CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

216490Orig1s000

Trade Name:	Yorvipath injection
Generic or Proper Name:	palopegteriparatide
Sponsor:	Ascendis Pharma
Approval Date:	August 9, 2024
Indication:	For the treatment of hypoparathyroidism in adults

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 216490

NDA APPROVAL

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 Stephanie 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 (FDCA) for Yorvipath (palopegteriparatide) injection.

We acknowledge receipt of your amendment dated November 14, 2023, which constituted a complete response to our April 28, 2023, action letter.

We acknowledge receipt of your major amendments dated May 2 and 8, 2024, which extended the goal date by three months.

This NDA provides for the use of Yorvipath (palopegteriparatide) injection for the treatment of hypoparathyroidism in adults.

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.

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 (text for the Prescribing Information, Instructions for Use, and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL

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

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, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 216490**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Yorvipath (palopegteriparatide) injection shall be 12 months from the date of manufacture when stored at 2 to 8 °C.

ADVISORY COMMITTEE

Your application for Yorvipath (palopegteriparatide) injection was not referred to an FDA advisory committee because this application did not raise efficacy, safety, or public health questions requiring advice from external experts.

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 this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

[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.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of palopegteriparatide to an infant during lactation.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

4677-1 Perform 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.

The timetable you submitted on August 8, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2025
Final Protocol Submission:	8/2025
Study Completion:	8/2027
Final Report Submission:	8/2028

We have also determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess known serious risks of osteosarcoma and major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

4677-2 Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to palopegteriparatide during pregnancy to assess risk of pregnancy and maternal complications, and adverse effects on the developing fetus,neonate, and infant. Assess infant outcomes through at least the first year of life. The study should also

collect adverse event data for lactating women and infants exposed to palopegteriparatide through breastfeeding to assess for any potential risks to the infant from breastfeeding. The minimum number of patients will be specified in the protocol.

The timetable you submitted on August 8, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2025
Final Protocol Submission:	08/2025
Interim study report #1:	08/2027
Interim study report #2:	08/2029
Study Completion:	08/2035
Final Report Submission:	08/2036

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit clinical protocols to your IND 133469 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

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.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

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

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.[7]

REQUESTED ENHANCED PHARMACOVIGILANCE (EPV)

1. We request that for Yorvipath you submit all serious and non-serious domestic and foreign reports of osteosarcoma as 15-day “Alert reports” described under 21 CFR 314.80(c)(1). We recommend using the follow Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) to retrieve reports: Extraskeletal osteosarcoma, Extraskeletal osteosarcoma metastatic, Extraskeletal osteosarcoma recurrent, Osteosarcoma, Osteosarcoma metastatic, Osteosarcoma recurrent.

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[7] https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products

We also request that you provide a narrative summary including analyses of osteosarcoma reports as part of your required periodic safety reports [e.g., periodic adverse drug experience report (PADER) required under 21 CFR 314.80(c)(2)], quarterly during the first 3 years post-approval and annually thereafter, through the 15th year following initial U.S. approval date.

Your analyses should include interval and cumulative data relative to the date of approval of Yorvipath. Your analyses should provide an assessment of causality, with documentation of indication, temporal association, duration of therapy, associated signs and symptoms, confounders, underlying risk factors, treatment given for the event, outcome, and drug disposition.

2. We request that for Yorvipath you provide a narrative summary including analyses of events (e.g., hypocalcemia, hypercalcemia) possibly related to delivered dose variability as part of your required periodic safety reports [e.g., PADER required under 21 CFR 314.80(c)(2)], quarterly during the first 3 years post-approval and annually thereafter, through the 5th year following initial U.S. approval date. We recommend, at a minimum, using the following MedDRA terms to retrieve reports:

    a. Hypocalcemia: Adjusted calcium decreased (PT), Blood calcium decreased (PT), Calcium ionised decreased (PT), Hypocalcaemia (PT), Hypocalcaemic seizure (PT), Chvostek's sign (PT), Trousseau's sign (PT)

    b. Hypercalcemia: Adjusted calcium increased (PT), Blood calcium increased (PT), Calcium ionised increased (PT), Hypercalcaemia (PT), Hypercalcaemic nephropathy (PT)

    c. Terms that may indicate a dosing issue: Drug effect less than expected (PT), Drug ineffective (PT), Extra dose administered (PT), Incorrect dose administered (PT), Incorrect dose administered by device (PT), Loss of therapeutic response (PT), Overdoses and underdoses NEC (High Level Group Term), Tachyphylaxis (PT), Therapeutic product effect decreased (PT), Therapeutic product effect delayed (PT), Therapeutic product effect incomplete (PT), Therapeutic product effect variable (PT), Therapeutic response changed (PT), Therapeutic response decreased (PT), Treatment failure (PT), Wrong dose (PT)

Your analyses should include interval and cumulative data relative to the date of approval of Yorvipath. For reports relevant to these events, you should attempt to obtain information about the lot numbers of the products utilized by the patient in addition to pertinent laboratory information. Your analyses should provide an assessment of causality, with documentation of indication, temporal association, duration of therapy, lot numbers of the products preceding the event, associated signs and symptoms, laboratory values, confounders, underlying risk factors, treatment given for the event,

outcome, and dechallenge/rechallenge. Also include a reporting rate analysis stratified by lot numbers.

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[8].

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 (OCHEN)
Office of New Drugs (OND)
Center for Drug Evaluation and Research

[8] https://www.uspnf.com/

ENCLOSURES:

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

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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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