CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214375Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 23, 2022
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 214375
Product Name and Strength:	Xenoview (xenon Xe 129 hyperpolarized) for oral inhalation, 1,000 mL (75 mL Dose Equivalent)
Applicant/Sponsor Name:	Polarean Inc. (Polarean)
OSE RCM #:	2020-2131-3
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Polarean Inc. (Polarean) submitted revised dose delivery bag container label, dose delivery bag carton labeling, and xenon Xe 129 gas cylinder container label on December 21, 2022 for Xenoview (xenon Xe 129 hyperpolarized) for oral inhalation under NDA 214375. We reviewed the revised dose delivery bag container label, dose delivery bag carton labeling, and xenon Xe 129 gas cylinder container label for Xenoview (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review and based on recommendations from the Office of Pharmaceutical Quality (OPQ).[a]

2 CONCLUSION

Polarean Inc. implemented all of our recommendations and we have no additional recommendations at this time.

[a] Kane, D. Label and Labeling Review for Xenoview (NDA 214375). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 AUG 18. RCM No.: 2020-2131-2.

2 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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/

DEVIN R KANE
12/23/2022 11:17:45 AM

HINA S MEHTA
12/23/2022 11:21:31 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 18, 2022
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 214375
Product Name, Dosage Form, and Strength:	Xenoview (hyperpolarized xenon Xe 129) gas for oral inhalation, 1,000 mL (75 mL Dose Equivalent)
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Polarean Inc. (Polarean)
FDA Received Date:	October 5, 2020, July 12, 2021, July 21, 2021, and March 30, 2022
OSE RCM #:	2020-2131-2
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Polarean Inc. (Polarean) submitted a Class 2 Resubmission for NDA 214375 for Xenoview (hyperpolarized xenon Xe 129) gas for oral inhalation on March 30, 2022. Xenoview is proposed [redacted] (b) (4) We reviewed the proposed Xenoview prescribing information (PI), dose delivery bag container label, dose delivery bag carton labeling, Xenon 129 gas cylinder label, Xenon Hyperpolarizer System Operator Manual, Xenon Hyperpolarizer System Quick Reference Guide, Polarization Measurement Station Operating Manual, and Dose Delivery Bag Instructions for Use for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND OR REGULATORY HISTORY

Polarean Inc. submitted a use-related risk analysis (URRA), formative human factors (HF) data, and additional HF questions as part of Type C and Type B meeting packages under IND 75010 to determine whether HF validation study results should be submitted as part of the marketing application. The review concluded that results from an HF validation study did not need to be submitted for Agency review for the proposed product.[a]

NDA 214375 received a Complete Response (CR) letter on October 5, 2021 due to drug quality issues and device issues.[b] We previously reviewed the label and labeling (see Appendix B). However, comments on the proposed labeling were reserved until the application is otherwise adequate.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A

[a] Whaley, E. Xenon 129 Gas (IND 75010) Use-Related Risk Analysis Review. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 02. RCM No. 2019-950.

[b] Skarupa, L. Complete Response Letter. 2021 OCT 05. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8061b430

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed prescribing information (PI), dose delivery bag container label, dose delivery bag carton labeling, Xenon 129 gas cylinder label, Xenon Hyperpolarizer System Operator Manual, Xenon Hyperpolarizer System Quick Reference Guide, Polarization Measurement Station Operating Manual, and Dose Delivery Bag Instructions for Use for Xenoview to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. We note Polarean Inc. proposed the dosage form (b) (4) (b) (4) for Xenoview. However, we note the Office of Pharmaceutical Quality proposes revising the dosage form and route of administration for Xenoview to be "gas for oral inhalation". We note OPQ has provided recommendations to revise the proposed PI and carton and container labels to align with this dosage form and route of administration. In addition, the placement of 'hyperpolarized' in the established name was relocated to after xenon. Thus, the established name should read as "Xenoview (xenon Xe-129 hyperpolarized)".

Our evaluation of the proposed PI, dose delivery bag container label, dose delivery bag carton labeling, Xenon 129 gas cylinder label, Xenon Hyperpolarizer System Operator Manual, Xenon Hyperpolarizer System Quick Reference Guide, Polarization Measurement Station Operating Manual, and Dose Delivery Bag Instructions for Use for Xenoview identified areas of vulnerability that may lead to medication errors. For the PI, we recommend removing the use of symbols and replacing them with their intended meanings, including the appropriate units after all numeric values, adding subheadings to Section 2.1 in order to improve readability, and adding Xenoview dose expiration information to Section 16.2. For the dose delivery bag container label, dose delivery bag carton labeling, and Xenon 129 gas cylinder label, we recommend removing (b) (4) We provide our recommendations below.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Xenoview prescribing information (PI), dose delivery bag container label, dose delivery bag carton labeling, Xenon 129 gas cylinder label, Xenon Hyperpolarizer System Operator Manual, Xenon Hyperpolarizer System Quick Reference Guide, Polarization Measurement Station Operating Manual, and Dose Delivery Bag Instructions for

Use identified areas of vulnerability that may lead to medication errors. Below, we have provided recommendations in Section 4.1 for the Division and Section 4.2 for the Applicant. We ask that the Division convey Section 4.2 in its entirety to Polarean Inc. so that recommendations are implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR DIVISION OF MEDICAL IMAGING AND RADIATION MEDICINE (DIRM)

A. General Comments for Highlights of Prescribing Information and Full Prescribing Information

1. We note the use of the symbol "-" used to represent the word "to". We recommend removing the use of the symbol throughout the prescribing information and replacing it with its intended meaning of "to". For example, in the first bullet under Highlights of Dosage and Administration, revise "250 mL – 750 mL" to read "250 mL to 750 mL".
2. As currently presented, there are numeric values presented in the PI that are not immediately followed by their appropriate units. We recommend including the appropriate units after all numeric values presented in the PI in order to avoid confusion. For example, under Highlights of Dosage Forms and Strengths, revise "250-750 mL" to read "250 mL to 750 mL".
3. We note the use of the symbol "≥" used throughout the Highlights of Prescribing Information and Full Prescribing Information to mean "greater than or equal to". We recommend removing the use of the symbol throughout the PI and replacing it with its intended meaning of "greater than or equal to".

B. Highlights of Prescribing Information

1. Dosage and Administration
   a. We recommend including a bullet at the end of the Highlights of Dosage and Administration section that states "See Full Prescribing information (b) (4)
2. Dosage Forms and Strengths
   a. The first sentence of the highlights of dosage forms and strengths currently states (b) (4) We recommend removing this first sentence as it is not required as a part of the highlights of dosage forms and strengths section.

C. Prescribing Information

1. Section 2: Dosage and Administration
   a. We note Section 2.1 Recommended Dose and Administration Information contains the reference to (b) (4) We recommend removing the

language [redacted]

2. Section 16: How Supplied/Storage and Handling

   a. As currently presented, there are numeric values greater than 1,000 presented in Section 16: How Supplied/Storage and Handling without the use of a comma. We recommend including a comma for all numeric values greater than 1,000 in order to avoid misinterpretation of the numeric value. Revise "6350" to read "6,350".

   b. We note [redacted] states that Xenoview [redacted] Additionally, we note that information regarding the expiry of Xenoview is not provided. We recommend including a statement in Section 16.2 that says "Do not use and discard Xenoview 60 minutes after [redacted]

