

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212279Orig1s000

OTHER REVIEW(S)

Division of Medical Imaging Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 0212279

Name of Drug: ExEm[®] Foam

Applicant: GISKIT B.V.; Represented in the US by James Boiani, Epstein Becker & Green, P.C.

Labeling Reviewed

Submission Dates: October 6, 2018; August 2, 2019; October 10, 2019; and October 28, 2019

Receipt Dates: October 9, 2018; August 2, 2019; October 10, 2019; and October 28, 2019

Background and Summary Description:

NDA 212279 for ExEm[®] Foam is indicated for the assessment of fallopian tube patency in combination with ultrasound imaging in women with known or suspected infertility (b) (4)

The Applicant GISKIT B.V, requested meetings with the Agency on July 17, 2017, and February 23, 2018, to discuss the requirements for a 505(b)(2) NDA submission and subsequently submitted this 505(b)(2) NDA on October 6, 2018.

Review

This Package Insert was reviewed by Stephanie Coquia, Clinical Reviewer and Anthony Fotenos, Team Leader and Cross Discipline Team Leader (CDTL); Dhanalakshmi Kasi and Danae Christodoulou, Branch Chief (CMC-Product); Laurie Nelson and (CMC-Process) and Maritere Carattini (CMC-Micro) Reviewers. Sunny Awe, Nonclinical Reviewer and his team Leader, Adebayo Laniyonu; Sam Habet, Clinical Pharmacology Reviewer, and his supervisor Christy John. Casmir Ogbonna DMEPA Reviewer and her Team Leader, Hina Mehta; and David Foss, ODPD Reviewer. All the reviews are in DARRTS and in Panorama for CMC reviews. Michele Fedowitz, Associate Director for Labeling, supervised the overall review of the labelling.

The FDA revised Package Insert, Carton and Container labeling comments were first communicated to the Applicant on July 3, and September 26, 2019, respectively, and the Applicant's responses with their revisions were received on August 2, 2019.

The Agency made further updates to the Dosage and Administration section of the Package Insert in

response to the Applicant’s revisions of August 2, 2019. This was communicated to the Applicant October 7, 2019, and the Applicant accepted the Agency’s revisions to the Package Insert and Carton and Container Labels with their submission of October 10, 2019. The Agency made additional updates to the Package Insert on October 21, 2019, and the Applicant through submission of October 28, 2019, accepted all the FDA’s revisions.

Recommendations

The submitted draft labeling, identified as “NDA 0212279 specifically, the label submitted on October 6, 2018”, was recommended for approval after the Applicant’s acceptance of the FDA and Applicant’s revisions.

The entire Package Insert is included showing all the revisions. The attached labeling is the agreed upon labeling between FDA and the Applicant.

<u>Modupe Fagbami</u> Regulatory Project Manager	Date
<u>Kyong (Kaye) Kang, Pharm D.</u> Chief, Project Management Staff	Date
<u>Michele Fedowitz, M.D.</u> Associate Director, Labelling	Date

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MICHELE B FEDOWITZ
11/05/2019 07:09:45 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
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)

Date of This Memorandum: October 18, 2019

Requesting Office or Division: Division of Medical Imaging Products (DMIP)

Application Type and Number: NDA 212279

Product Name and Strength: ExEm Foam (air polymer-type A) intrauterine foam, 5 mL clear gel [polymer type-A (hydroxyethyl cellulose); glycerin, and purified water], 5 mL sterile purified water

Applicant/Sponsor Name: GISKIT B.V.

OSE RCM #: 2018-2192-2

DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels, and carton labeling received on October 10, 2019 for ExEm Foam (air polymer-type A) intrauterine foam, 5 mL clear gel [polymer type-A (hydroxyethyl cellulose); glycerin, and purified water], 5 mL sterile purified water . We reviewed the revised container labels and carton labeling for ExEm Foam (air polymer-type A) intrauterine foam, 5 mL clear gel [polymer type-A (hydroxyethyl cellulose); glycerin, and purified water], 5 mL sterile purified water (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^{ab} We note GISKIT reviewed the draft guidance for the requirements of the DSCSA product identifier and determined that ExEm Foam is excluded from the requirements because it is an imaging agent.

2 CONCLUSION

^a Ogbonna C. Label and Labeling Review for ExEm Foam (air polymer-type A) intrauterine foam, 5 mL clear gel [polymer type-A (hydroxyethyl cellulose); glycerin, and purified water], 5 mL sterile purified water (NDA 212279). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAY 08. RCM No.: 2018-2192.

^b Mehta H. Label and Labeling Review Memo for ExEm Foam (air polymer-type A) intrauterine foam, 5 mL clear gel [polymer type-A (hydroxyethyl cellulose); glycerin, and purified water], 5 mL sterile purified water (NDA 212279). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 SEP 08. RCM No.: 2018-2192-1

The revised container labels, and carton labeling are acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON OCTOBER 10, 2019

Container label



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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
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)

Date of This Memorandum: September 26, 2019

Requesting Office or Division: Division of Medical Imaging Products (DMIP)

Application Type and Number: NDA 212279

Product Name and Strength: ExEm Foam (air polymer-type A) intrauterine foam, 5 mL clear gel [polymer type-A (hydroxyethyl cellulose); glycerin, and purified water], 5 mL sterile water

Applicant/Sponsor Name: GISKIT B.V.

OSE RCM #: 2018-2192-1

DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels, and carton labeling received on August 2, 2019 for ExEm Foam (air polymer-type A) intrauterine foam, 5 mL clear gel [polymer type-A (hydroxyethyl cellulose); glycerin, and purified water], 5 mL sterile water. We reviewed the revised container labels, and carton labeling for ExEm Foam (air polymer-type A) intrauterine foam, 5 mL clear gel [polymer type-A (hydroxyethyl cellulose); glycerin, and purified water], 5 mL sterile water (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container labels, and carton labeling are not acceptable from a medication error perspective. Specifically, we recommend revisions for clarity of individual syringes and contents of the carton. We provide recommendations for the Applicant below.

3 RECOMMENDATIONS FOR GISKIT B.V.

^a Ogbonna C. Label and Labeling Review for ExEm Foam (air polymer-type A) intrauterine foam, 5 mL clear gel [polymer type-A (hydroxyethyl cellulose); glycerin, and purified water], 5 mL sterile water (NDA 212279). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAY 08. RCM No.: 2018-2192.

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

A. Carton Labeling

1. Revise the non-proprietary name per communication dated September 17, 2019 and include the finished dosage form "intrauterine foam" in the same line as the non-proprietary name or directly below. For example:
ExEm Foam
(air polymer-type A)
Intrauterine Foam
2. Revise the contents of the kit on the principal display panel (PDP) to clearly depict the contents of each syringe. Revise to "One Pre-filled Syringe of clear gel [polymer type-A (hydroxyethyl cellulose), glycerin, and purified water], 5 mL" and "One Pre-filled Syringe Sterile Water, 5 mL" and "One CombiFix Adaptor (coupling device)".
3. Revise the mixing statement on the PDP for clarity. Revise to "Generate 10 mL ExEm Foam by mixing the 5 mL clear gel syringe with 5 mL Sterile Water syringe".
4. Consider revising the statement [REDACTED] (b) (4) to read "Single Dose Only – Discard Unused Portion" to include the appropriate package-type term.
5. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.¹ The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling.

