NDA 214375

NDA APPROVAL

Polarean Inc.
Attention: Jason Mercer, PhD, RAC
Authorized US Agent
Product Development Champion
c/o Facet Life Sciences
215 E Deer Run
Durham, NC 27523

Dear Dr. Mercer:

Please refer to your new drug application (NDA) dated and received on October 05, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for XENOVIEW (xenon Xe 129 hyperpolarized) for oral inhalation and the HPX Hyperpolarization System (HPX Gas Handling Manifold, HPX Hyperpolarizer, HPX Polarization Measurement Station, and XENOVIEW Dose Delivery Bag).

We acknowledge receipt of your amendment dated March 30, 2022, which constituted a complete response to our October 5, 2021, action letter.

This NDA provides for the use of XENOVIEW (xenon Xe 129 hyperpolarized) with magnetic resonance imaging (MRI) for evaluation of lung ventilation in adults and pediatric patients aged 12 years and older.

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, Operator's Manual, Quick Reference Guide, and Information Sheet) as well as annual reportable changes not included in the enclosed labeling.

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

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

We acknowledge your December 21, 2022, submission containing final printed carton and container labeling.

DATING PERIOD

Based on the stability data submitted to date, the expiry for XENOVIEW (xenon Xe 129 hyperpolarized) for oral inhalation shall be 5 minutes after final Dose Equivalent (DE) measurement when stored at 20°C to 25°C (68°F to 77°F). The expiry for xenon Xe 129 Gas Blend for Hyperpolarization shall be (b) (4) months when stored at 20°C to 25°C (68°F to 77°F).

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.

We are waiving the pediatric study requirement for ages less than 6 years because necessary studies are impossible or highly impracticable. This is because patients in this age group cannot typically comply with the breathing instructions or undergo MRI without sedation.

We are deferring submission of your assessment for ages 6 to less than 12 years for this application because the product is ready for approval for use in adults but the development of an age-appropriate presentation that would allow for direct administration of the correct dose in this population (Dose Delivery Bag(s) of the appropriate volume(s) with appropriately sized mouthpiece(s)/mask(s) and any necessary modifications to the HPX Polarization Measurement Station) has not been completed for ages 6 to less than 12 years.

This product is appropriately labeled for use in ages 12 years to 16 years with MRI for evaluation of lung ventilation.

[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.

Your deferred age-appropriate presentation required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act/FDCA is a postmarketing requirement. The status of this postmarketing requirement must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the Federal Food, Drug, and Cosmetic Act/FDCA. This required age-appropriate presentation is listed below.

4324-1 Develop an age-appropriate presentation of hyperpolarized Xe 129 that would allow administration of an accurate dose to pediatric patients 6 years to less than 12 years of age.

Submission of Summary Development Plan: 06/2023
Final Report Submission: 07/2024

Reports of this pediatric postmarketing requirement must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4324-2 Polarean to describe supplier qualifying procedure and (b) (4) acceptance criteria (specification) for (b) (4) Xe-129 (enriched xenon gas) sourced through the (b) (4) supply chain. Include procedure and complete test results on site at (b) (4) and Polarean. Complete test results for 3 batches (b) (4) should be kept on site to qualify (b) (4) and future suppliers.

Amend the NDA post-action with complete test data for at least one batch from (b) (4). After qualification, (b) (4) may be accepted by Polarean/ (b) (4) by identity testing and inspection of supplier's CoA per ICH Q7 7.31. Submit a final report of the results as a Changes Being Effected Supplement (CBE-0).

The timetable you submitted on December 14, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2023

Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and

314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

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.*[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]

REPORTING REQUIREMENTS

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

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.

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, call Lisa Skarupa, Regulatory Project Manager, at 301-796-2219.

Sincerely,

{See appended electronic signature page}

Charles Ganley, M.D.
Director
Office of Specialty Medicine
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Operator's Manual
  - Quick Reference Guide
  - Information Sheet
- Carton and Container Labeling

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/

CHARLES J GANLEY
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