D. Xenon Hyperpolarizer System Operating Manual

1. We note the use of the symbol "-" to represent the word "to" throughout the proposed Xenon Hyperpolarizer System Operating Manual. We recommend removing the use of the symbol and replacing it with its intended meaning of "to". For example, revise "8.5 ft – 6 ft" in Section 3.2 to read "6 ft to 8.5 ft".
2. As currently presented, there are numeric values presented immediately followed by units without a space between them. We recommend including a space between all numeric values and the appropriate units throughout the [redacted] Manual. For example, in Section 4.2 revise "5L/min" to read "5 L/min".
3. We note under Section [redacted] Optical Pumping Cell that temperature values are presented in terms of degrees Celsius without being followed by the Fahrenheit equivalent values presented in parenthesis. We recommend presenting the Fahrenheit equivalent values in parenthesis following all Celsius temperature values.
4. We note under Section [redacted] Optical Pumping Cell that a numeric value is presented with the use of a trailing zero. We recommend removing the use of trailing zeros in order to avoid a ten-fold misinterpretation of the numeric value.
5. As currently presented under Section [redacted] Performance Specifications, there are numeric values greater than 1,000 presented without the use of a comma. We recommend including a comma for all numeric values greater than 1,000 in order to avoid misinterpretation of the value. Revise "1000" to read "1,000".
6. We note from the Xenoview Prescribing Information that the prepared dose of Xenoview is only good for 60 minutes. As currently presented, the Xenon Hyperpolarizer System Operating Manual does not provide this important information. We recommend including the statement "Do not use and discard the dose of Xenoview 60 mins after [redacted]" in step [redacted] of Thawing [redacted] Xenon in Section [redacted]
7. As currently presented under Section 9.2, there are numeric values presented that are not immediately followed by their appropriate units. We recommend

including the appropriate units after all numeric values in order to avoid confusion.

E. Xenon Hyperpolarizer Quick Reference Guide
    1. We note the use of the symbol "-" throughout the Xenon Hyperpolarizer Quick Reference guide to represent the word "to", and the symbol "~" used to represent "about" or "around". We recommend removing the use of the symbol and replacing it with its intended meaning.
    2. We note there are numeric values presented in the Xenon Hyperpolarizer Quick Reference Guide that are presented without their units. We recommend including units after all numeric values. Additionally, we note some numeric values are immediately by their units without a space between them. We recommend including a space between all numeric values and their respective units.
    3. As currently presented, the symbol "~" is used in order to represent "about" or "around" throughout the Quick Reference Guide. We recommend removing the use of this symbol and replacing it with its intended meaning in order to improve readability.

F. Polarization Measurement Station Operating Manual

G. Dose Delivery Bag Instructions for Use
    1. We note in the Introduction the dose delivery bag is defined as (b) (4) (b) (4) We recommend referring to the dose delivery bag as "single-dose delivery bag" throughout the Instructions for Use.

2. [redacted]

4.2 RECOMMENDATIONS FOR POLAREAN INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments regarding Dose Delivery Bag Container Label and Dose Delivery Bag Carton Labeling
   1. We note [redacted] We recommend revising the presentation of the proprietary name [redacted]

B. Dose Delivery Bag Container Label
   1. We note the proposed dose delivery bag container label does not include information regarding the expiration of the prepared dose of Xenoview. We recommend including the statement "Do not use and discard Xenoview 60 minutes after [redacted]" under the date and time blanks for the DE measurement information.
   2. Revise the storage statement to read "XENOVIEW can be stored at 20° to 25°C (68° to 77°F), for no more than 5 minutes after final DE measurement."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xenoview received on March 30, 2022 from Polarean Inc..

Table 2. Relevant Product Information for Xenoview	
Initial Approval Date	N/A
Active Ingredient	hyperpolarized xenon Xe 129
Indication	(b) (4)
Route of Administration	Inhalation
Dosage Form	gas for oral inhalation
Strength	1,000 mL (75 mL Dose Equivalent)
Dose and Frequency	The recommended dose of XENOVIEW is 75 mL DE (Dose Equivalent) of hyperpolarized Xe-129 gas with a range of 250 mL-750 mL total Xe administered within 5 minutes of measurement.
How Supplied	(b) (4)
Storage	Store (b) (4) gas blend at (b) (4) 20° to 25°C (68° to 77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F).
Container Closure	The XENOVIEW gas blend for preparation of XENOVIEW is supplied (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 6, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, Xenoview and Hyperpolarized Xenon Xe 129. Our search identified 3 previous reviews[c,d,e], and we considered our previous recommendations to see if they are applicable for this current review.

[c] Whaley, E. Human Factors Use-Related Risk Analysis Review for Xenon 129 (IND 75010). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 02. RCM No.: 2019-950.

[d] Kane D. Label and Labeling Review for Xenoview (NDA 214375). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 JUN 21. RCM No.: 2020-2131.

[e] Kane, D. Label and Labeling Review for Xenoview (NDA 214375). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUL 22. RCM No.: 2020-2131-1.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following Xenoview labels and labeling submitted by Polarean Inc..

- Dose Delivery Bag Container Label received on March 30, 2022
- Dose Delivery Bag Carton Labeling received on July 21, 2021
- Xenon Xe 129 Gas Cylinder Container Label received on July 12, 2021
- Prescribing Information (Image not shown) received on March 30, 2022, available from \\CDSESUB1\evsprod\nda214375\0028\m1\us\draft-labeling-text-tc.pdf
- Xenon Hyperpolarizer System Operating Manual (Image not shown) received on March 30, 2022, available from \\CDSESUB1\evsprod\nda214375\0028\m3\32-body-data\32r-reg-info\32r492-xenon-hyperpolarizer-system-operating-manual-tc.pdf
- Xenon Hyperpolarizer Quick Reference Guide (Image not shown) received on March 30, 2022, available from \\CDSESUB1\evsprod\nda214375\0028\m3\32-body-data\32r-reg-info\32r493-xenon-hyperpolarizer-quick-reference-guide-tc.pdf
- Polarization Measurement Station Operating Manual (image not shown) received on October 5, 2020, available from \\CDSESUB1\evsprod\nda214375\0000\m3\32-body-data\32r-reg-info\32r494-polarization-measurement-station-operating-manual.pdf
- Dose Delivery Bag Instructions for Use (Image not shown) received on March 30, 2022, available from \\CDSESUB1\evsprod\nda214375\0028\m3\32-body-data\32r-reg-info\32r494-xenoview-dose-delivery-bag.pdf

[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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/

DEVIN R KANE
08/18/2022 03:22:45 PM

HINA S MEHTA
08/22/2022 09:42:00 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 13, 2022

To: Lisa Skarupa, Senior Regulatory Project Manager
Division of Imaging and Radiation Medicine (DIRM)

Younsook Kim, Associate Director for Labeling, DIRM

From: Nazia Fatima, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for XENOVIEW (xenon Xe-129 hyperpolarized), for oral inhaltion use

NDA: 214375

In response to DIRM consult request dated April 13, 2022, OPDP has reviewed the proposed product labeling (PI) and carton/container labeling for the original NDA submission for XENOVIEW (xenon Xe-129 hyperpolarized), for oral inhalation use (Xenoview).

OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DIRM on August 3, 2022. We have no additional comments at this time.

OPDP's comments on the proposed carton/container labeling for Xenoview are based on the draft carton/container labeling received by electronic mail from DIRM on August 3, 2022 and are provided below.

Thank you for your consult. If you have any questions, please contact Nazia Fatima 240-402-5041 or Nazia.Fatima@fda.hhs.gov.

17 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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/

NAZIA FATIMA
08/13/2022 10:10:15 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research
Office of New Drugs, ODE-IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date of Consult Request:	April 13, 2022
From:	The Division of Imaging and Radiation Medicine (DIRM)
To:	Division of Pediatric and Maternal Health (DPMH)
NDA Number:	214375
Drug:	Hyperpolarized 129-Xe
Applicant:	Polarean Inc
Indication:	indicated for use in conjunction with MRI (b) (4) [redacted]

DG submitted a consult request to DPMH on April 13, 2022: " DIRM will be finishing labeling review and initiate negotiations with Polarean.
a) to review labeling for resubmission.
b) to confirm recommendations made at PeRC meeting 9/14/21

- The PeRC agrees with granting partial waiver for pediatric patients less than 6 years of age because studies are impossible or highly impracticable as patients in the age range cannot comply with the breathing instructions.
- The PeRC agrees with granting a deferral for pediatric patients 6 to 12 years of age to allow the development of an age-appropriate presentation that would allow for direct administration of the correct dose in this population.
- The PeRC agrees with the pediatric assessment for pediatric patients 12 years of age and older.".