¹ <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>

6. As currently presented, the placement of the lot number and expiration date is not provided. Please provide information on the placement. In addition, to minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
7. Revise [REDACTED] (b) (4) statement to read "Dosage: See Prescribing Information".

B. Container Labels

1. Referring to the component as (b) (4) appears as though this is a proprietary name. For clarity in instructions we recommend revising to "Syringe A". For example:
Syringe A (1 of 2)
(contains clear gel [polymer type-A (hydroxyethyl cellulose), glycerin, and purified water])
5 mL
For preparation of ExEm Foam only
Use as directed
2. Referring to the component as (b) (4) appears as though this is a proprietary name. For clarity in instructions we recommend revising to "Syringe B". For example:
Syringe B (2 of 2)
(contains Sterile Water)
5 mL
For preparation of ExEm Foam only
Use as directed

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

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

Memorandum

Date: August 23, 2019

To: Stephanie Coquia, M.D.
Division of Medical Imaging Products (DMIP)

Modupe Fagbami, Regulatory Project Manager, DMIP
Michele Fedowitz, Associate Director of Labeling, DMIP

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for EXEM FOAM

NDA: 212279

In response to DMIP's consult request dated November 9, 2018, OPDP has reviewed the proposed product labeling (PI) [REDACTED] (b) (4) and carton and container labeling for the original NDA submission for ExEm Foam.

PI [REDACTED] (b) (4): OPDP's comments on the proposed labeling are based on the draft PI [REDACTED] (b) (4) received by electronic mail from DMIP on August 15, 2019, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 2, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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DAVID F FOSS
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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: May 8, 2019
Requesting Office or Division: Division of Medical Imaging Products (DMIP)
Application Type and Number: NDA 212279
Product Name and Strength: ExEm Foam, 10 mL syringe
Product Type: Single-Ingredient Product
Rx or OTC: Prescription (Rx)
Applicant/Sponsor Name: GISKIT B.V.
FDA Received Date: October 9, 2018 and January 15, 2019
OSE RCM #: 2018-2192
DMEPA Safety Evaluator: Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader: Hina Mehta, PharmD
DMEPA Associate Director: Mishale Mistry, PharmD, MPH
DMEPA Associate Director for Human Factors: QuynhNhu Nguyen, MS

1 REASON FOR REVIEW

The Division of Medical Imaging Products (DMIP) requested DMEPA to review the Prescribing Information (PI), (b) (4) carton and container labeling for areas of vulnerability that may lead to medication errors. GISKIT B.V. submitted NDA 212279 for ExEm Foam supplied in a kit containing 5 mL of (b) (4) gel (glycerol 85% and hydroxyethyl cellulose in purified water) and 5 mL water. GISKIT B.V. is seeking approval for ExEm Foam as a contrast agent for assessing fallopian tube patency through intrauterine infusion in combination with ultrasound imaging in women with known or suspected infertility (b) (4)

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
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS 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

DMEPA evaluated the proposed Prescribing Information (PI), (b) (4) carton and container labeling for areas of vulnerability in regards to medication error. In evaluating the product labeling, we have identified specific use-related risks that may necessitate the need for additional human factor validation data. The paragraphs below provide our analysis of the product and the use-related risk, our comparison with other products and intended users, and our discussions with the review team.

We note that ExEm Foam will be supplied in a kit containing a 5 mL syringe of (b) (4) gel (glycerol 85% and hydroxyethyl cellulose in purified water), 5 mL syringe of water, and an adapter. The foam is created by connecting the two syringes together with the adapter and pushing the contents of one syringe into the other syringe. This is done back and forth 10 times to form a milky white foam. (b) (4)

(b) (4) We sent Information Request (IR) on November 21, 2018 and November 30, 2018 to clarify the intended users and use environments and to request for a use-related risk analysis.

In responding to our IR, GISKIT B.V submitted a use-related risk analysis (URRA) and additional information on the preparation of ExEm Foam (see Appendix F). DMEPA reviewed the URRA and identified concerns about the Applicant's assessment of the risk mitigation for the critical task of pushing the contents of the syringes back and forth at least 10 times (Task #3) during the preparation step, and the applicant's classification of the risk as negligible.

Per the submitted URRA and discussions with both the Division of Bone, Reproductive and Urologic Products (DBRUP) and the Division of Medical Imaging Product (DMIP), failure to mix the products at least 10 times may result in a lower imaging power, non-interpretable image, and would necessitate re-imaging. Additionally, a lower power image may result in a false positive (occluded tube) diagnosis if a tube is truly patent. According to the sponsor, a false positive may influence therapeutic options, including laparoscopic surgery to fix the blockage or use of in vitro fertilization (IVF). However, according to the DBRUP medical officer, in the event of non-interpretable image, the next step in the workup would be a standard hysterosalpingogram (HSG) and, proceeding directly to laparoscopic surgery or IVF (as stated by the sponsor) would be unlikely.

In addition, it was brought to DMEPA's attention during the meeting that there was a study conducted to evaluate the "ExEm Foam Analysis - Effects of untrained operators on foam preparation". We acknowledge that the three participants in the study were asked to mix the product at least ten times; however, we do not have any information from this study as to what may occur if the product is not mixed at least ten times. Subsequently, we inquired through a combined DMIP/DMEPA IR on January 25, 2019 for more information about how the sponsor arrived at the requirement of mixing the product "at least ten times". The sponsor stated that "the number 10 was chosen based on the observation that foam characteristics were observed visually after 6 transfers, thus 10 was a conservative estimate for the number of transfers to produce the foam". In addition, the sponsor confirmed that they have not performed any foam characterization studies with mixing the foam less than 10 cycles and they are not aware of any clinical data generated with mixing performed fewer than 10 times.

Furthermore, DMEPA was informed by DMIP that there were data from published actual use studies documenting the efficacy and safety of ExEm Foam, and that there are over (b) (4) procedures (outside of the United States (US) without serious adverse effects as summarized in the ISS submitted by GISKIT B.V. and peer review literature. DMEPA defers to the DMIP in terms of the adequacy of the actual use study data.

We also considered other similar products (i.e., Lumason and Optison) that require the users to mix the product to form a milky white product prior to administration as part of an imaging procedure. Lumason is indicated for use in suboptimal echocardiograms, ultrasonography of the liver and of the urinary tract. In our evaluation of Lumason, we noted that users are required to reconstitute the Lumason lyophilized powder with a prefilled syringe containing 5 mL of 0.9% Sodium Chloride Injection diluent. After emptying the contents of the syringe into

the vial, the vial and syringe then needs to be shaken vigorously for 20 seconds, mixing all of the contents in the vial to form a homogenous white milky liquid which indicates the formation of sulfur hexafluoride lipid microspheres (per Section 2.3 of the Prescribing Information). Optison is indicated for use in suboptimal echocardiograms and is available in a 3 mL single patient use vial containing a clear liquid lower layer, a white liquid upper layer, and a headspace filled with perflutren gas. Optison requires users to invert the vial and gently rotate to resuspend the microspheres until complete resuspension is achieved as shown by formation of an opaque and milky-white liquid. While we recognize that there are differences in the method of reconstitution for these products as compared to ExEm Foam, we note that in all of these products, reconstitution results in the formation of a milky white product. In all of these instances the user needs to confirm visually that the product is ready for administration. We also confirmed that the reconstitution instructions convey this visual confirmation information.

