CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214375Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214375
PDUFA Goal Date	December 30, 2022
OSE RCM #	2020-2428
Reviewer Name	Victoria Sammarco, PharmD, MBA
Team Leader	Carolyn Tieu, PharmD, MPH
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	December 19, 2022
Subject	Evaluation of Need for a REMS
Established Name	Hyperpolarized xenon-129 gas for inhalation
Trade Name	Xenoview
Name of Applicant	Polarean Inc.
Therapeutic Class	Inhalation Diagnostic Agent
Formulation	2105 pounds per square inch gauge (psig) in aluminum cylinders
Dosing Regimen	75 mL dose equivalent (DE) DE = total volume Xe gas × Xe-129 isotopic enrichment × polarized %

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for Xenoview (hyperpolarized Xenon-129) is necessary to ensure the benefits outweigh its risks. Polarean Inc. submitted a New Drug Application (NDA) 214375 for Xenoview proposed for use with magnetic resonance imaging for evaluation of lung ventilation in adults and pediatric patients aged 12 years and older. The risks associated are image degradation by concurrent supplemental oxygen administration and transient hypoxia. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM has determined that a REMS is not needed to ensure the benefits of Xenoview outweigh its risks. The risks can be conveyed in labeling and are generally known risks of inhaled drugs.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for Xenoview (hyperpolarized Xenon-129) is necessary to ensure the benefits outweigh its risks. Polarean Inc. submitted a New Drug Application (NDA) 214375 for Xenoview proposed for use with magnetic resonance imaging (MRI) for evaluation of lung ventilation in adults and pediatric patients aged 12 years and older.[1] This application is under review in the Division of Imaging and Radiation Medicine (DIRM). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Xenoview is a drug-device combination comprised of hyperpolarized xenon-129 gas and device components consisting of a gas handling manifold, hyperpolarizer, dose delivery bag, and a polarization measurement station. Xenoview was submitted using the 505(b)(2) pathway and it is not a new molecular entity. However, it is a new isotope (first in class) and is being treated similarly to a new molecular entity.[a] Xenoview is not approved and in any other jurisdiction, however, non-isotopically enriched xenon gas is approved for use as an anesthetic outside of the US when administered through steady breathing.

Xenon-129 is a stable, non-radioactive, naturally occurring isotope of xenon with a nuclear magnetic moment that allows it to be directly detected by magnetic resonance imaging (MRI). Hyperpolarization of xenon-129 greatly increases its imaging capacity with MRI. Hyperpolarized xenon-129 is produced by the Hyperpolarizer from a gas blend of helium, nitrogen, and xenon that is isotopically enriched. The resultant gas is collected from the Hyperpolarizer device into a dose delivery bag as a total of 250 mL to 750 mL of xenon gas, a fraction of which is xenon-129. A dose equivalent (DE) calculation accounts for

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity*

the total volume of xenon, fraction of Xe-129 isotopic enrichment, and fraction of hyperpolarization. The DE result must meet a recommended range to ensure adequate imaging signal. Nitrogen gas is added as an inert buffer to achieve a total dose volume of 1 L.

Exposure to hyperpolarized xenon-129 is short. A patient inhales the entire one liter dose in a single breath and holds their breath while imaging is completed, up to 15 seconds which is also the half-life of the drug.[b]

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 214375 relevant to this review:

- 10/05/2020: NDA 214375 submission proposed for (b) (4) (b) (4)
- 04/13/2021: Midcycle Communication was sent to the Applicant and the Agency communicated that although the review was still ongoing, no REMS was determined to be required at that time.
- 10/05/2021: Complete Response (CR) letter sent to the applicant due to needed drug product specification, cGMP considerations, and needed device history and specifications.
- 03/30/2022: NDA 214375 class 2 resubmission received.
- 09/29/2022: Review extension granted for major amendment.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Xenoview is proposed for use with magnetic resonance imaging (MRI) for evaluation of lung ventilation in adults and pediatric patients aged 12 years and older and was studied for use prior to lung resection or lung transplant in adults and pediatric patients aged 12 years and older. Lung resection may be considered in a number of lung conditions including cancer and infectious disease, trauma and for diagnostic purposes. Additionally, approximately 4,500 lung transplants occur per year.[2] Incidentally, a large number of patients may be evaluated for lung resection or lung transplant.[c] Patients evaluated for lung resection or lung transplant must undergo various assessments which may include lung imaging. In patients who are being evaluated for lung resection who are higher risk, imaging of regional ventilation can be used to predict the ventilation capacity that will likely remain postoperatively. In patients who are being evaluated for lung transplant, imaging of regional ventilation can help identifying the more

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*
[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

dysfunctional lung that should be targeted for transplant. The ability to visualize regional ventilation may lead to better outcomes in patients with serious disease.[d]

3.2. Description of Current Diagnostic Agents

Chest computerized tomography (CT) and cross-sectional imaging with single-photon emission computerized tomography (SPECT) techniques can be used to estimate postoperative ventilation following lung resection. Other available imaging agents that are FDA-approved for ventilation imaging include Xe-133 gas and aerosolized and intravenous (albumin bound) Tc99m. Xenon-127 and Krypton-81m are other radioactive gases that are FDA-approved for ventilation imaging but have been withdrawn from the market for reasons unrelated to safety or efficacy. These options all require some radiation exposure whereas hyperpolarized Xe 129 gas does not.

