CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216490Orig1s000

OTHER ACTION LETTERS

NDA 216490

COMPLETE RESPONSE

Ascendis Pharma Bone Diseases A/S
c/o Ascendis Pharma, Inc.
Attention: Stephanie Chan, MS
Director, Regulatory Affairs
1000 Page Mill Road
Palo Alto, CA 94304

Dear Ms. Chan:

Please refer to your new drug application (NDA) dated and received August 31, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for palopegteriparatide injection.

We also acknowledge receipt of your amendment dated April 6, 2023, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

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.

PRODUCT QUALITY / DEVICE

Your application has unresolved deficiencies concerning:

- Significant variability of the delivered dose, a product critical quality attribute
- Lack of adequate data to support the feasibility of your revised assay and delivered volume specification with respect to limiting the variability of the deliverable dose to (b) (4) µg at each dose setting
- An anticipated high-level of batch failure with your proposed specifications, indicative of inadequate formulation and device design, and
- Inadequate stability data to support shelf-life determination of your product per the revised specification for the delivered dose.

Below, we discuss these deficiencies in greater detail.

You have revised your delivered dose specifications during the NDA review and are proposing tightening your assay (active pharmaceutical ingredient) acceptance limits to (b) (4)% (at shelf) and pen delivered volume limits to (b) (4) µL at every dose setting. Based on these specifications, the amount of delivered drug can vary by as much as (b) (4) µg (for the 6 µg dose) up to (b) (4) µg (for the (b) (4) µg dose) between pens of two different lots, and the amount of delivered drug can vary by as much as (b) (4) µg (for the 6 µg dose) up to (b) (4) µg (for the (b) (4) µg dose) for a single pen. This large degree of variability could lead to dosing inaccuracy and dose overlapping (i.e., where the actual dose delivered at one dose level is the same as the actual dose that could be delivered at a lower dose level or higher dose level). We are concerned this can cause erratic dosing leading to efficacy and safety concerns (episodic hypocalcemia when a lower than intended amount of drug is administered and episodic hypercalcemia when a higher than intended amount of drug is administered). You have not provided data to assure that the anticipated dose variability and dose overlapping will not impact patients adversely.

You acknowledge "that the revised dose accuracy and content acceptance criteria are insufficient for achieving a net delivered daily dose variability of less than (b) (4)µg (corresponding to (b) (4) µg from the target dose) and eliminating the risk of dose overlap calculated from release specifications". Therefore, you propose to apply a new test/control in the specification to limit the variability of the deliverable dose to (b) (4) µg at each dose setting (so that the delivered drug amount does not vary by more than (b) (4)µg). You propose to reject batches that do not meet this (b) (4) µg criterion even if they meet the acceptance limits of (b) (4)% (at shelf) and pen delivered volume limits of (b) (4) µL. However, this approach does not appear to be viable because of the extent of variability possible with the assay and volume specifications (for example, dosing variability could be as high as ~(b) (4)). You have not provided design verification testing data confirming that the (b) (4) µg dose delivered specification can be consistently achieved by your device per your quality control strategy. In fact, per your delivered dose specification criteria, approximately one-half of your developmental batches (including some registration stability batches) failed with respect to either content/assay and/or deliverable volume. We have no assurance that the released batches will reliably and consistently meet the delivered dose specification for every pen at every dose setting. In addition, because there are no stability data with respect to the delivered dose, it is unclear if acceptable batches that are released will meet the shelf-life criteria. Note that Good Manufacturing Practices regulations require that the manufacturing processes be designed and controlled to assure that the finished drug product meets predetermined quality requirements and does so consistently and reliably.

(b) (4) your submitted data show that there was very minimal dosing variability in the tested batches used in the phase 3 trial compared to the expected variability that can occur with your commercial product based on your

proposed specification range. In addition (b) (4) Therefore, based on the available batch data from the phase 3 trial we cannot conclude that patients in the trial were exposed to the same extent of dose variability as would occur if your product is marketed with your proposed specifications.