In addition, in responding to our IRs, the sponsor indicated that ExEm Foam is intended for use by physicians who are gynecologists, infertility and in vitro fertilization (“IVF”) specialists, radiologists, and by ultrasound technicians who are performing an evaluation under the direction, and in the presence, of a physician who is a gynecologist, infertility/IVF specialist, or radiologist. We note that the intended users for this product and the similar products discussed above (Lumason and Optison) will be healthcare providers. Although, their specialties may be different due to differences in indications, the use environment for these products would all be the medical imaging suite.

In discussion with DMIP regarding the detailed preparation, administration, (b) (4) instructions in Section 2 of the PI, the Division has determined (b) (4) the instructions to preparation and administration (b) (4) (b) (4), all preparation and administration for healthcare professionals will be included in Section 2 of the PI.

In addition, our review of the PI, carton and container labeling indicated that revisions should be made to improve the clarity of the information presented. We provide recommendations for the Division in Section 4.1, and for GISKIT B.V. in section 4.2 to address these deficiencies.

Furthermore, we note the use of the terminology “single-use kit” throughout labeling. We defer to the Office of Pharmaceutical Quality (OPQ) for the appropriateness of the package-type terminology.

4 CONCLUSION & RECOMMENDATIONS

From the URRAs, we noted the risk of incorrect mixing which could lead to non-interpretable image, and we acknowledge from the clinical team that the risk can be managed through a standard hysterosalpingogram (HSG) and that proceeding directly to laparoscopic surgery or IVF (as stated by the sponsor) would be unlikely. We also acknowledge that there are data from actual use studies. However, we note that there are differences in study methodology between evaluating products in the context of clinical trials and human factors validation studies, as well as specific human factors considerations for studies conducted outside of the US. We considered other similar products (i.e., Lumason and Optison) that require the users to mix the

product to form a milky white product prior to administration as part of an imaging procedure; however, the mixing steps that users need to perform to achieve the milky white product are not identical. Furthermore, we considered that for the proposed product, the intended user populations are gynecologists, infertility and in vitro fertilization (“IVF”) specialists, who are not identical to the intended users of other imaging products.

When taking into considerations all of the factors above and determining whether we can leverage from other products and from our expectations of how this product may be used, the concern that we have is that we do not have data such as data from a human factors validation study that demonstrate that the critical task of mixing can be performed appropriately by the intended users in the intended use environments and data to demonstrate that mitigations (e.g. the mixing instructions) proposed by the sponsor are optimized to support the user to perform the mixing step. DMEPA remains concerned from a medication error perspective of a scenario where the users may not mix the product back and forth 10 times and whether the users recognize that a visual confirmation is necessary to ensure that the product is milky white and that it has been properly mixed. Therefore, DMEPA continues to recommend that data from a human factors validation study be submitted for review. However, we defer to the division on the final determination taking into consideration the totality of the data provided within the application and deciding whether there is a greater public health interest in approving this product. If an approval is necessary, we provide recommendations in Section 4.1 for the PI and recommendations in section 4.2 for the carton labeling and container label to increase readability and prominence of important information and promote the safe use of the product. We recommend that these recommendations are implemented prior to approval.

4.1 RECOMMENDATIONS FOR THE DIVISION

1. Highlights of Prescribing Information (HPI) and Full Prescribing Information (FPI)

- a. To avoid confusion and increase clarity we recommend adding the unit of measure after each numeric (e.g., revise “2 to 3 mL” to “2 mL to 3 mL”).

2. Highlights of Prescribing Information (HPI)

- a. Revise bullet in Dosage and Administration regarding the dose to read “Recommended dose is 2 mL to 3 mL (b) (4) 2 mL to 3 mL as needed to achieve visualization of the fallopian tubes.” for increased clarity. This should be relocated to the first bullet in this section.
- b. Revise first bullet to “See Full Prescribing Information for preparation and administration instructions.” to improve clarity and to avoid medication error. This should be relocated to the second bullet.

3. Full PI

a. Section 2: Dosage and Administration

- i. Relocate the recommended dose to Section 2.1 and title as “2.1 Recommended Dosage”. Revise the dosing information to:

(b) (4)

(b) (4)

- ii. Relocate the preparation and administration information to Section 2.2 Preparation and Administration.

- Revise the (b) (4)

b. Section 16: How Supplied/Storage and Handling Section

- i. For Consistency and clarity, revise the storage statement to include the temperature range in Centigrade “20° to 25°C” next to the already listed temperature range in Fahrenheit (68° to 77°F) to be consistent with the listed temperature excursions which are listed in both Centigrade and Fahrenheit.

4.2 RECOMMENDATIONS FOR GISKIT B.V.

We recommend the following be implemented prior to approval of this NDA 212279:

A. Container Label for (b) (4) Gel, 5 mL:

1. In February 26, 2004, Federal Register (69 FR 9120), FDA published a final rule requiring certain human drug and biological product labels to have a linear barcode that contains, at a minimum, the drug’s NDC number (21 CFR 201.25). The linear barcode must appear on the drug’s label as defined by section 201(k) of the FD&C Act (21 U.S.C. 321(k)). As stated in the preamble to the final rule, barcodes can help reduce or detect potential medication errors by enabling healthcare professionals to check whether they are giving the right drug via the right dose and right route of administration to the right patient at the right time. Therefore, we recommend that you add a linear barcode, that contains at a minimum, the drug’s NDC number to the container label. The barcode should be surrounded by sufficient white space to allow scanners to read the barcode properly. In addition, consider orienting the linear barcode in a vertical position to improve scannability of the barcode.
2. As currently presented, the NDC number is missing. Please add the NDC number and submit for Agency review in accordance with 21 CFR 207.35(b)(3)(i).
3. As currently presented, the route of administration is missing. Add the route of administration statement per Draft Guidance: Container and Carton, April 2013 (lines 136-143).
4. As currently presented, storage information does not match the storage statement in the PI, since the temperature excursions are missing. Please revise

to “Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]; excursions permitted between 15° to 30°C (59° to 86°F)” to avoid confusion.

5. Separate the unit of measure (mL) from the quantity (5) with a space. i.e. change from 5mL to 5 mL to prevent confusion.

B. Container Label for ^{(b) (4)} Water, 5 mL:

1. See A.1. and A.2., and A.4
2. To prevent confusion between the two syringes revise to read as follows:

Sterile Water

For ExEm Foam

For foam preparation only – use as directed

5 mL

C. Carton Labeling for ExEm Foam

1. See A.1., A.2., and A.4
2. Revise the word “Contains:” in the Principal Display Panel to “Each kit contains:” to improve clarity of contents in each kit.
3. As currently presented, there is no established name in the carton label. Revise the carton label and add the establish name where appropriate per 21 CFR 201.10(g)(2), and Draft Guidance: Container and Carton, April 2013 (line 140-146, 188, 194-196, 336-342, 344-349).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for ExEm Foam received on October 9, 2018, and January 15, 2019 from GISKIT B.V..