DPMH attended the meetings and provided comments to the pediatric labeling comments and maternal health Pregnancy and Lactation Labeling Rule (PLLR) last review cycle.

DPMH has no further comments at this time, thus, this memorandum will close out the consult request.

DPMH DDD:	John Alexander
DPMH Maternal MTL:	Miriam Dinatale
DPMH Pediatric MTL:	Shetarra Walker

DPMH Maternal Reviewer:	Wenjie Sun
DPMH Pediatric Reviewer:	Amy Taylor
DPMH RPM:	Denise Pica-Branco
DPMH SCSO:	Rosemary Addy

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/

DENISE J PICA-BRANCO
08/09/2022 01:11:44 PM

Clinical Inspection Summary (CIS)

Date	September 10, 2021
From	John Lee, M.D., Medical Officer Phillip Kronstein, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE)
To	Lisa Skarupa, Regulatory Project Manager Brenda Ye, M.D., Clinical Reviewer Alex Hofling, M.D., Ph.D., Clinical Team Leader Division of Imaging and Radiologic Medicine (DIRM)
Application	NDA 214375
Applicant	Polarean, Inc.
Drug	Hyperpolarized xenon-129 gas for inhalation (XenoView®)
NME / Original NDA	Yes
Review Timeframe	Standard
Proposed Indication	For use with MRI in evaluating lung function
Consultation Date	February 3, 2021
CIS Goal Date	August 5, 2021 (original); September 10, 2021 (extended)
Action Goal Date	October 4, 2021
PDUFA Due Date	October 5, 2021

I. OVERALL ASSESSMENT OF FINDINGS

Two studies (POL-Xe-001, POL-Xe-002) were audited in support of this NDA review by good clinical practice (**GCP**) inspections of two representative study sites: a contract research organization (**CRO**) where the primary efficacy endpoint data were generated, and a clinical investigator (**CI**) site where the major secondary efficacy endpoint as well as safety data were generated. No significant GCP violations were identified at either inspection. The clinical data generated by the inspected study sites (CRO and CI site) appear to be acceptable in support of this NDA.

II. BACKGROUND

This NDA from Polarean, Inc. supports the marketing approval of XenoView®, a drug-device combination product for diagnostic use with magnetic resonance imaging (**MRI**) in evaluating lung function. The active ingredient in XenoView® is hyperpolarized, non-radioactive xenon-129 gas intended for inhalation.

The two pivotal studies (POL-Xe-001, POL-Xe-002) for this NDA were conducted at three clinical investigator (**CI**) sites and three contract research organizations (**CROs**). The images acquired at the CI sites were transferred to the imaging CRO (b) (4) (b) (4) for formal image interpretation (primary efficacy endpoint data).

The sponsor's study responsibilities (including study oversight) were contracted out to two additional CROs: to (b) (4) (CI site monitoring and data management), and to Facet (study reports and NDA preparation). (b) (4) (major imaging CRO, primary efficacy data generation) and Duke (largest CI site, subject management and generation of secondary efficacy and adverse event data) were identified for good clinical practice (**GCP**) inspections in auditing the following two pivotal studies supporting this original NME NDA.

Study POL-Xe-001: *Evaluation of Hyperpolarized ^{129}Xe MRI as Compared to ^{133}Xe Scintigraphy for the Assessment of Pulmonary Function in Patients being Evaluated for Possible Lung Resection Surgery*

This randomized, pair-controlled, cross-over study was conducted between September 2018 and November 2019 in 33 subjects (per protocol analysis set, verifiable at (b) (4) inspection) at two CI sites. The primary study objective was to demonstrate that MRI using non-radioactive XenoView® (hyperpolarized ^{129}Xe) is as accurate as conventional scintigraphy using radioactive ^{133}Xe in evaluating lung function.

Adult subjects (age ≥18 years) under evaluation for resection of a lung zone for focal disease (e.g., localized emphysema or pulmonary mass) with a baseline resting oxygen saturation > 90% (with or without routine supplemental oxygen) were each given (by inhalation administration) the following two imaging agents in random order, each agent in conjunction with its respective imaging procedure (MRI or scintigraphy):

- 75 mL of hyperpolarized ^{129}Xe in 1.0 L of xenon-nitrogen gas mixture, administered with a dose delivery bag (inhalation and breath held for 10 seconds during MRI)
- Commercially available ^{133}Xe gas administered using a respirator system (inhalation administration per product label, nuclear medicine scintigraphy)

Lung function as indicated by the scans was quantified using a commercially available software as the sum of the contributions from the six pre-specified lung zones (pre-operative baseline lung function and post-operative predicted residual fraction of pre-operative baseline lung function).

The primary efficacy endpoint was the residual pulmonary function (proportion) predicted after the resection of a pre-specified lung area. The major secondary efficacy endpoints were post-operative forced expiratory volume over one second (**FEV-1**) and ventilation fraction, from each of the six lung zones. The sponsor claims that MRI using XenoView® is as accurate as (nuclear medicine) scintigraphy in predicting residual pulmonary function following lung resection, with a significant (non-radioactive) safety advantage.

Study POL-Xe-002: *Evaluation of Hyperpolarized ^{129}Xe MRI as Compared to ^{133}Xe Scintigraphy for the Assessment of Pulmonary Function in Patients being Evaluated for Possible Lung Transplant Surgery*

This randomized, pair-controlled, cross-over study was conducted between August 2018 and November 2019 in 49 subjects (per protocol analysis set, verifiable at (b) (4) inspection) at three CI sites. This lung transplantation study was similar to the lung resection study (POL-Xe-001), including nearly identical primary study objective and study design. The major differences were:

- Adult subjects under evaluation for unilateral or bilateral lung transplant for severe extensive disease (e.g., emphysema, pulmonary fibrosis, or interstitial disease) were each given the imaging agents.
- The primary efficacy endpoint was defined as the contribution by the right lung (percent volume) to the overall lung function. The secondary efficacy endpoint was the contribution by each of the six lung zones.

III. INSPECTION RESULTS

1. (b) (4)

Inspection dates: (b) (4)

There were 82 subjects enrolled in the two studies combined, 33 in POL-Xe-001 at three CI sites and 49 in POL-Xe-002 at two CI sites. The on-site inspection included a review of the source records (including electronic case report forms, **eCRFs**), (b) (4) contractual agreement and communication with Polarean, standard operating procedures (**SOPs**), imaging manuals, independent review charters (**IRC**), software validation, and reader documentation (qualification, training, and financial disclosures).

(b) (4) provided training and on-going assistance to the CI sites with MRI image acquisition and electronic image transfer. For each study, a central reader at (b) (4) evaluated the images received from the CI sites, generated recorded source records from the images, and delivered the results to the sponsor Polarean (imaging data with annotated image overlays). The readers for the two studies were qualified based on their training and experience (medical imaging) and were further trained (remotely via WebEx) specifically on the IRC as outlined in the site training manual.

No significant GCP deficiencies were observed. Noteworthy observations were limited to minor deficiencies that appeared unlikely to be significant (e.g., final sign-off on reader training certification late by three months). Study files and subject case records including MRI and scintigraphy images were well maintained and readily available for review. No unreported protocol deviations were discovered. The primary efficacy (imaging) endpoint data were verifiable against the data reported in the NDA.