We considered whether your quantitative systems pharmacology (QSP) modeling could justify the acceptability of the anticipated dosing variability. However, the QSP model was used as a supportive tool and was not intended to be used for decision making. In addition, palopegteriparatide is proposed to be titrated up to (b) (4) µg once daily, which is (b) (4) the doses used to develop and validate the QSP modeling for patients. Because it is unclear that extrapolation of the pharmacokinetic or pharmacodynamic response for higher doses is scientifically justified, we do not agree that the (b) (4) .

You note that palopegteriparatide has a relatively long terminal elimination half-life (60 hours) and that dosing variability could potentially be "evened out" by the amount of palopegteriparatide accumulated if random dose variations occur. However, this would not be the case in certain worst-case scenarios, such as if there is consecutive administration of the lower boundary of a dose setting with one pen, followed by consecutive administration of the higher boundary of the same dose setting with another pen.

(b) (4) Note that a drug device combination product needs to meet product quality standards, including viable specifications for critical quality attributes, and control strategy for manufacturability, reproducibility of delivered dose (dose accuracy) and device design verification data for approval from a quality/device perspective (b) (4) .

PATH FORWARD

To resolve the identified deficiencies, we recommend the following:

(b) (4)

(b) (4)

Alternatively, you could address the above-listed CMC deficiencies and provide data verifying that your existing device is capable of consistently meeting your proposed (b) (4) µg dose delivered specification at release and stability per your revised quality control strategy.

Regardless of the approach chosen, you will also need to provide a statistical control plan for lot release testing of device Essential Performance Requirements.

PRESCRIBING INFORMATION

We acknowledge receipt of your amendment dated April 6, 2023, which contained revised draft labeling responding to our electronic communication dated January 31, 2023. We reserve further comment on the proposed labeling until the application is otherwise adequate. You should include revised draft labeling with your resubmission that is updated to reflect any changes necessary based on your responses to the deficiencies listed above.

Prior to resubmitting the labeling, use the Selected Requirements for Prescribing Information (SRPI) checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[1]

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, 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, which include:

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The SRPI − a checklist of important format items from labeling regulations and guidances
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading, and
- Additional resources for the PI, patient labeling, and carton/container labeling.

CARTON AND CONTAINER LABELING

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

PROPRIETARY NAME

Refer to correspondence dated, November 28, 2022, which addresses the proposed proprietary name, Yorvipath. This name was found acceptable pending approval of the application in the current review cycle. Resubmit the proposed proprietary name when you respond to the application deficiencies.

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 subject 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.

POSTMARKETING REQUIREMENTS UNDER 505(o)(3)

As described in our electronic communication dated January 31, 2023, we have determined that, if this application is approved, you will be required to conduct postmarketing studies of palopegteriparatide to assess a known risk of hypocalcemia/ hypercalcemia and to identify other unexpected serious risks of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant potentially associated with palopegteriparatide use during pregnancy and lactation.

Specifically, we have determined that, if your NDA is approved, you will be required, pursuant to section 505(o)(3) of the FDCA, to conduct the following:

(1) A lactation study (milk only) in lactating women who have received therapeutic doses of palopegteriparatide, using a validated assay to assess

concentrations of palopegteriparatide in breast milk and the effects on the breastfed infant.

(2) A worldwide descriptive study that collects prospective and retrospective data in women exposed to palopegteriparatide during pregnancy and/or lactation to assess the risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant potentially associated with palopegteriparatide use during pregnancy. Infant outcomes are to be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

Any additional specific details of these required postmarketing studies, including a timetable and annual reporting requirements, will be described more fully in the approval letter for this application, if it is approved.

If you complete either of these studies prior to re-submitting your application, you may include the final report and relevant data sets in your Complete Response submission to facilitate review of the information.

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*.[4]

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

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[4] 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.

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

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, MD, MMSc
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/

HYLTON V JOFFE
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