Table 2. Relevant Product Information for ExEm Foam	
Initial Approval Date	N/A
Active Ingredient	glycerol and hydroxyethyl cellulose (HEC) in purified water
Indication	As an ultrasound contrast imaging product that can be infused into the Fallopian tubes to aid in assessing tubal patency in women known or suspected infertility (b) (4)
Route of Administration	Intra-uterine (via (b) (4) Fr catheter)
Dosage Form	Foam
Strength	10 mL syringe
Dose and Frequency	- Administer 2 mL to 3 mL of ExEm Foam. - Repeat infusion of 2 mL to 3 mL of foam, as needed, to achieve visualization of the fallopian tubes. - Administer foam within 5 minutes of preparation using (b) (4) Fr catheter. - Discard unused portion.
How Supplied	As a single-use kit. Each kit contains: - One sterile 11-mL syringe containing 5 mL of (b) (4) Gel - One sterile 11-mL syringe containing 5 mL of (b) (4) Water - One sterile CombiFix® Adaptor (coupling device) - Prescribing Information (PI) (b) (4)
Storage	Store the kit and components at controlled room temperature between (68° to 77°F); temperature excursions between 15° to 30°C (59° to 86°F) are allowed. Do not store in refrigerator. Do not freeze. Do not use the EXEM Foam Kit after the expiration date of the (b) (4) Gel, the (b) (4) Water and/or the coupling device.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 15, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, ExEm Foam. Our search identified no previous reviews.

APPENDIX F. Interactions with the Applicant:

- **DMEPA Information Request (IR) on November 21, 2018:** DMEPA noted [REDACTED] (b) (4) [REDACTED] DMEPA sent an Information Request (IR) requesting the Applicant to “specify the intended user population and the intended use environments for this product.”
- **Applicant Response on November 27, 2018:** The Applicant stated the following:
 - *The intended user population includes (1) physicians who are gynecologists, infertility and in vitro fertilization (“IVF”) specialists, and radiologists, and (2) ultrasound technicians who are performing an evaluation under the direction, and in the presence, of a physician who is a gynecologist, infertility/IVF specialist, or radiologist.*
 - *The intended use environments include examination rooms in physician offices; obstetrics/gynecology (“OB/GYN”) and radiology departments in hospitals; ultrasound imaging centers; and infertility/IVF medical centers (provided they have transvaginal ultrasound equipment).*
- **DMEPA IR on November 30, 2018:** In order to ensure that all potential risks involved in using ExEm Foam have been considered and adequately mitigated and the residual risks are acceptable, DMEPA sent an IR requesting that the applicant submit a comprehensive use-related risk analysis (URRA)^a for the unique preparation of the product.
- **Applicant Response on December 6, 2018:** The Applicant stated the following:
 - *The ability of intended users to prepare ExEm Foam was validated through several peer-reviewed, published actual use studies documenting the efficacy and safety of ExEm Foam.*
 - *Clinical use in over [REDACTED] (b) (4) procedures without serious adverse effects as summarized in the ISS.*

^a The comprehensive use-related risk analysis is a comprehensive and systematic evaluation of all the steps involved in using the product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures. The risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods the applicant intends to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in the use of your product have been considered and adequately mitigated and the residual risks are acceptable.

- *The method of preparation for ExEm Foam itself was designed by physicians, is prepared using minimal steps, and includes visual cues that allow the user to assess the preparation in real time.*
- *The Applicant provided the use-related risk analysis (URRA) below:*

Table 2. ExEm Foam Preparation Task List and Risk Analysis

Task	Potential User Errors	Theoretical Risk	Potential Clinical Harm	Actual Risk of Harm and Risk Mitigation	
1	Handle components using aseptic techniques (e.g., using gloved hands)	User does not handle using aseptic procedures	Increased potential for microbial contamination	An increase in microbial contamination could potentially increase risk of infection.	(b) (4)
2	Remove caps from syringes and connect with connector device	User does not remove caps User does not connect the two syringes	No foam will be prepared	Minor inconvenience due to delay in procedure	
3	Push plunger of syringes back and forth at least 10 times	Mixing less than 10 times	Risk of reduced ultrasound signal	Lower imaging power may increase the likelihood that a physician (a) considers an image to be non-interpretable, or (b) makes a false positive (occluded tube) diagnosis if a tube is truly patent. A non-interpretable image would necessitate re-imaging. A false positive may influence consideration of therapeutic options, including laparoscopic surgery to fix the blockage, or use of <i>in vitro</i> fertilization ("IVF"). Laparoscopic surgery would be preceded by additional diagnostic assessment, likely laparoscopy with dye prior to conducting surgery. IVF would typically be based on a variety of clinical information, and if an occlusion were to be the sole reason for IVF, it is likely that the test would be repeated at another time due to the potential for temporary occlusions due to, e.g., spasm during a procedure. If a patient hopes not to conceive (e.g., if they have been treated with the Essure® device to intentionally create a tubal blockage), the risk to the patient is the increased potential for an unwanted pregnancy.	

4	Begin to infuse within 5 minutes of mixing	User infuses after 5 minutes	Risk of reduced ultrasound signal Risk of microbial growth after holding > 5 minutes	After 5 minutes, the echogenicity of ExEm Foam may begin to dissipate. The results of reduced echogenicity would be reduced ultrasound signals with the same potential harms as detailed for Task 3. If a product is held for a very long time after it is initially prepared there could be some risk of microbial growth, which could increase risk of infection.	(b) (4)

- **DMIP/DMEPA IR on January 25, 2019:** In response to the sponsor’s December 6, 2018 Applicant response, DMIP/DMEPA sent the following IR:

1. Your preparation instructions state that (b) (4) How was the number 10 chosen as the minimum number of transfers?

Applicant’s Response on February 7, 2019:

- *The number 10 was chosen based on the observation that foam characteristics were observed visually after about 6 transfers, thus 10 was a conservative estimate for the number of transfers to produce foam.*
2. Module 3 included analyses of the effect of transfers on bubble size distribution and concentrations, with all users mixing the foam 10 cycles or more. The reports also included qualitative and quantitative evaluations of image quality and signal half-life. Do you have similar data with mixing performed fewer than 10 times?

Applicant’s Response on February 7, 2019:

- *We have not performed any foam characterization studies with mixing the foam less than 10 cycles and we are not aware of any clinical data generated with mixing performed fewer than 10 times. Since ExEm Foam was first introduced in Europe, it has required mixing 10 or more times, and published studies cited in the ISS and ISE note that they have followed these instructions, except for Zizolji et al. 2018 in the ISS, which used a different proportion of water and gel than the 1:1 ratio specified in the product’s labeling. Consequently, the focus on characterization testing was to model the technique of preparation used in studies submitted to support approval.*
3. We note that the clinical studies submitted to support efficacy only state that the foam was prepared as per manufacturer’s instructions. Since market entry, has the minimum number of transfers for mixing changed on the preparation instructions? Do you have clinical data that shows the effect on image quality and diagnostic performance if the product is mixed less than 10 times?

Applicant’s Response on February 7, 2019:

- *As noted in the response above, the minimum number of transfers has not changed since the introduction of ExEm Foam. We are not aware of clinical data evaluating diagnostic performance with fewer than 10 transfers, which is why we have proposed that as the minimum mixing requirement in the labeling.*

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,^b along with postmarket medication error data, we reviewed the following ExEm Foam labels and labeling submitted by GISKIT B.V..

