Clinical/Division Signatory Review

Application Type	505(b)(2), Efficacy Supplement
Application Number(s)	NDA 214375/S-001
Priority or Standard	Standard
Submit Date	07/31/2024
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PDUFA Goal Date	05/31/2025
Division/Office	Division of Imaging and Radiation Medicine, Office of Specialty Medicine
Review Completion Date	05/30/2025
Established/Proper Name	xenon Xe 129 hyperpolarized
Trade Name	XENOVIEW/ (b) (4)
Pharmacologic Class	Hyperpolarized contrast agent
Applicant	Polarean, Inc.
Dosage form	Gas for oral inhalation
Recommended Dosing Regimen	The recommended target dose of XENOVIEW for adults and pediatric patients aged 6 years and older is 75 mL to 100 mL Dose Equivalent (DE) volume of hyperpolarized xenon Xe 129 by oral inhalation of the entire contents of one XENOVIEW Dose Delivery Bag. Each bag contains at least 75 mL DE of hyperpolarized xenon Xe 129 measured within 5 minutes of administration, in a volume of 250 mL to 750 mL total xenon with additional nitrogen, NF (99.999% purity) added to reach a total volume of the Dose Delivery Bag. Select the Dose Delivery Bag based on the patient's Total Lung Capacity (TLC) according to Table 1. If TLC is not available at the time of the procedure, select the Dose Delivery Bag based on patient's Forced Vital Capacity (FVC). If neither TLC nor FVC values are available in the patient's medical records, select the Dose Delivery Bag based on estimates of the patient's TLC using American Thoracic Society (ATS)-endorsed plethysmography-based predictive equations based on sex and height.

Table 1. Recommended Dose Delivery Bag Volume Based on TLC

TLC (L)	FVC† (L)	Dose Delivery Bag (mL)
<2.0	<1.5	300
2.0 to <3.3	1.5 to <2.5	500
3.3 to <5.0	2.5 to <3.8	750
≥5.0	≥3.8	1,000

†FVC is used when TLC is not available.

Recommended Indication	XENOVIEW, prepared from the Xenon Xe 129 Gas Blend, is a hyperpolarized contrast agent indicated for use with magnetic resonance imaging (MRI) for evaluation of lung ventilation in adults and pediatric patients aged 6 years and older. Limitations of Use XENOVIEW has not been evaluated for use with lung perfusion imaging.
Regulatory Action	Approval

XENOVIEW (xenon Xe 129 hyperpolarized, also referred to as hyperpolarized Xe 129) is the drug constituent of a combination product that includes several device constituents, namely the HPX Gas Handling Manifold, HPX Hyperpolarizer, HPX Polarization Measurement Station, and XENOVIEW dose delivery bags. In December of 2022, XENOVIEW was approved as a hyperpolarized contrast agent indicated for use with MRI for evaluation of lung ventilation in adults and pediatric patients aged 12 years and older. In the initial NDA review, efficacy was extrapolated to the pediatric population from adult studies while literature supported pediatric safety down to age 6 years. However, XENOVIEW was approved only down to age 12 years because an age-appropriate dose could not be accurately administered to younger children with the initially proposed 1000 mL dose delivery bag. A pediatric postmarketing requirement (PREA PMR 4324-1) specified that Polarean was to 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. Evaluation of XENOVIEW in patients less than 6 years old was waived because necessary studies were impossible or highly impracticable due to potential inability of children of such age to follow instructions to inhale and breath hold hyperpolarized Xe 129 or undergo MRI without sedation.

To fulfill PMR 4324-1, Polarean developed three smaller dose delivery bags (300 mL, 500 mL, and 750 mL) that when combined with the original 1000 mL size allow for administration of XENOVIEW across a patient population that includes adults and pediatric patients 6 years of age and older. This supplement contains the PMR final report including information related to the three smaller dose delivery bags, dosing recommendations based on measured or estimated lung volumes, updated literature on the use of hyperpolarized Xe 129, proposed labeling reflecting indication of patients down to 6 years of age, and data from validation activities for the HPX Polarization Measurement Station, which required modifications to accommodate the smaller dose delivery bag sizes.

The review team from the Center for Devices and Radiological Health (CDRH) found the new smaller dose delivery bags, related hardware and software modifications to the HPX Polarization Measurement Station, and changes to the dose delivery bag filling and dose measurement procedures to be acceptable from a device perspective. CDRH review also confirmed that no modifications to the separately cleared XENOVIEW 3.0T Chest Coil were needed.

Dosing recommendations and imaging effectiveness in the expanded pediatric population were approached with consideration of the relatively simple pharmacokinetics and pharmacodynamics of hyperpolarized Xe 129, which is inhaled in a single breath, immediately imaged during breath holding, and exhaled with little uptake in the blood. As noted in the clinical pharmacology review, no clinical pharmacology studies were included in this supplement and dosing recommendations were deferred to other disciplines.

Per the Applicant's proposal, choice of dose delivery bag size and hence total inhaled volume is now appropriately based on lung volumes across the indicated pediatric and adult age range. Total lung capacity (TLC) as measured by pulmonary function testing is preferred for dose delivery bag selection, but measured forced vital capacity (FVC) can be used when measured TLC is unavailable. If neither measured value is available, estimated TLC calculated by predictive equations based on sex and height can be used. FDA consultants from the Division of Pulmonology, Allergy, and Critical Care (DPACC) found this dosing approach to be acceptable and supported by published studies of hyperpolarized Xe 129 in pediatric subjects. The single-sized mouthpiece supplied with the dose delivery bags was also found to be acceptable given the precedent of similarly sized mouthpieces cleared for use in a similarly wide range of adult and pediatric patients.

The same approach used in the initial NDA approval of extrapolating imaging effectiveness from adequate and well-controlled studies in adults to pediatric patients aged 12 years and older was appropriately applied to pediatric patients aged 6 years and older in this supplement. Recommended dosing maintains the previous dose equivalent volume target of 75 mL to 100 mL across the indicated age range, which poses no safety concerns in younger patients and could potentially facilitate acquisition of thinner slice images through smaller lungs.

As previously noted, safety was demonstrated down to age 6 years through published clinical studies in the initial NDA review. Updated literature in the current supplement revealed no new safety signals in the proposed younger pediatric population.

Drug product review by the chemistry, manufacturing, and controls team found the submitted batch data and updated documentation to adequately support the new pediatric strengths and the related new dose specifications.

Recommendations of the Associate Director for Labeling appropriately describe the expanded pediatric population and new dosing approach in the prescribing information and incorporate advice from the Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Pediatrics and Maternal Health. With input from CDRH, appropriate recommendations were similarly provided for the HPX Hyperpolarization System Operator's Manual, HPX Hyperpolarization System Quick Reference Guide, and XENOVIEW Dose Delivery Bag Information Sheet, as well as the dose delivery bag outer assembly, container, and carton labels. DMEPA appropriately concluded that a human factors validation study was not needed to support the changes proposed in this supplement.

Given the findings of the multidisciplinary review team, expansion of the population indicated for MRI evaluation of lung ventilation with XENOVIEW and the HPX Hyperpolarization System

from pediatric patients aged 12 years and older to pediatric patients at least 6 years of age and the accompanying dosing recommendations and device modifications are adequately supported. Per discussion with the FDA Pediatric Review Committee, PMR 4324-1 is now considered to be fulfilled.

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