4. Benefit Assessment

Studies POL-Xe-001 and POL-Xe-002 are the pivotal trials conducted by the Applicant to support the efficacy of Xenoview.

POL-Xe-001 was a randomized, open-label, cross-over, multicenter, phase 3 study designed to show equivalence of hyperpolarized Xe-129 MRI to Xe-133 scintigraphy for the evaluation of pulmonary ventilation and to assess the efficacy and safety of hyperpolarized Xe-129 gas. Thirty-two adult patients being evaluated for lung resection surgery completed the study which consisted of screening, imaging (during which patients underwent both imaging modalities), phone follow-up, and three-month postoperative follow-up if applicable. The primary efficacy endpoint was the scan-estimated percentage of remaining ventilation after planned resection of a specified lung area.

POL-Xe-002 was a randomized, open-label, cross-over, multicenter, phase 3 study also designed to show hyperpolarized Xe-129 MRI and Xe-133 scintigraphy equivalence in determining pulmonary ventilation and to assess the efficacy and safety of hyperpolarized Xe-129 gas. The study enrolled 49 adult patients being evaluated for lung transplant surgery. The primary efficacy endpoint was the scan-estimated percentage of overall pulmonary ventilation contributed by the right lung.

In both POL-Xe-001 and study POL-Xe-002, results of the primary endpoint analyses met a pre-specified equivalence margin of ±14.7% for hyperpolarized Xe-129 MRI and Xe-133 scintigraphy. Secondary analyses in both trials further demonstrated concordance in ventilation measurements in individual lung zones. Per the clinical team, studies POL-Xe-001 and POL-Xe-002 provide substantial evidence of effectiveness in imaging that can be extrapolated to pediatric patients due to the simple pharmacokinetics and mechanism of action.[3,e]

---

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

5. Risk Assessment & Safe-Use Conditions

The safety database included 147 adults from four trials submitted by the Applicant that include the two pivotal trials described in section four, a phase one safety and feasibility study that included 34 healthy subjects and 10 patients with COPD who received up to four doses plus a calibration dose, and a pharmacokinetic study that included only healthy subjects. Isotopic enrichment of Xe-129 and hyperpolarization of Xe-129 does not add additional safety risk beyond that of xenon gas itself. For imaging purposes, xenon exposure will not approach that required for significant anesthetic effect.

One death (Study POL-Xe-002) occurred unrelated to the study drug. Two patients had three serious adverse events unrelated to study drug. One of these patients was the one that had died. There was one discontinuation attributed to study drug in a patient with a history of hypersensitivity reactions to a number of agents. A total of 38% (56/147) of subjects reported one or more treatment-emergent adverse events (TEAEs), of which the majority were mild. In the pivotal trials, POL-Xe-001 and POL Xe-002, the most common adverse reactions were oropharyngeal pain (n = 4), headache (n = 2), and dizziness (n = 2). Of note, 46.9% of patients in POL-Xe-001 and 89.7% of patients in POL-Xe-002 regularly used supplemental oxygen.[f] Discontinuation of oxygen for a short duration before administration and during imaging in these patients, as practiced in the clinical trials, did not affect the imaging compared to Xe-133 scintigraphy.

Supportive scientific literature was narrowed to eight adult (n=123 patients) and five pediatric (n=120 patients) studies that included similar dosing protocols to what has been proposed. Adverse events reported in adults included transient numbness, tingling, euphoria, and dizziness which lasted less than three minutes. In pediatric patients, transient and non-serious blood oxygen desaturation and heart rate elevation were described as well as numbness, tingling, dizziness, and euphoria that quickly resolved.

Overall, no serious adverse events or deaths related to hyperpolarized Xe-129 were identified. Adverse reactions in the submitted trials and review of the literature were transient and consistent with those expected from brief exposure to an anesthetic or anoxic gas. The warnings will include the risk of decreased image quality from supplemental oxygen, and patients on supplemental oxygen will be instructed to withhold oxygen inhalation for two breaths prior to Xenoview inhalation, and resume oxygen inhalation immediately following the imaging breath hold. The warnings section will also include the risk of transient hypoxia substantiated by the pediatric literature and the need to monitor patients for oxygen saturation and symptoms of hypoxemia and treat as clinically indicated.

During this review cycle, no additional safety data was submitted and the clinical reviewer did not identify any additional safety concerns.[5]

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

6. Expected Postmarket Use

Xenoview is proposed for use with MRI and hence will be used in specialized settings, including hospitals and outpatient radiology centers.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Xenoview beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of Xenoview on the basis of the efficacy and safety information currently available. There were no serious adverse events or deaths related to hyperpolarized Xe-129 identified.