- Container label received on October 9, 2018
- Carton labeling received on October 9, 2018

(b) (4)

- Prescribing Information received on January 15, 2019

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^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

HINA S MEHTA on behalf of CASMIR I OGBONNA
05/08/2019 02:17:02 PM

HINA S MEHTA
05/08/2019 02:17:46 PM

MISHALE P MISTRY
05/08/2019 02:19:50 PM

QUYNHNHU T NGUYEN
05/09/2019 02:25:02 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
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Division of Pediatric and Maternal Health Memorandum

Date: April 16, 2019 **Date Consulted:** November 29, 2018

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Lynne Yao, MD, Director
Division of Pediatric and Maternal Health (DPMH)

To: Modupe Fagbami, Regulatory Project Manager (RPM)
Division of Medical Imaging Products (DMIP)

Drug: ExEm Foam

NDA: 212279

Proposed Indication: Contrast agent indicated for assessing fallopian tube patency through intrauterine infusion in combination with ultrasound imaging in women with known or suspected infertility (b) (4)

Applicant: Giskit B.V.

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- NDA 212279 submitted on October 6, 2018

Consult Question: DMIP requests review of PLLR labeling for this new NDA

INTRODUCTION

On October 6, 2018, the applicant, Giskit B.V., submitted an original new drug application (NDA) for ExEm Foam via the 505(b)(2) regulatory pathway. The Division of Medical Imaging Products (DMIP) consulted the Division of Pediatric and Maternal Health (DPMH) on November 29, 2018, to assist with the labeling review for the *Pregnancy, Lactation, and Females and Males of Reproductive Potential* subsections.

BACKGROUND

Regulatory History

- ExEm Foam is a contrast agent indicated for assessing fallopian tube patency through intrauterine infusion in combination with ultrasound imaging in women with known or suspected infertility (b) (4).
- ExEm Foam was approved in the European Union (EU) in 2009 and is currently approved for marketing in more than 50 countries.
- The applicant is relying on the published literature to establish efficacy and safety for this 505(b)(2) application.

ExEm Foam Drug Characteristics¹

- *Drug Class:* contrast agent
- *Dosage and administration:* ExEm Foam is created by mixing the (b) (4) Gel with purified water. Administer 2 to 3 mL of ExEm Foam with repeat infusion of 2 to 3 mL of foam, as needed, to achieve visualization of the fallopian tubes with ultrasound guidance.
- *Dosage forms and strengths:* ExEm Foam is supplied as a single-use kit containing one syringe with 5 mL (b) (4) Gel, one syringe with 5 mL (b) (4) purified water, and a coupling device to connect the two syringes.
- *Mechanism of Action:* when (b) (4) Gel (containing glycerol and hydroxyethyl cellulose as excipients) is mixed with an equal amount of (b) (4) purified water, (b) (4) creating an echogenic contrast agent.
- *Pharmacodynamics:* ExEm Foam has no known (b) (4) pharmacological activity (b) (4).
- *Contraindications:* do not use if the patient is pregnant or may be pregnant
- *Adverse reactions:* pain, vasovagal reaction, and spotting

Reviewer's Comment

(b) (4)

REVIEW

PREGNANCY

Nonclinical Experience

Animal reproduction studies have not been conducted with ExEm Foam.

¹ ExEm Foam (NDA 212279) proposed prescribing information

Applicant's Review of Pharmacovigilance Database

Giskit B.V. has maintained a postmarket surveillance and reporting system for ExEm Foam since the time of initial EU approval in 2009. Giskit B.V. stated a total of 12 complaints have been reported cumulatively, which makes the overall complaint rate approximately (b) (4) % (12 total complaints / (b) (4) estimated procedures). None of the reported complaints involved serious adverse events and none were related to pregnancy, lactation, or fertility. These 12 complaints were related to pain and vasovagal discomfort or side effects associated with the method/procedure rather than to ExEm Foam.

Applicant's Review of Published Literature

ExEm Foam is contraindicated in pregnancy. The applicant's pre-specified literature review strategy was developed with input from the FDA to identify all adverse events related to the use of ExEm Foam (for details, refer to the applicant's *Literature Safety Review Protocol*). No articles related to ExEm Foam use in pregnancy were identified.

DPMH's Review of Published Literature

This Reviewer performed a search in PubMed, Embase, Micromedex², TERIS³, Reprotox⁴, and Briggs⁵ to find relevant articles not cited by the applicant. Search terms included: "ExEm Foam," "glycerol," OR "hydroxyethyl cellulose," AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," or "miscarriage." No relevant articles were retrieved.

Reviewer's Comment

No published literature or postmarketing reports were identified regarding pregnancy and ExEm Foam or its inactive ingredients glycerol and hydroxyethyl cellulose (HEC). Glycerol and HEC are widely used as inactive ingredients in FDA-approved drugs through many routes of administration and in a variety of FDA-cleared medical devices, including ultrasound gels and over-the-counter products. Nevertheless, ExEm Foam use in pregnancy is contraindicated due to the anticipated risk of pregnancy disruption (including miscarriage and ectopic pregnancy) with intrauterine administration of this product during the hysterosalpingo-foam sonography (HyFoSy) procedure, which has been reported with similar procedures such as hysterosalpingogram.⁶

LACTATION

Nonclinical Experience

Animal lactation studies have not been performed with ExEm Foam.

Applicant's Review of Pharmacovigilance Database

As discussed above, the applicant stated no reports related to lactation or breastfeeding have been received in the pharmacovigilance database since initial EU approval in 2009.

²Truven Health Analytics information, <http://www.micromedexsolutions.com>, Accessed 3/29/19.

³TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 3/29/19.

⁴Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 3/29/19

⁵ Briggs GG, et al. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*, 9th Ed. 2011.

⁶ Ahmadi F, et al. Unsuspected pregnancy during HSG. *Iran J Radiol.* 2014 Aug; 11(3):e5033. PMID: 25763083.

Applicant's Review of Published Literature

The applicant's pre-specified literature review strategy was developed with input from the FDA to identify all adverse events related to the use of ExEm Foam (for details, refer to the applicant's *Literature Safety Review Protocol*). No articles related to ExEm Foam use in lactation were identified.

DPMH's Review of Published Literature

This Reviewer performed a search in *Medications and Mother's Milk*⁷, LactMed⁸, Micromedex², Reprotox⁴, Briggs⁵, PubMed, and Embase using the terms "ExEm Foam," "glycerol," OR "hydroxyethyl cellulose," AND "lactation" OR "breastfeeding."

- *Medication and Mother's Milk* lactation recommendation for glycerin is "L3-No data-Probably Compatible." The author notes glycerin is a normal constituent in all humans and is virtually non-toxic. "There are no data on the use of exogenous glycerol in breastfeeding women, but it is unlikely to be hazardous. Most would be metabolized by the gut." The molecular weight is 92.1 Daltons and the half-life 30-45 minutes.

Reviewer's Comment

There are no available data on the presence of ExEm foam components (glycerol and HEC) in breastmilk. DPMH discussed the anticipated amount of systemic absorption of ExEm Foam with the Clinical Pharmacology Review Team. Glycerol is completely systemically absorbed but is not expected to impact normal fasting endogenous glycerol plasma levels; whereas HEC is expected to be negligibly systemically absorbed.