2. Matthew G. Hartwig, M.D.

Duke University Medical Center
Durham, NC 27710
Inspection dates: June 14-17, 2021

All major areas of study conduct were audited at this inspection: informed consent, subject selection, study therapy, endpoint assessment, protocol compliance, and recordkeeping. Subject case records were reviewed in detail for all subjects enrolled in the following two pivotal studies:

- POL-Xe-001: 18 subjects screened, 12 enrolled, and 10 completing study
- POL-Xe-002: 38 subjects screened, 30 enrolled, and 28 completing study

No significant GCP deficiencies were observed for either study. The observed deficiencies appeared to be minor, isolated, and unlikely to be significant, for example: (a) exceeding the time limit between study medication preparation and administration (unreported protocol deviation), and (b) not signing or dating the data transmission form (recordkeeping oversight). No unreported clinical AEs were discovered. Study records (including subject case histories) were complete, organized, and readily available for audit review. The major secondary efficacy (spirometry) endpoint data were adequately verifiable against the data reported in the NDA.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

{See appended electronic signature page}

Phillip D. Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Document Room / NDA 214375

DIRM / Team Leader / Alex Hofling
DIRM / Medical Officer / Brenda Ye
DIRM / Regulatory Project Manager / Lisa Skarupa

OSI / Office Director / David Burrow
OSI / DCCE / Acting Division Director / Kassa Ayalew
OSI / DCCE / GCPAB / Branch Chief / Kassa Ayalew
OSI / DCCE / GCPAB / Team Leader / Phillip Kronstein
OSI / DCCE / GCPAB / Medical Officer / John Lee
OSI / DCCE / GCPAB / Program Analyst / Yolanda Patague
OSI / Database Project Manager / Dana Walters

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/

JONG HOON LEE
09/10/2021 01:48:54 AM

PHILLIP D KRONSTEIN
09/10/2021 06:22:54 AM

KASSA AYALEW
09/10/2021 09:55:49 AM

DIVISION OF PULMONOLOGY, ALLERGY AND CRITICAL CARE (DPACC)
MEDICAL OFFICER CONSULTATION

Date:	July 20, 2021
To:	Lisa Skarupa, RPM, DIRM
From:	Elisabeth Boulos, Medical Officer, DPACC
Through:	Kelly Stone, Clinical Team Leader, DPACC
Through:	Banu Karimi-Shah, Deputy Division Director, DPACC
Subject:	Hyperpolarized Xenon-129 for pre-operative imaging of lung ventilation

General Information

NDA:	214375
Sponsor:	Polarean Inc.
Drug Product:	Hyperpolarized Xenon-129
Request From:	Lisa Skarupa, DIRM
Date of Request:	June 25, 2021
Sponsor Meeting:	N/A
Reviewed:	Investigator's Brochure Sponsor's proposed label Response to Clinical / DPMH IR, June 30, 2021 Response to Clinical / DPMH IR, June 4, 2021 IND [redacted] (b) (4) DSUR December 4, 2020 DPMH Review, June 16, 2020

Executive Summary

This is a Medical Officer response to a request for consultation from DIRM regarding pediatric dosing of hyperpolarized Xenon-129 (Xe-129) to be used as an inhaled contrast agent for pulmonary MRI. DIRM is working towards approval of NDA 214375 for Xe-129 as a drug / device combination with the indication of [redacted] (b) (4) DIRM, in consultation with DPMH, denied the Sponsor's request for a full pediatric waver, and the Sponsor subsequently submitted two amendments outlining their strategy for pediatric dosing in accordance with a 505(b)2 pathway. At the time of this response, the most likely approach will include labeling the same dose for adults and pediatric patients down to 12 years of age [redacted] (b) (4) DIRM requests DPACC's assessment of the Sponsor's pediatric dosing and drug administration strategy.

Regulatory History and Product Overview

Xe-129 is not currently approved for any indication in any country. Xenon-133, the radioactive isotope, is approved for use with scintigraphy, and stable Xenon gas is approved in parts of the EU as an anesthetic. Polarean Inc. submitted NDA 214375 under

the 505(b)2 pathway on October 5, 2020 with the proposed commercial name of Xenoview. Xenoview will comprise a gas cylinder containing 1% isotopically-enriched Xe-129, a hyperpolarizer, which will polarize the Xe-129 atoms for NMR, a dose-delivery bag, and a measurement station. Polarean has developed its dosing strategy using the concept of dose equivalent (DE), i.e., the amount of imageable Xe-129 atoms in the total volume of gas delivered, as outlined in the figure below:

Table 1 Composition of the ^{129}Xe Final Drug Product Used in All Clinical Studies

Component	Amount	Function	Quality Standard
Hyperpolarized ^{129}Xenon	(b) (4) mL total Xe	Active	In House
Nitrogen, NF	q.s. to volume	(b) (4)	99.9999% purity
Total Volume	1 L		

Figure 1. Table 1 from Polarean IB: DE of Xe-129 for adults and children ≥ 12 years will be (b) (4) mL with purified N2 used to complete total volume of dose-delivery bag of 1 L.

Xenoview will be administered to patients via a single breath hold of 10 seconds duration.

The rationale for the development of Xenoview is to provide an imaging modality that can obtain more detailed regional anatomic images of lung ventilation without exposure to radiation or radioactive isotopes, as in traditional scintigraphy with Xenon-133. Xenon, an 'inert' gas, is relatively inactive physiologically, rapidly eliminated through exhalation after a single pass through the circulatory system, and expected to have minimal to no systemic absorption. At higher concentrations or during prolonged inhalation, Xenon can cause CNS and respiratory depression associated with transient hypoxemia, apnea, euphoria, and disassociation.

The Sponsor's clinical development program includes a safety database of approximately 150 subjects, among whom the majority of TEAEs were mild-moderate and self-limited. One death, one treatment discontinuation, and four SAEs were not attributed to study drug. (b) (4)

Questions from DIRM

We are asking for DPACC to opine on the appropriateness and practicality of such a strategy for determining volumes to be dosed in children. Any alternative pediatric dosing suggestions would be welcome as well.

Polarean initially proposed to market Xenoview (b) (4) For pediatric dosing, Polarean submitted the following label revision and table (b) (4)

2 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

II. Conclusion

Overall, we find the Sponsor's dose and dose delivery strategy to be reasonable. We are not aware of alternative strategies that would be obviously superior, and we do not have outstanding concerns regarding safety. (b) (4)

References

1. (b) (4)
2.
3.
4.
5. Refer to Table 1 from Polarean's response to clinical IR June 4, 2021 for additional literature references.

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/

ELISABETH S BOULOS
07/27/2021 06:53:27 PM

KELLY D STONE
07/27/2021 06:58:05 PM

BANU A KARIMI SHAH
07/28/2021 08:25:31 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 22, 2021
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DIRM)
Application Type and Number:	NDA 214375
Product Name and Strength:	Xenoview (hyperpolarized xenon Xe 129) gas, 1 L (75 mL Dose Equivalent)
Applicant/Sponsor Name:	Polarean Inc.
OSE RCM #:	2020-2131-1
DMEPA 2 Safety Evaluator:	Devin Kane, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Polarean Inc. submitted revised dose delivery bag container label, dose delivery bag carton labeling, and Hyperpolarized Xenon Xe 129 gas cylinder container label on July 12, 2021 for Xenoview (hyperpolarized xenon Xe 129) gas for inhalation under NDA 214375. We reviewed the revised dose delivery bag container label, dose delivery bag carton labeling, and Hyperpolarized Xenon Xe 129 gas cylinder container label for Xenoview (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that were made during a previous label and labeling review.[a]

2 CONCLUSION

The revised dose delivery bag container label, dose delivery bag carton labeling, and hyperpolarized xeon Xe 129 gas cylinder container label are unacceptable from a medication error perspective. We note (b) (4) (b) (4). Additionally, we note the dosage form is presented as (b) (4) We provide our recommendations below for Polarean Inc.

[a] Kane D. Label and Labeling Review for Xenoview (NDA 214375). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 JUN 21. RCM No.: 2020-2131.