The risk of decreased image quality with concurrent oxygen administration can be described through labeling with the instruction to stop supplemental oxygen before imaging. Transient hypoxia was seen in data from the pediatric literature, however this risk is common of inhaled drugs (ex. DRAXIMAGE DTPA[4]) and is well known. Exposure to hyperpolarized Xe-129 from Xenoview is short and carries no further safety risk than non-isotopically enriched xenon gas which is approved for use as an anesthetic abroad when administered through steady breathing and hence longer exposure times. Overall, the risks are transient and consistent with those expected from brief exposure to medicinal gases.

This reviewer has determined that a REMS is not necessary to ensure the benefits of Xenoview outweigh its risks.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for Xenoview to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. References

1. Draft Prescribing Information for Xenoview as currently edited by the FDA, last updated December 15, 2022.

2. Chambers DC, Perch M, Zuckermann A, Cherikh WS, Harhay MO, Hayes D Jr, Hsich E, Khush KK, Potena L, Sadavarte A, Lindblad K, Singh TP, Stehlik J; International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-eighth adult lung transplantation report - 2021; Focus on recipient characteristics. J Heart Lung Transplant. 2021 Oct;40(10):1060-1072. doi: 10.1016/j.healun.2021.07.021. Epub 2021 Jul 31. PMID: 34446355.

3. Food and Drug Administration. Division of Imaging and Radiation Medicine (DIRM). Xenoview (hyperpolarized Xenon-129). NDA 214375. Unireview, October 5, 2021.

4. Prescribing Information for Draximage DTPA. Revised May 2022

5. Division of Imaging and Radiation Medicine. UniReview draft for Xenoview NDA 214375, December 16, 2022.

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/

VICTORIA C SAMMARCO
12/19/2022 06:13:29 PM

CAROLYN N TIEU
12/19/2022 06:26:26 PM

CYNTHIA L LACIVITA
12/19/2022 06:57:30 PM

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214375
PDUFA Goal Date	10/05/2021
OSE RCM #	2020-2428
Reviewer Name(s)	Ingrid N. Chapman, Pharm.D., BCPS
Team Leader	Naomi Boston, Pharm.D.
Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	10/05/2021
Subject	Deferral memo on DRM evaluation of the need for a REMS
Established Name	Hyperpolarized Xe-129 gas for inhalation
Trade Name	Xenoview
Name of Applicant	Polarean Inc.
Therapeutic Class	Inhalation Diagnostic Agent
Formulation(s)	2105 pounds per square inch gauge (psig) in aluminum cylinders
Dosing Regimen	75 mL dose equivalent (DE) DE = total volume Xe gas × Xe-129 isotopic enrichment × polarized %

This memo is to defer the Division of Risk Management's (DRM) evaluation of the need for a risk evaluation and mitigation strategy (REMS) for the New Drug Application (NDA) 214375. Polarean, Inc. submitted NDA 214375 for Xenoview (hyperpolarized Xenon-129) with the proposed indication: (b) (4)

Xenoview (hyperpolarized Xenon-129) is not a new molecular entity (NME). The NDA is a 505(b)(2) application being treated similarly to an NME because it is a new isotope (first in class). Xenoview is a drug-device combination comprised of hyperpolarized Xe-129 (drug component) and an HPX Hyperpolarization System. Hyperpolarized Xe-129 is a clear, colorless, non-radioactive gas for inhalation (diagnostic agent). The HPX Hyperpolarization System includes a gas handling manifold, hyperpolarizer, dose delivery bag, and a polarization measurement station.

The Division of Imaging and Radiation Medicine (DIRM) received the NDA for Xenoview on October 5, 2020. The Office of Pharmaceutical Quality (OPQ) recommends a Complete Response for this NDA taking into account "withhold" cGMP recommendations for (b) (4) (manufacturer of gas blend), (b) (4) (proposed commercial manufacturer), and Polarean (applicant, specifications developer, tester). Manufacturing record deficiencies (b) (4) include lack of measurements of degree of Xe-129 polarization and adequate justification/specification development of acceptance criteria for this critical quality attribute by Polarean (b) (4) [1]

Therefore, DRM defers comment on the evaluation of the need for a REMS for Xenoview during this review cycle. The evaluation of the need for a REMS for Xenoview will be undertaken by DRM when the Applicant resubmits the NDA for review. Please send DRM a new assignment at such time.

This memo serves to close the existing assignment to DRM for Xenoview under NDA 214375.

1 Appendices

1.1 References

1. Food and Drug Administration. Division of Imaging and Radiation Medicine (DIRM). Xenoview (hyperpolarized Xenon-129). NDA 214375. Unireview, draft. September 30, 2021.

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/

INGRID N CHAPMAN
10/05/2021 08:23:16 AM

DORIS A AUTH
10/05/2021 08:58:04 AM