The FDA classifies glycerin as a substance generally recognized as safe (GRAS).⁹ Similarly, toxic oral doses of hydroxyethyl cellulose would have to be in excess of 2g/kg.¹⁰ For comparison, the amount of drug component delivered to a woman in a single HyFoSy procedure is 0.4g for glycerol and 0.08g for HEC. Therefore, DPMH concludes that no adverse effects in breastfed infants are anticipated following maternal administration of ExEm Foam, based on the wide safety margin for glycerol in infants and the expected negligible systemic absorption of HEC.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Animal fertility studies have not been conducted with ExEm Foam.

Applicant's Review of Pharmacovigilance Database

As discussed above, the applicant stated no reports related to fertility have been received in the pharmacovigilance database since initial EU approval in 2009.

⁷ Hale, Thomas (2017) *Medications and Mother's Milk*. Amarillo, Texas. Hale Publishing.

⁸ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. 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 database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 3/29/19

⁹ 21CFR182.1320, <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=182.1320>

¹⁰ <https://toxnet.nlm.nih.gov>. Accessed 4/11/19.

Applicant's Review of Published Literature

The applicant's pre-specified literature review strategy was developed with input from FDA to identify all adverse events related to the use of ExEm Foam (for details, refer to the applicant's *Literature Safety Review Protocol*). The applicant noted ExEm Foam may have a positive impact on fertility and submitted the following relevant published literature:

- A retrospective study¹¹ assessed occurrence of pregnancy of 111 women who received the ExEm Foam HyFoSy procedure and were in heterosexual relationships, creating the possibility of spontaneous conception. Within 6 months post-procedure, 59 underwent assisted reproduction treatment (ART) and 52 did not. Of those patients, twenty-four women (40.7%) conceived with ART and 24 women (46.2%) conceived spontaneously.
- An abstract¹² reporting on 294 subjects, of whom 157 provided data regarding pregnancy status out to one year post ExEm Foam HyFoSy. The study found that 54 of 157 subjects (34.4%) conceived spontaneously: 15 had spontaneous abortions and 2 had an ectopic pregnancy, and 37 (23.5%) had a live birth. Cumulative pregnancy rates were 10.2% within 1 month of the procedure, 29.9% within 6 months, and 34.4% within 12 months.

Reviewer's Comment

The potential for the HyFoSy procedure to improve fertility is not unexpected. Improvements in conception rate after tubal flushing has been reported over the past several decades with other procedures such as hysterosalpingogram (HSG).¹³ A Cochrane meta-analysis reported a pregnancy rate between 29% and 55% with tubal flushing with oil- soluble contrast media compared to 17% with no intervention.¹⁴

DPMH's Review of Published Literature

This Reviewer performed a search in PubMed, Embase, and Reprotox⁴ using the terms "ExEm Foam," "glycerol," OR "hydroxyethyl cellulose," AND "fertility," "contraception," "oral contraceptives," OR "infertility." No additional published literature was identified.

DISCUSSION and CONCLUSIONS

Pregnancy

There are no available published literature or postmarketing data related to ExEm Foam use in pregnant women. Because ExEm Foam is administered intrauterine to distend the fallopian tube enhancing visualization with hysterosalpingo-foam sonography, this product should be used only in the pre-ovulatory phase of the menstrual cycle and avoided in pregnancy due to its potential to disturb implantation of an embryo. Due to the anticipated risk to early pregnancy with the HyFoSy procedure, DPMH recommends subsection 8.1 of labeling state ExEm Foam use is contraindicated in patients with known or suspected pregnancy.

¹¹ Tanaka K, et al. Hysterosalpingo-foam sonography (HyFoSy): Tolerability, safety and the occurrence of pregnancy post-procedure. *Obstet Gynaecol* 58:114-118 (2018).

¹² Exacoustos C, et al. Can tubal flushing with hysterosalpingo-foam sonography (HyFoSy) media increase women's changes of pregnancy? *Journal of Minimally Invasive Gynecology* 22:S1-S253 (2015).

¹³ Weir WC, et al. Therapeutic value of salpingograms in infertility. *Fertil Steril* 1951; 2:514-522.

¹⁴

(b) (4)

Lactation

There are no data on the presence of ExEm Foam components (glycerol and hydroxyethyl cellulose) in human milk, the effects on the breastfed infant, or the effects on milk production. The amount of systemic absorption of ExEm Foam is unclear. Considering the wide safety margins for glycerol and the expected negligible systemic absorption of HEC, adverse effects in breastfed infants are not anticipated following maternal administration of ExEm Foam. Therefore, DPMH recommends subsection 8.2 of labeling include the following risk/benefit statement for lactation, “the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ExEm Foam and any potential adverse effects on the breastfed infant from ExEm Foam from the underlying maternal condition.”

Females and Males of Reproduction Potential

(b) (4)

Because the use of ExEm Foam is contraindicated for use in pregnancy, DPMH recommends section 2 and subsection 8.3 of labeling include a pregnancy testing subheading to alert prescribers to perform pregnancy testing prior to administering ExEm Foam.

LABELING RECOMMENDATIONS

DPMH revised Highlights, section 4, and subsections 2.1, 5.1, 8.1, 8.2, and 8.3 of labeling for compliance with the PLLR. DPMH discussed our labeling recommendations with the Division at the April 16, 2019 labeling meeting. DPMH refers to the final NDA action for final labeling.

DPMH Proposed ExEm Foam Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----CONTRAINDICATIONS -----

- Pregnancy. (4)

-----WARNINGS AND PRECAUTIONS-----

- (b) (4)

FULL PRESCRIBING INFORMATION

2 DOSAGE AND ADMINISTRATION

2.1 Important Pre-Administration Information

To ensure that the patient is not pregnant prior to ExEm Foam administration [*see Contraindications (4) and Warnings and Precautions (5.1)*]:

- Confirm that the patient has a negative pregnancy test within 24 hours before ExEm Foam administration.
- Confirm the patient is in the pre-ovulatory phase of her menstrual cycle (cycle days 6 through 11).

4 CONTRAINDICATIONS

(b) (4) Pregnancy [*see Warnings and Precautions (5.1)*]

5 WARNINGS AND PRECAUTIONS

5.1 Risk for Fetal Harm

ExEm Foam is contraindicated for use in pregnancy due to the potential risk to the fetus from an intrauterine procedure. To ensure that the patient is not pregnant prior to ExEm Foam administration confirm that the patient has a negative pregnancy test within 24 hours before ExEm Foam administration and confirm that the patient is in the pre-ovulatory phase of her menstrual cycle (cycle days 6 through 11) (b) (4)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

ExEm Foam is contraindicated for use in (b) (4) due to the potential risk to the fetus from an intrauterine procedure [see *Contraindications (4)* and *Warnings and Precautions (5.1)*]. There are no available data on the use of ExEm Foam in pregnant women. Animal reproduction studies have not been conducted with ExEm Foam.

