CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761184Orig1s000

OTHER ACTION LETTERS

BLA 761184

COMPLETE RESPONSE

Pfizer Ireland Pharmaceuticals
C/O Pfizer Inc.
Attention: Gurunandan Mavinkurve, MS, RPh, US Agent
Director, Global Regulator Affairs
235 E. 42nd Street (219/9/81)
New York, NY 10017

Dear Mr. Mavinkurve:

Please refer to your biologic license application (BLA) dated and received October 22, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for MOD-4023 injection.

We acknowledge receipt of your major amendment dated September 15, 2021, which extended the goal date by three months.

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.

Clinical/Immunology:

(1) In Trial CP-4-006[1], annualized height velocity (AHV) at 12 months was noninferior to Genotropin, although not superior. However, there was a high rate of anti-drug antibody formation (ADA) due to MOD-4023 exposure in clinical studies versus the active comparator (Genotropin): In Trial CP-4-006, 77% of MOD-4023-treated subjects were ADA-positive compared to 16% of Genotropin-treated subjects. 76% of ADA-positive subjects had persistent (greater than 6 months) antibodies in MOD-4023 group versus 5% of ADA-positive subjects in the Genotropin group. Five subjects in Trial CP-4-006 developed neutralizing antibodies, and one of those subjects had a concerning reduction in AHV from 11.8 cm/year (at Month 12) to 3.0 cm/year (at Month 18). There are insufficient follow up data to determine whether the reduction in AHV in this patient was caused by immunogenicity, and we consider attenuation of effectiveness due to immunogenicity to be a potential risk at this time. Because of the homology in

[1] A Phase 3, Open-Label, Randomized, Multicenter, 12 Months, Efficacy and Safety Study of Weekly MOD-4023 Compared to daily Genotropin Therapy in Pre-Pubertal Children with Growth Hormone Deficiency.

amino acid sequence among MOD-4023, native growth hormone, and other recombinant human growth hormone (hGH) products, there is concern that antibodies that are cross reactive to other growth hormone products could develop. If persistent these could potentially result in non-responsiveness to other hGH replacement therapy. Given the availability of other hGH replacement therapies that have similar efficacy and that do not carry this risk, MOD-4023 does not appear to address any identifiable unmet need that would justify its approval in light of this uncertainty, and we have concluded that the benefit–risk profile for MOD-4023 is unfavorable at this time.

Provide reassurance that the anti-drug antibody (ADA) formation caused by MOD-4023 is not expected to have an impact on long-term growth achieved with MOD-4023 and does not interfere with other hGH formulations. At a minimum, provide data to show that ADA (including neutralizing antibodies) meaningfully decrease or resolve with MOD-4023 discontinuation and/or changing patients to other approved hGH formulations. If neutralizing antibodies do not resolve, provide data that long-term growth is not impacted. Provide mitigation strategies to address the potential impact of neutralizing antibodies.

Product Quality

(b) (4)

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[2] and Pregnancy and Lactation Labeling Final Rule[3] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

[2] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[3] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated January 27, 2021, which addresses the proposed proprietary name, Ngenla. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

FACILITY INSPECTIONS

Inspections of the Pfizer Ireland Pharmaceuticals, Dublin, Ireland (FEI: 3004145594) and Pfizer Manufacturing Belgium NV (FEI: 1000654629) facilities are required before this application can be approved as the FDA must assess the ability of those facilities to conduct the listed manufacturing operations in compliance with CGMP. Due to U.S. Government and/or Agency-wide restrictions on travel, we were unable to complete these inspections during the current review cycle for your application. You may respond to the other deficiencies in this Complete Response letter while the travel restrictions remain in effect. However, even if all other deficiencies are addressed, the application cannot be approved until the required FDA inspections are completed and the findings are assessed with regard to your application.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies/trials of the product 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 product. Include an updated estimate of use for product marketed in other countries.

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

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

Product Quality

(b) (4)

2 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

(9) The MOD-4023 DP (prefilled pen) shipping qualification included shipping container qualification and simulated shipping studies. Your MOD-4023 DP shipping qualification did not include real-time shipping studies designed to qualify the actual shipping conditions of commercial DP. To verify that product quality is not impacted by worse-case shipping conditions, provide quality assessment of commercial product in the intended primary and, if applicable, secondary container, prior to and after shipment. Stability-indicating critical quality attributes (CQAs) should be assessed in the commercial shipping studies. In addition, temperature monitoring data recorded continuously throughout shipping from thermal couple probes placed inside and outside of the shipping container should be provided. In the absence of commercial shipping data, a shipping qualification protocol may be submitted to conduct concurrent shipping qualification.

(10) Include in Sections 3.2.S.2.2 and/or 3.2.S.2.4 your definitions for regulatory terminologies used for manufacturing controls, e.g., definitions for CMA, critical and non-critical parameter (CPP and non-CPP), as these are not clearly stated in the BLA in Sections 3.2.S.2.2 and/or 3.2.S.2.4.

(11) (b) (4) (b) (4) Provide rationale (b) (4) and clarify how the acceptable ranges were defined for the MOD-4023 commercial manufacturing process and provide supportive data.

(12) Provide updated data from the following ongoing studies:

a. (b) (4)

b. [redacted] (b) (4)

c. The on-going MOD-4023 DS, DPS, and DP (prefilled pen) stability studies (in Sections 3.2.S.7 and 3.2.P.8).

(13) Provide any updated batch analysis data for DS and DPS and DP (prefilled pen) as applicable for batches released since your original BLA submission.

Microbiology

(14) Qualify the bioburden test method [redacted] (b) (4) Method qualification must be carried out using material from 3 separate batches.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b). 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 601.3(c). 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 Sejal Kiani, Regulatory Project Manager, at (301) 796-6445.

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, MD
Deputy Director
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LISA B YANOFF
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