3 RECOMMENDATIONS FOR POLAREAN INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments Regarding Dose Delivery Bag Container Label, Dose Delivery Bag Carton Labeling, and Hyperpolarized Xenon Xe 129 Gas Cylinder Container Label

1. We note (b) (4) We recommend revising the presentation of the proprietary name (b) (4) (b) (4)
2. As currently presented, the dosage form for Xenoview is presented on the carton and container labels as (b) (4) We note the dosage form for Xenoview is presented in the PI as (b) (4) For consistency with the PI, we recommend displaying the dosage form on the carton and container labels as (b) (4)

4 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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/

DEVIN R KANE
07/22/2021 08:23:55 AM

HINA S MEHTA
07/22/2021 05:31:46 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	June 21, 2021
Requesting Office or Division:	Division of Medical Imaging and Radiation Medicine (DMIRM)
Application Type and Number:	NDA 214375
Product Name, Dosage Form, and Strength:	Xenoview (Hyperpolarized Xenon 129 (Xe 129)) gas, 1 L (75 mL Dose Equivalent)
Product Type:	Combination Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Polarean Inc.
FDA Received Date:	October 5, 2020
OSE RCM #:	2020-2131
DMEPA Safety Evaluator:	Devin Kane, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Polarean Inc. submitted 505(b)(2) NDA 214375 Xenoview (Hyperpolarized Xenon 129 (Xe 129)) gas on October 5, 2020. Xenoview is proposed as an indication (b) (4) We evaluated the proposed Xenoview prescribing information (PI), dose delivery bag container label, dose delivery bag carton labeling, Xenon 129 gas cylinder label, Xenon Hyperpolarizer System Operator Manual, Xenon Hyperpolarizer System Quick Reference Guide, Polarization Measurement Station Operating Manual, and Dose Delivery Bag Instructions for Use for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

Polarean Inc. submitted a use-related risk analysis (URRA), formative human factors (HF) data, and additional HF questions as part of Type C and Type B meeting packages under IND 75010 to determine whether HF validation study results should be submitted as part of the marketing application. The review concluded that results from an HF validation study did not need to be submitted for Agency review for the proposed product.[a]

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

[a] Whaley, E. Xenon 129 Gas (IND 75010) Use-Related Risk Analysis Review. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 02. RCM No. 2019-950.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Polarean Inc. submitted a 505(b)(2) application to obtain marketing approval of Xenoview gas for inhalation.

Hyperpolarized Xenon 129 gas is created using the Xenon Hyperpolarizer System. (b) (4) We note the amount of Xenoview in the dose delivery bag is measured by the Polarization Measurement Station prior to patient administration. The hyperporalized Xe-129 is mixed with a necessary volume of Nitrogen (99.999% purity) to achieve a final volume of up to 1 L. Additionally, we note the patient will inhale the entire contents from the dose delivery bag using a Xe-129 chest coil.

We performed a risk assessment of the proposed prescribing information (PI), dose delivery bag container label, dose delivery bag carton labeling, Xenon 129 (Xe 129) gas cylinder label, Xenon Hyperpolarizer System Operator Manual, Xenon Hyperpolarizer System Quick Reference Guide, Polarization Measurement Station Operating Manual, and Dose Delivery Bag Instructions for Use to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. Our evaluation of the proposed PI, dose delivery bag container label, dose delivery bag carton labeling, Xenon 129 (Xe 129) gas cylinder label Xenon Hyperpolarizer System Operator Manual, Xenon Hyperpolarizer System Quick Reference Guide, Polarization Measurement Station Operating Manual, and Dose Delivery Bag Instructions for Use for Xenoview identified areas of vulnerability that may lead to medication errors. We provide our recommendations below.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Xenoview prescribing information (PI), dose delivery bag container label, dose delivery bag carton labeling, Xenon 129 (Xe 129) gas cylinder label, Xenon Hyperpolarizer System Operator Manual, Xenon Hyperpolarizer System Quick Reference Guide, Polarization Measurement Station Operating Manual, and Dose Delivery Bag Instructions for Use identified areas of vulnerability that may lead to medication errors. Below, we have provided recommendations in Section 4.1 for the Division and Section 4.2 for the Applicant. We ask that the Division convey Section 4.2 in its entirety to Polarean Inc. so that recommendations are implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR DIVISION OF MEDICAL IMAGING AND RADIATION MEDICINE (DIRM)

A. Highlights of Prescribing Information

1. Dosage and Administration

    a. We note the use of the symbol "-" to present the range with the intended meaning "to". We recommend removing the use of the symbol and replacing it with its intended meaning "to".

    b. We recommend including a bullet at the end of the Highlights of Dosage and Administration section that states "See Full Prescribing information [redacted (b) (4)]

2. Dosage Forms and Strengths

    a. The first sentence of the highlights of dosage forms and strengths currently states [redacted (b) (4)] We recommend removing this first sentence as it is not required as a part of the highlights of dosage forms and strengths section.

    b. We note there are values presented in the Highlights of Dosage Forms and Strengths section without their respective units. We recommend including the appropriate units after each value in order to avoid confusion.

    c. We note the use of the symbol "-" to present the range with the intended meaning "to". We recommend removing the use of the symbol and replacing it with its intended meaning "to".

B. Prescribing Information

1. Section 2: Dosage and Administration

    a. We note the use of the symbol "-" to present the range with the intended meaning "to". We recommend removing the use of the symbol and replacing it with its intended meaning "to".

    b. As currently presented, Section 2.1 presents the recommended dose [redacted (b) (4)] We recommend including subheadings in Section 2.1 in order to increase the readability of important information. We recommend including one subheading for recommended dose and one subheading for preparation and administration.

2. Section 3: Dosage Forms and Strengths

    a. We note there are values presented in the Dosage Forms and Strengths section without their respective units. We recommend including the appropriate units after each value in order to avoid confusion.

    b. We note the use of the symbol "-" to present the range with the intended meaning "to". We recommend removing the use of the symbol and replacing it with its intended meaning "to".

3. Section 16: How Supplied/Storage and Handling

   a. We note the use of the symbol "-" to present the range with the intended meaning "to". We recommend removing the use of the symbol and replacing it with its intended meaning "to".

   b. As currently presented, numeric values greater than 1,000 are presented in Section 16.1 without a comma. We recommend including a comma for all numeric values greater than 1,000 in order to avoid misinterpretation of the value.

   c. As currently presented, (b) (4) states that Xenoview (b) (4) Additionally, we note that information regarding the expiry of Xenoview is not provided. We recommend including a statement (b) (4) that says "Do not use and discard Xenoview 60 minutes after (b) (4)".

   d. We note that Section 16 does not contain any information regarding the expiration of the unused gas compressed in the aluminum cylinders. We recommend including expiry information regarding the unused compressed gas (b) (4)

C. Xenon Hyperpolarizer System Operating Manual

1. We note numeric values are presented in the Xenon Hyperpolarizer System Operating Manual immediately followed by the respective units. We recommend including a space between all numeric values and the appropriate units in order to improve readability.

2. We note in the Table 1: Abbreviations and Acronyms the symbol "µ" is used for the abbreviation for the unit "microwatt". We recommend removing the use of the symbol and using "microW" as the abbreviation for microwatt throughout the Xenon Hyperpolarizer System Operating Manual.

3. As currently presented, the symbol "-" is used to represent the word "to" for numeric ranges. We recommend removing the use of the symbol and replacing it with its intended meaning of "to" throughout the Operating Manual.

4. We note there are numeric values presented in the Operating Manual that are not followed by the appropriate units. We recommend including units after all numeric values in the Xenon Hyperpolarizer System Operating Manual.

5. We note the use of the symbol "<" to represent "less than" and the symbol ">" to represent "greater than" in the Operating Manual. We recommend removing the use of these symbols throughout the operating manual and replacing them with their intended meanings in order to improve the readability.

6. As currently presented, the symbol "~" is used in order to represent "about" or "around" throughout the Operating Manual. We recommend removing the use

of this symbol and replacing it with its intended meaning in order to improve readability.