8.2 Lactation

Risk Summary

There are no data on the presence of (b) (4) components (b) (4) in human milk, the effects on the breastfed infant, or the effects on milk production. (b) (4) following maternal administration of ExEm Foam, based on the wide safety margin for glycerol in infants and the expected negligible (b) (4) absorption of hydroxyethyl cellulose [see *Clinical Pharmacology (12.3)*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ExEm Foam and any potential adverse effects on the breastfed infant from ExEm Foam from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

(b) (4)
Confirm that the patient has a negative pregnancy test within 24 hours before ExEm Foam administration (b) (4) [see *Dosage and Administration (2.1)*, (b) (4)

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/s/

KRISTIE W BAISDEN
04/16/2019 01:23:15 PM

LYNNE P YAO
04/16/2019 03:27:44 PM



NDA 212279 – ICC190018: ExEm Foam Kit

DATE: March 29, 2019

FROM: Jason Roberts, Ph.D., Biomedical Engineer
ODE/DRGUD/OGDB

TO: Modupe Fagbami, Consumer Safety Officer
CDER/OND/ODEIV/DMIP

CC: Sharon Andrews, Branch Chief
ODE/DRGUD/OGDB

Joyce Whang, Deputy Director
ODE/DRGUD

APPLICANT: GISKIT B.V.

Submission purpose / Scope of consult:

The applicant has submitted this file for the ExEm Foam Kit to request approval for marketing in interstate commerce.

In the current submission, the initiating division, CDER/OND/ODEIV/DMIP, has asked that I comment on the compatibility of the syringes in the kit with currently cleared catheters (balloon and non-balloon) indicated for hysterosalpingography/sonohysterosalpingography. The initiating division would also like any relevant information about the catheters that may affect overall diagnostic accuracy of the ExEm kit.

Regulatory background:

There have been no previous submissions of this combination product for which CDRH/OPEQ/OHT3 has provided a review.

Indications for use:

Per the prescribing information provided in the submission, the ExEm Foam kit is indicated for the following:

“ExEm® Foam is a contrast agent indicated (b) (4) assess (b) (4) fallopian tube patency (b) (4) in women with known or suspected infertility (b) (4).

Device Description:

Overview

The product comprises two 11mL syringes, one with 5mL (b) (4) Gel, and one with 5mL (b) (4) water, and an adaptor called the Combifix, which is intended to aid in the mixing of the gel. The two syringe fluids are mixed immediately prior to usage to create a “foam,” which is an unstable complex emulsion of the two liquids along with mixed air.

The product is intended to be utilized with a (b) (4) Fr catheter,” a “side-opening speculum,” and an “ultrasound.” However, these components are not provided in the kit.

(b) (4) Gel/Foam

The (b) (4) Gel is comprised of glycerol ((b) (4) % w/w), hydroxyethyl cellulose (HEC) ((b) (4) % w/w) and water (q.s. (b) (4)).

The material compositions for the product are as follows:

Table 1. Quantitative Composition of (b) (4) Gel

Excipient	Function	Quantity, in % (w/w)	Amount (mg) in 5 mL of ExEm Gel	Monograph
Glycerol 85%	(b) (4)	(b) (4)	434.8 ^a	EP
Hydroxyethyl cellulose (HEC)		(b) (4)	80.97 ^c	USP/NF
Purified water		(b) (4)	--	USP

^a (b) (4) 434.8 mg
^b (b) (4)
^c (b) (4) 80.97 mg

Table 2. Quantitative Composition of ExEm Foam

Formulation Component	Quantity, in % (w/w)	Amount (mg) in 10 mL ExEm Foam ^a
Glycerol, 85%	(b) (4)	434.8
HEC	(b) (4)	80.97
Purified Water	(b) (4)	--

^a See Table 1
^b (b) (4)

Combifix

The Combifix device is an adaptor that allows for attachment of the (b) (4) Gel and (b) (4) Water syringes. It appears to be simply a female-female luer adaptor. It is unclear how this device in combination with the prefilled syringes introduces air to the foam.

Review:

The initiating division has requested that CDRH comment on the compatibility of the product with cleared HSG catheters.

There are many different cleared HSG catheters, which are regulated as Class II devices under 21 CFR 884.4530, Obstetric-Gynecologic Specialized Manual Instrument, and product code LKF, cannula, manipulator/injector, uterine.

These devices are typically indicated for either fluoro HSG, sono-HSG, or both. They may have balloons or other mechanical stops to reduce backflow through the cervix during contrast delivery, and may contain additional features, such as pressure limiters. Some catheters may also include syringes that are a part of, or intended to be connected to, the catheter

With respect to compatibility of ExEm foam with catheters, there are several general considerations:

- Chemical/material compatibility
- Physical compatibility, including connection and physical operating parameters

In addition, there are considerations related to the affect a particular catheter on the performance of the contrast agent.

With respect to chemical/material compatibility, I do not have concerns with breakdown or reaction of the catheter materials, as the component materials of the ExEm foam are expected to be inert (glycerol, water and HEC).

With respect to connections, the syringes provided should be able to be connected to catheters with luer fittings, as these are standardized. However, I recommend the labeling specify that catheters to be used with the product must have a luer connection.

With respect to physical operating parameters, HSG/sono-HSG catheters are typically evaluated for leakage when a set pressure is applied. The amount of pressure applied is dependent on the viscosity of the media, diameter of the lumen of the catheter, the intended procedure (HSG/sonoHSG), and the design features of the catheter (e.g., pressure limiters). As it pertains to the ExEm foam, use of a more viscous solution may necessitate additional pressure to force the liquid through the device. Further, the current NDA submission does not provide a discussion of the ExEm procedure that details the pressures required to achieve acceptable contrast flow in the fallopian tubes. The applicant should discuss the required pressure and flow rates for the procedure, as compared to HSG and sono-HSG procedures. This information is necessary for me to understand whether additional testing may be required to demonstrate compatibility. If the required pressures or flow rates for the ExEm foam are higher than that typically required for HSG and sono-HSG procedures, the applicant will need to provide performance testing to demonstrate that cleared catheters can accommodate the increase in

pressure/flow without malfunction. In addition, the applicant should provide a comparison of the viscosity of the ExEm Foam as compared to HSG and sono-HSG media. If the viscosity of the ExEm Foam is in excess of approved contrast agents, the applicant will need to provide further justification for why the ExEm foam is compatible with cleared HSG/sono-HSG catheters (i.e., acceptable flow and pressure in these catheters).

With respect to features of the catheter that may affect diagnostic accuracy, there are several potential concerns I have with respect to the choice of catheter. The ExEm foam is an unstable emulsion. It comprises two immiscible phases, which will eventually separate given sufficient time. The visualization of the contrast agent will be dependent on the size and concentration of air bubbles in the emulsion. Therefore, anything that has the potential to affect these parameters has the ability to affect the visibility of the contrast. The diameter and materials of the catheter could impact the distribution of bubbles in the foam prior to being delivered to the uterus due to surface interactions. Smaller diameter catheters have the most surface area to volume, and therefore I believe have the most potential for disruption of the emulsion. In addition, the overall length of the catheter may also impact this disruption, as there is more surface area in a longer catheter. Therefore, I would recommend to CDER that the applicant provide some evidence to support that the ExEm foam maintains an adequate bubble distribution after passing through a catheter. Since the (b) (4) for the product note that the foam can be used up to 5 minutes, I would recommend that testing include immediately prepared foam and foam that has been left to sit for 5 minutes. I would further recommend that the applicant specify the acceptable lengths of catheter in the labeling, and include up to the longest labeled length in their evaluation. It may be acceptable for the applicant to show that the ExEm foam maintains performance in a worst-case scenario (e.g., longest and smallest diameter labeled catheter). As the applicant may have data (e.g., clinical) available to address this concern, I will not specify a particular evaluation, but will leave it open for the applicant to provide a response. In addition, the CDER diagnostic review team may consider whether the information they have reviewed may adequately address this concern. I also believe the applicant may be able to address this concern by better defining the catheter dimensions or models that were utilized in studies evaluating the product in their labeling (i.e., if the applicant limits the labeling to those devices used in the clinical studies, and the clinical studies support the performance of the product then I would not have concerns).

