA 213244.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

During a recent inspection of the (b) (4) (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies, and verification by the FDA, is required before this application may be approved.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Jennifer Johnson, Regulatory Health Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Theresa E. Kehoe, M.D.
Director
Division of General Endocrinology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

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/s/

THERESA E KEHOE
05/19/2021 02:42:02 PM

NDA 213224

RESCIND APPROVAL

Sun Pharmaceutical Industries, Inc.
U.S. Agent for Sun Pharmaceutical Industries Limited
Attention: Neha Rana
Director, Drug Safety
2 Independence Way
Princeton, NJ 08540

Dear Ms. Rana:

Please refer to your new drug application (NDA) dated and received March 28, 2019, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Bynfezia Pen (octreotide acetate) injection, 2.5 mg/mL.

We also refer to our letter dated January 28, 2020, informing you that this application was approved. We further refer to our letter dated February 4, 2021, which documented the information communicated to you in our January 8, 2021, teleconference, and to your response submitted on February 5, 2021.

As detailed in our February 4, 2021, letter, we had preliminarily determined that FDA erred in approving NDA 213224 on January 28, 2020, because the information available to the Agency at the time indicated that the compliance status of the (b) (4) (b) (4) was not acceptable to support approval.

In the February 4, 2021, letter, we also confirmed the opportunity, provided to you in our January 8 teleconference, to submit in writing, by February 8, 2021, your position on whether the compliance status of the facility identified was acceptable on the date of approval. In your response submitted on February 5, 2021, you outlined what corrective actions you have taken at the (b) (4) since the (b) (4) inspection of the facility by FDA; however, you did not demonstrate that the facility had an acceptable CGMP compliance status on the date of approval. Your submission also included a request that FDA exercise regulatory discretion to allow your product to continue to be marketed based on your assertion that the Bynfezia Pen "fulfills a key unmet need" in the intended population.

As stated in our February 4, 2021, letter, in order to obtain approval, an NDA applicant must demonstrate that its drug will be manufactured in compliance with current good manufacturing practices (CGMP). Section 505(b)(1)(D) of the FD&C Act states the application shall include "a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug." Under

Section 505(d)(3), FDA must refuse to approve an application if "the methods used in, and the facilities and controls used for the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity."[1] If an NDA has not demonstrated that the facilities used for the manufacture, processing and packing of a drug are adequate to assure and preserve its identity, strength, quality, and purity, the NDA generally should not be recommended for approval.

We do not agree with your assessment that Bynfezia Pen "fulfills an unmet medical need" in the intended population. While we agree that Bynfezia Pen is used to treat or prevent a serious disease or medical condition, there are alternative drug products (e.g., other short or long acting octreotide products) that are approved and currently marketed in US for the same indication(s). The efficacy and safety of these products are similar in the intended populations. There is no information available to date (from well-controlled trial(s) or published literature) that Bynfezia Pen offers improved compliance/adherence as one of the potential benefits.

FDA is correcting its error and rescinding the approval letter issued for NDA 213224 on January 28, 2020. Your NDA is now in a pending status, and a "complete response" letter will be issued this same day consistent with this letter.

We remind you that this drug product may not be legally marketed or promoted until you have been notified in writing that this application is approved.

As described in our February 4, 2021, letter, we have administratively converted all approved supplements 001, 002, 003, and 004, to Chemistry, Manufacturing and Controls (CMC) amendments to the original application (NDA 213224).

We regret any inconvenience our error may cause you.

If you have any questions, call Jennifer Johnson, Regulatory Health Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Theresa E. Kehoe, M.D.
Director
Division of General Endocrinology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

[1] FDA's regulations also reflect these requirements. See 21 CFR 314.125(b)(1).

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/s/

THERESA E KEHOE
05/19/2021 08:10:56 AM

NDA 213224

NDA APPROVAL

Sun Pharmaceutical Industries Limited
C/o Sun Pharmaceutical Industries, Inc.
Attention: Mr. Ronak Patel
Authorized US agent
2 Independence Way
Princeton, NJ 08540

Dear Mr. Patel:

Please refer to your new drug application (NDA) dated and received March 28, 2019, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Bynfezia pen (octreotide acetate) injection.

This new drug application provides for the use of Bynfezia pen (octreotide acetate) injection for:

- Reduction of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) [somatomedin C] in adult patients with acromegaly who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation, and bromocriptine mesylate at maximally tolerated doses;
- Treatment of severe diarrhea/flushing episodes associated with metastatic carcinoid tumors in adult patients; and
- Treatment of profuse watery diarrhea associated with vasoactive intestinal peptide tumors (VIPomas) in adult patients.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

We note that your January 28, 2020, submission includes final printed labeling (FPL) for your: Prescribing Information and Instructions for Use. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at

FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (Prescribing Information and Instructions for Use) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the: enclosed carton and container labeling submitted on January 28, 2020, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 213224**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Meghna M. Jairath, Pharm.D., Regulatory Project Manager, at (301) 796-4267.

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, M.D.
Division Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Instructions for Use
- Carton and Container Labeling

26 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 4552089

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/s/

LISA B YANOFF
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