7. We note in Section 4 of the Xenon Hyperpolarizer System Operating Manual that the Dual-action oven has a heating and cooling capability up to 200°C. We recommend including the Fahrenheit temperature equivalent in parenthesis after all Celsius temperatures in Section 4 and throughout the Operating Manual.
8. As currently presented, numeric values that are greater than 1,000 are presented in the Xenon Hyperpolarizer System Operating Manual without the use of the comma. We recommend including the comma for all numeric values greater than 1,000 in order to avoid misinterpretation of the value.
9. We note the use of trailing zeros used in Section 4 under "Cryotrap". We recommend removing the use of all trailing zeros in Section 4 and throughout the Operating Manual in order to avoid ten-fold misinterpretation of the value.
10. We note from the Xenoview Prescribing Information that the prepared dose of Xenoview is only good for 60 minutes. As currently presented, the Xenon Hyperpolarizer System Operating Manual does not provide this important information. We recommend including the statement "Do not use and discard the dose of Xenoview 60 mins after (b) (4)" in step (b) (4) of Thawing (b) (4) Xenon in Section (b) (4)

D. Xenon Hyperpolarizer Quick Reference Guide

1. We note the use of the symbol "-" throughout the Xenon Hyperpolarizer Quick Reference guide to represent the word "to", and the symbol "~" used to represent "about" or "around". We recommend removing the use of the symbol and replacing it with its intended meaning.
2. We note there are numeric values presented in the Xenon Hyperpolarizer Quick Reference Guide that are presented without their units. We recommend including units after all numeric values. Additionally, we note some numeric values are immediately by their units without a space between them. We recommend including a space between all numeric values and their respective units.

E. Polarization Measurement Station Operating Manual

F. Dose Delivery Bag Instructions for Use

1. We note in the Introduction the dose delivery bag is defined as (b) (4) (b) (4) We recommend referring to the dose delivery bag as "single-dose delivery bag" throughout the Instructions for Use.
2. (b) (4)

4.2 RECOMMENDATIONS FOR POLAREAN INC.

We recommend the following be implemented prior to approval of this NDA:

A. Dose Delivery Bag Container Label

1. We note the proposed dose delivery bag container label contains a blank for (b) (4) We recommend revising this line to read "date and time (b) (4) Additionally, we note the dose equivalent must be measured no more than 5 minutes before administration to the patient. We recommend including the statement "*Measure Dose Equivalence within 5 Minutes of Patient Administration*" on the dose delivery bag container label.
2. As currently presented, the proposed dose delivery bag container label does not provide information regarding the expiry of Xenoview. We recommend including the statement "Do not use and discard 60 minutes after (b) (4) " next to the date and time (b) (4) line.

3. We note the proposed dose delivery bag container label does not contain the statement “Rx Only”. We recommend including the statement “Rx Only” on the container label.

4. As currently presented, the proposed dose delivery bag container label lacks a statement directing the end user to the Xenoview prescribing information. We recommend including the statement “Recommended Dosage: See Prescribing Information”.

5. We note the proposed dose delivery bag container label lacks information regarding the storage of the dose delivery bag. We recommend including the statement “Store at room temperature 20° to 25°C (68° to 77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F)” on the proposed container label.

6. As currently presented, the package type is not defined on the proposed dose delivery bag container label. We recommend including the statement “Single-Dose Container” on the dose delivery bag container label.

B. Dose Delivery Bag Carton Labeling

1. We note the proposed dose delivery bag carton labeling lacks information regarding the storage of the dose delivery bag. We recommend including the statement “Store at room temperature 20° to 25°C (68° to 77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F)” on the proposed carton labeling.

2. As currently presented, in the “contents” box the numeric value “1” is immediately followed by the units “L” without a space between the numeric value and the units. We recommend including a space between all numeric values and the appropriate units.

3. We note the statement (b) (4) presented in the Contents box on the proposed dose delivery bag carton labeling. We recommend revising this statement to read “1 prescribing information”.

4. As currently presented, the proposed dose delivery bag carton labeling lacks a statement directing the end user to the Xenoview prescribing information. We recommend including the statement “Recommended Dose: See Prescribing Information”.

5. We note the proposed dose delivery bag carton labeling has a placeholder for the expiration displayed as “xxxx”. We recommend that the expiration date appears in DD/MM/YYYY format is only numerical characters are used or in DD/MMM/YYYY is alphabetical characters are used to represent the month.

C. Hyperpolarized Xeon Xe 129 Gas Cylinder Label

1. As currently presented, numeric values greater than 1,000 are presented on the proposed Hyperpolarized Xeon Xe 129 Gas Cylinder Label without a comma. We recommend including a comma for all numeric values greater than 1,000 in order to avoid misinterpretation of the value.

2. We note the use of the symbol “-“ on the proposed Hyperpolarized Xenon Xe 129 Gas Cylinder label in order to represent the word “to” as part of the storage

information. We recommend removing the use of the symbol and replacing it with its intended meaning "to".

3. We note the storage temperature requirements displayed on the proposed Hyperpolarized Xeon Xe 129 Gas Cylinder Label differ from the storage temperature requirements presented in Section 16 of the Xenoview prescribing information. We recommend revising the storage temperature requirements in order to align with the presentation used in the PI. Revise the storage temperature requirements to read "Store at room temperature 20° to 25°C (68° to 77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F)".
4. As currently presented, the "Rx Only" statement is displayed (b) (4) on the proposed label. We recommend displaying the "Rx Only" statement (b) (4) (b) (4) and decreasing the prominence of this statement.
5. We note the proposed Hyperolarized Xenon Xe 129 Gas Cylinder label lacks a statement directing the end user to the Xenoview prescribing information. We recommend including the statement "Recommended Dosage: See Prescribing Information".
6. We note the proposed Hyperolarized Xenon Xe 129 Gas Cylinder label lacks a defined location for the expiration information. We recommend displaying the expiration information on the proposed label. We recommend that the expiration date appears in DD/MM/YYYY format is only numerical characters are used or in DD/MMM/YYYY is alphabetical characters are used to represent the month.
7. As currently presented, the package type is not defined on the proposed Hyperpolarized Xeon Xe 129 Gas Cylinder Label. We recommend including the statement "Multiple-Dose Container" on the Hyperpolarized Xeon Xe 129 Gas Cylinder Label.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xenoview received on October 5, 2020 from Polarean Inc..

Table 2. Relevant Product Information for Xenoview	
Initial Approval Date	N/A
Active Ingredient	Hyperpolarized Xenon 129 (Xe 129)
Indication	(b) (4)
Route of Administration	Inhalation
Dosage Form	gas
Strength	1 L (75 mL Dose Equivalent)
Dose and Frequency	The recommended dose of Xenoview is 75 mL DE (Dose Equivalent) of hyperpolarized Xe-129 gas with a range of 250 mL-750 mL total Xe.
How Supplied	(b) (4)
Storage	Store (b) (4) gas blend at (b) (4) 20° to 25°C (68° to 77°F), with excursions permitted to 15°C to 30°C (59°F to 86°F).
Container Closure	The Xenoview gas blend for preparation of Xenoview is supplied (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 4, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, Xenoview and Hyperpolarized Xenon 129. Our search identified 1 previous review[b], and we considered our previous recommendations to see if they are applicable for this current review.

Table 1. Summary of Previous DMEPA Reviews for Xenoview

OSE RCM #	Review Date	Summary of Recommendations
2019-950	June 2, 2020	Based on the review of the use-related risk analysis (URRA), data from the formative human factors (HF) questionnaire, and discussion with DMIRM, CDRH, and CDRH HF, DMEPA found that that the Sponsor does not need to submit the results of HF validation testing to support their marketing application. DMEPA discussed their recommendations with DMIRM, CDRH, and CDRH HF and they are aligned with our recommendation.

[b] Whaley, E. Human Factors Use-Related Risk Analysis Review for Xenon 129 (IND 75010). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUN 02. RCM No.: 2019-950.

APPENDIX G.LABELS AND LABELING

G.1List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Xenoview labels and labeling submitted by Polarean Inc..

- Dose Delivery Bag Container label received on October 5, 2020
- Dose Delivery Bag Carton labeling received on October 5, 2020
- Hyperpolarized Xenon Xe 129 Gas Cylinder Container Label received on October 5, 2020
- Prescribing Information (Image not shown) received on October 5, 2020, available from \\CDSESUB1\evsprod\nda214375\0000\m1\us\draft-labeling-text.pdf
- Xenon Hyperpolarizer System Operator Manual (image not shown) received on October 5, 2020, available from \\CDSESUB1\evsprod\nda214375\0000\m3\32-body-data\32r-reg-info\32r492-xenon-hyperpolarizer-system-operating-manual.pdf
- Xenon Hyperpolarizer System Quick Reference Guide (image not shown) received on October 5, 2020, available from \\CDSESUB1\evsprod\nda214375\0000\m3\32-body-data\32r-reg-info\32r493-xenon-hyperpolarizer-quick-reference-guide.pdf
- Polarization Measurement Station Operating Manual (image not shown) received on October 5, 2020, available from \\CDSESUB1\evsprod\nda214375\0000\m3\32-body-data\32r-reg-info\32r494-polarization-measurement-station-operating-manual.pdf
- Dose Delivery Bag Instructions For Use (image not shown) received on October 5, 2020, available from \\CDSESUB1\evsprod\nda214375\0000\m3\32-body-data\32r-reg-info\32r495-dose-delivery-bag-instructions-for-use.pdf

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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/

DEVIN R KANE
06/21/2021 01:47:03 PM

HINA S MEHTA
06/22/2021 03:44:06 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatrics and Maternal Health Review

Date: 6/16/2021 **Date consulted:** 10/27/2020

From: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatrics and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatrics and Maternal Health (DPMH)

To: Division of Imaging and Radiation Medicine (DIRM)

Drug: XenoView (hyperpolarized 129-Xe) gas for inhalation

NDA: 214375

Applicant: Polarean Inc.

Subject: Pregnancy and Lactation Labeling

Proposed Indication: For use in conjunction with MRI (b) (4) (b) (4)

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 214375
- DIRM consult form for DPMH, DARRTS Reference ID 4692914

Consult Question:

DIRM is seeking assistance from DPMH in developing Sections 8.1, 8.2 and 8.3 of the product's labeling.

INTRODUCTION AND BACKGROUND

On October 5, 2020, the applicant (Polarean Inc.) submitted a new NDA for XenoView (hyperpolarized 129-Xe) gas for inhalation for approval. The Division of Imaging and Radiation Medicine (DIRM) consulted the Division of Pediatric and Maternal Health (DPMH) on October 27, 2020, to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- Hyperpolarized Xe-129 is used in conjunction with MRI (b) (4) (b) (4) It has not been previously approved for use in the U.S. or any other countries.
- On October 5, 2020, the applicant submitted a new NDA under 505(b)2 pathway for XenoView, NDA 214375. The referenced listed drug (RLD) is Xe-133, approved in 1974, which is a small molecule radioactive diagnostic agent used for gamma scintigraphy. In contrast, Xenoview is a stable isotope (i.e, is not radioactive).
- The applicant requested a priority review.

Drug Characteristics Based on Applicant's Proposed labeling

XenoView is made up of 1% hyperpolarized Xe-129, 10% of Nitrogen, and 89% of helium. Xe-129 is the active ingredient and it is a monatomic, insert, stable, noble gas. Unlike Xe-133 used in scintigraphy, it is not radioactive. XenoView is prepackaged in individual container and administered by inhalation.

Drug Characteristic[1]

Drug Class	Inhalation diagnostic agent
Mechanism of action[2]	When hyperpolarized Xe-129 gas is inhaled, a multi-nuclear capable MRI scanner can be used to image the hyperpolarized Xe-129 distribution throughout the lungs. Hyperpolarized Xe-129 provides an MRI signal which is dependent on the number of polarized Xe-129 nuclei. Hyperpolarized Xe-129 gas MRI provides an ionizing-radiation-free method to image pulmonary structure and function.
Dose and administration[3]	(b) (4) mL Dose Equivalent of hyperpolarized Xe-129 gas
Molecular weight[3]	128.90 g/mol
Proposed Metabolism[3]	Not metabolized, it is eliminated via lung extraction and exhalation.
Half-life[3]	14.5 seconds for a 75% xenon/25% N2 gas mixture and 14.3 seconds for a 25% xenon/75% N2 gas mixture
Protein Binding[3]	NA
Bioavailability[3]	NA

[1] Based on Applicant's Proposed Labeling with DIRM Review Team Input.
[2] Based on discussion with DIRM Pharmacology Toxicology Team. 3/8/21
[3] Based on discussion with DIRM Clinical Pharmacology Team. 3/8/21

Serious Adverse Reactions[4]	No serious adverse reactions.

Reviewer's table

Reviewer comment:
In discussion with DIRM Clinical Pharmacology team, it was noted that inhaled hyperpolarized xenon gas is minimally absorbed systemically.

Current State of the Labeling for the approved RLD, Xenon Xe 133 gas, NDA 17284

- Approved labeling is not in Physician Labeling Rule (PLR) or Pregnancy and Lactation Labeling Rule (PLLR) format because it was approved in 1974.
- There is no boxed warning.
- There is no contraindication for use.

Pregnancy notes the following:

Category C

"Animal reproductive studies have not been conducted with Xenon Xe 133 Gas. It is also not known whether Xenon Xe 133 Gas can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Xenon Xe 133 Gas should be given to a pregnant woman only if clearly needed.
Ideally, examination using radiopharmaceuticals, especially those elective in nature in a woman of childbearing capability, should be performed during the first few (approximately 10) days following the onset of menses."

Nursing Mothers notes the following:

"It is not known whether Xenon Xe 133 is excreted in human milk. Many drugs are excreted in human milk, therefore formula feedings should be substituted for breast feeding, because of the potential for adverse reactions in nursing infants."

- There are no existing pregnancy testing/contraception recommendations.
- There are known drug-drug interactions with hormonal contraceptives.

REVIEW

Nonclinical Experience

Adequately designed animal reproduction studies have not been conducted with Hyperpolarized Xe-129. Although not adequately designed to evaluate reproductive and developmental toxicity, there was animal reproduction data available in the literature. Animal reproduction studies were conducted in rats by administering an 80% Xe/20% O2 gas mixture for 2 hours twice a week for 2 and 10 weeks, with no observed effects on fertility or pregnancy. Gas mixtures containing 70%-75% Xe gas and 25%-30% O2 gas were found to be non-teratogenic in rats when administered for 24 hours. In a separate study, rats were administered an 80%/20% Xe/O2 gas mixture for 2 hours twice a week from the 1st to 19th day of pregnancy with no observed effects on embryo-fetal development or signs of teratogenicity.

The reader is referred to full Pharmacology/Toxicology review by Ron Honchel, Ph.D. and Bayo Laniyonu, Ph.D.

[4] Based on discussion with DIRM Clinical Team. 3/8/21

Review of Clinical Trials
There were no reports of any pregnancy in the clinical trials.

Review of Literature
DPMH's Review of Literature
DPMH conducted an updated published literature review using Embase, Pubmed, Micromedex,[5] ReproTox,[6] Shepard,[7] and TERIS.[8] Search terms used were "xenon AND pregnancy," "xenon AND pregnancy AND fetal malformations/congenital malformations/birth defects/stillbirth/spontaneous abortion/miscarriage."

- No relevant articles were found.

Micromedex[5] does not contain any information on xenon gas; however, there was information on Xe-133, a radioactive isotope of xenon. Micromedex[5] states it is unknown if Xe-133 crosses the placenta. There are no adequate or well controlled studies of Xe-133 use in pregnant females. Micromedex[5] gives the Pregnancy Rating: "Fetal risk cannot be ruled out."

ReproTox[6] states that xenon is used in lamps and has been used as an anesthetic. The radionuclide Xe-133 is used in diagnostic imaging. Experimental animal studies do not suggest that xenon increases the risk of congenital anomalies.

Xenon was not found in Shepard's[7] or TERIS.[8]

Reviewer comment:
Overall, the applicant provided an adequate review of their clinical trials. There are no published studies or case reports of use of xenon gas in pregnancy. Because the systemic absorption of hyperpolarized xenon following administration by inhalation is minimal, maternal use is not expected to result in fetal exposure to the drug. This was confirmed by discussion with the DIRM Clinical Pharmacology team. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

LACTATION
Nonclinical Experience
No animal studies were submitted with this NDA. It is not known if xenon gas is present in animal milk.

Review of Clinical Trials
There were no lactating females in the clinical trial.

[5] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 10/29/2020.
[6] ReproTox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 10/29/2020.
[7] 2020 Shepard's: A Catalog of Teratogenic Agents, compilations of scientific reviews on the teratogenic effects of over 2000 drugs chemicals, and other physical and biologic agents. Accessed 10/29/2020.
[8] Teris database, Truven Health Analytics, Micromedex Solutions, Accessed 10/29/2020.

Review of Literature

DPMH's Review of Literature

DPMH conducted a published literature review using Embase, Pubmed, Micromedex,[9] ReproTox,[10] LactMed[11], Hale[12], and Briggs.[13] Search terms used in Embase and Pubmed were "xenon AND lactation," "xenon AND breastfeeding." DPMH was able to locate the following article.

- A case series described four lactating persons, a few months postpartum, exposed to xenon, propofol and remifentanil in surgery with various indications. Xenon, propofol, and remifentanil levels in blood and milk were measured. Concentration of xenon was measured in milk samples from two patients' at 0- and 300-minutes post extubation. No trace of xenon gas was found in the maternal milk at any time after extubation. Infants resumed breastfeeding from 1.5 to 5 hours after the end of surgery. None of the infants had noticeable symptoms of dizziness or drowsiness. All infants fared well at home after their mothers were discharged.[14]

LactMed[11] and ReproTox[10] quote the case series[14] above and conclude that xenon is unlikely to be a hazard to the breastfeeding infant. While Hale[12] and Micromedex[9] contain no information on the use of Xe-129 during lactation, both contain information on the use of Xe-133 during lactation. Hale[12] states that the International Commission on Radiological Protection recommends no interruption of breastfeeding after exposure to Xe-133.[15, 16] Information about xenon was not found in Briggs.[13]

Reviewer comment:

Overall, the applicant provided an adequate review of their clinical trials. The systemic absorption of hyperpolarized xenon following administration by inhalation is minimal; therefore, maternal use of xenon is not expected to result in exposure of the breastfed infant. There is only one lactation pharmacokinetic study of xenon gas use, as anesthetic, in lactation, and xenon was undetectable in breastmilk after extubation. This is consistent with the fact the systemic

[9] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 10/29/2020.

[10] ReproTox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 10/29/2020.

[11] http;//toxnet nlm.nih.gov/newtoxnet/lactmed htm. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The Lactmed data base provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfeeding infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility. Accessed 10/29/2020.

[12] Hale, Thomas. Hale's Medications and Mother's Milk 2019. Springer Publishing Company, New York, NY.

[13] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015. Online, accessed 10/29/2020.

[14] Stuttmann R, et al. The breast feeding mother and xenon anaesthesia: four case reports. Breast feeding and xenon anaesthesia. BMC Anesthesiology 2010; 10:1.

[15] International Commission on Radiological Protection (ICRP). Radiation dose to patients from radiopharmaceuticals. Addendum 3 to ICRP Publication 53. ICRP Publication 106. Annex D. Ann ICRP. 2008; 38:163-84.

[16] Mattsson S, Johansson L, Svegborn S et al. Radiation dose to patients from radiopharmaceuticals: a compendium of current information related to frequently used substances. Annex D. Recommendations on breast-feeding interruptions. Ann ICRP 2015;44(2Suppl):319-21.

absorption of inhaled xenon is minimal. In addition, based physical properties of xenon gas, which is an inert noble gas with a short biologic half-life of 14 seconds, xenon is unlikely to be present in breastmilk. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data, submission, and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

No animal studies on mutagenic of carcinogenic potential have been performed. Adequately designed studies to evaluate fertility have not been performed. In a study available in the literature, male and female rats were administered an 80%/20% mixture of Xe/O2 for 2 hours twice a week with no effect on fertility. In a second study, male and female rats were administered an 80%/20% mixture of Xe/O2 for 2 hours twice a week for 2 and 10 weeks prior to breeding with unexposed animals. No effects on fertility were found.

The reader is referred to full Pharmacology/Toxicology review by Ron Honchel, Ph.D. and Bayo Laniyonu, Ph.D.

Review of Clinical Trials

There were no cases of infertility detected in the clinical trials.

Review of Literature

DPMH's review of literature

DPMH conducted a review of published literature using Embase, Pubmed, Micromedex,[17] ReproTox,[18] and TERIS.[19] Search terms used were "xenon AND reproduction," "xenon AND infertility," and "xenon AND contraception."

- There are no articles regarding xenon use adversely affecting human fertility.

ReproTox[18] was unable to locate any references on possible fertility effects of this agent.

Reviewer comment:

Overall, the applicant provided an adequate review of their clinical trial regarding xenon use in females and males of reproductive potential. Xenon use does not adversely affect fertility in rats. The systemic absorption of hyperpolarized xenon following administration by inhalation is minimal; therefore, its use is not expected to result in adverse effect on fertility. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data, submission, and recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy

The systemic absorption of hyperpolarized xenon following administration by inhalation is minimal; therefore, maternal use is not expected to result in fetal exposure to the drug. There are

[17] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 9/18/2020

[18] Reprotox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 9/18/2020.

[19] TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 9/18/20

no available data on xenon use in pregnant females to evaluate for a drug- associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not shown xenon to be teratogenic or have any adverse effects on embryo-fetal development. Because Xenoview has minimal systemic absorption, DPMH does not recommend a postmarking pregnancy safety study at the current time.

Lactation

The systemic absorption of hyperpolarized xenon following administration by inhalation is minimal; therefore, maternal use is not expected to result in infant exposure to the drug via lactation. DPMH does not recommend a postmarketing clinical lactation study.

Females and Males of Reproductive Potential

There are no data to suggest xenon use adversely affects human fertility. The systemic absorption of hyperpolarized xenon following administration by inhalation is minimal; therefore, its use is not expected to adversely affect fertility or interact with hormonal contraceptives. In animal reproduction studies, xenon had no effects on fertility in rats. DPMH recommends omitting subsection 8.3 of the labeling.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

XENOVIEW is minimally absorbed systemically following the inhalation route of administration, and maternal use is not expected to result in fetal exposure to the drug *[see Clinical Pharmacology (12.3)]*. Adequately designed animal reproduction studies have not been conducted with Hyperpolarized Xe-129. Although not adequately designed to evaluate reproductive and developmental toxicity, there was animal reproduction data available in the literature. Animal reproduction studies were conducted in rats by administering an 80% Xe/20% O2 gas mixture for 2 hours twice a week for 2 and 10 weeks, with no observed effects on fertility or pregnancy. Gas mixtures containing 70%-75% Xe gas and 25%-30% O2 gas were found to be non-teratogenic in rats when administered for 24 hours. In a separate study, rats were administered an 80%/20% Xe/O2 gas mixture for 2 hours twice a week from the 1st to 19th day of pregnancy with no observed effects on embryo-fetal development or signs of teratogenicity.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

XENOVIEW is minimally absorbed systemically following the inhalation route of administration, and breastfeeding is not expected to result in exposure of the infant to the drug *[see Clinical Pharmacology (12.3)]*. There is no information on the presence of hyperpolarized Xe-129 in human milk, the effect on the breastfed infant, or the effect on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XENOVIEW and any potential adverse effects on the breastfed infant from XENOVIEW or from the underlying maternal condition.

APPEARS THIS WAY ON ORIGINAL

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/

WENJIE SUN
06/16/2021 04:14:02 PM

MIRIAM C DINATALE
06/16/2021 04:20:44 PM

LYNNE P YAO
06/17/2021 08:43:08 AM