Recommendations:

I have identified several concerns regarding the potential compatibility of the ExEm Foam with cleared HSG/sono-HSG catheters. Please consider the following recommendations, which are written in the form of deficiencies to the applicant:

In your submission, you note that ExEm Foam may be used with a (b) (4)Fr or larger catheter. However, you did not provide any discussion as to why ExEm foam is compatible with this catheter size. Additional information is required for FDA to understand how ExEm foam is intended to be utilized with HSG/sono-HSG catheters. Please address the following concerning ExEm Foam compatibility with cleared HSG/sono-HSG catheters:

1. In your submission, you note that any catheter (b) (4)Fr or larger may be utilized with ExEm foam. However, you did not provide any supporting information as to why these sizes were chosen. Please provide a rationale for why the prescribing information specifies these size catheters. In addition, please clarify whether you intend to claim compatibility of ExEm Foam with all catheters of at least (b) (4)Fr, including all lengths and any additional features (e.g., pressure limiters). If you do not intend for the ExEm foam to be utilized with all (b) (4)Fr or above catheters,

please specify which catheters you intend for ExEm foam to be utilized with (including diameter, length, and additional features), and modify your labeling to more strictly define the dimensions and features of catheters to be utilized with ExEm foam. If you intend your device to be utilized with catheters with luer connections, please modify your labeling to specify that ExEm syringes should be utilized with catheters with luer connections.

2. In your submission, you do not provide a discussion of the ExEm procedure that details the pressures required to achieve acceptable contrast flow in the uterus and fallopian tubes. This information is necessary for FDA to understand whether ExEm foam is compatible with cleared HSG/sono-HSG catheters. Please provide a discussion of the required pressure and flow rates for the ExEm procedure, as compared to traditional HSG and sono-HSG procedures. If the required pressures or flow rates for the ExEm foam procedure are higher than that typically required for HSG and sono-HSG procedures, please provide performance testing to demonstrate that cleared HSG/sono-HSG catheters in the range of sizes specified in your labeling can accommodate the increase in pressure/flow without malfunction. Malfunction could include failure of the catheter or excessive leakage of media.
3. In your submission, you did not provide a comparison of the viscosity of the ExEm Foam as compared to marketed HSG and sono-HSG media. The viscosity of the contrast medium will affect the pressure and flow rates through catheters of different lengths and diameters. Please provide a comparison of the viscosity of the ExEm foam as compared to marketed HSG and sono-HSG media. If the viscosity of the ExEm Foam is in excess of marketed contrast agents, please provide evidence to support ExEm foam can be delivered at sufficient pressure/flow rates for the ExEm procedure for the range of sizes of catheters specified in your labeling.
4. In your submission, you did not provide a discussion of the effect catheters of various dimensions may have on the composition (i.e., bubble size/concentration) of ExEm foam prior to its deposition in the uterine cavity. The passage of the media through the catheter has the potential to disrupt the foam and affect the visualization of contrast. Please provide evidence to support that the ExEm foam performs adequately after passing through catheters of the range of dimensions specified in your labeling. As a note, (b) (4) for the product note that the foam can be used up to 5 minutes. Therefore, we recommend that you provide evidence to support that performance is adequate for immediately prepared foam and foam that has been left to sit for 5 minutes. Further, we recommend that your labeling specify the acceptable dimensions of catheter (including diameter and length) based upon the evidence you provide (i.e., the labeling reflects the data provided). If you evaluate a subset of catheter dimensions, please provide a justification for why the results of the subset are applicable to the range of dimensions allowed in your labeling.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Jason Roberts -S 2019.04.01 12:31:55 -04'00'
Branch Chief Sign-Off	Sharon M. Andrews -S 2019.04.01 12:45:49 -04'00'

**Food and Drug Administration (FDA)
Center for Drug Evaluation and Research (CDER)
Office of New Drugs (OND) Office of Drug Evaluation (ODE) III
Division of Bone, Reproductive, and Urologic Products (DBRUP)**

Memorandum of Consultation

Re: NDA # 212279
ExEm Foam Kit

Applicant: GISKIT B.V.

To: Libero Marzella, MD, Director
Division of Medical Imaging Products (DMIP)

From: Jennifer Lawrence, MD, Medical Officer
Christina Chang, MD, MPH, Clinical Team Leader
Audrey Gassman, MD, Deputy Director
Division of Bone, Reproductive and Urologic Products
(DBRUP)

Date consult submitted: November 29, 2018
Date consult completed: March 8, 2019

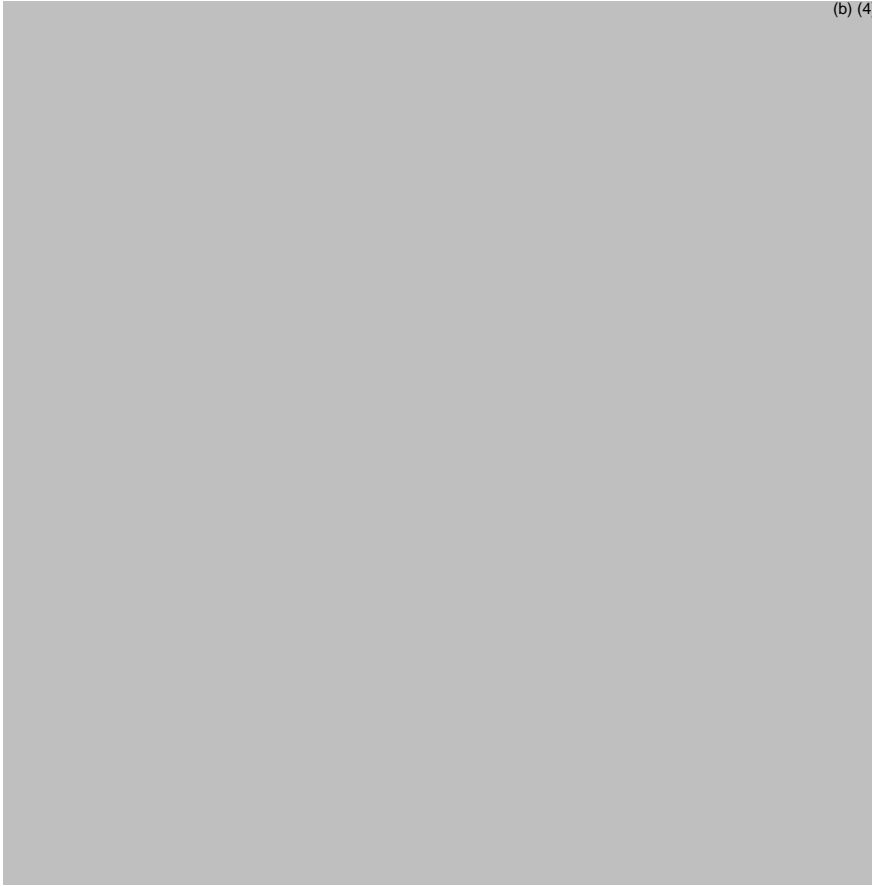
1. Introduction:

This DBRUP memo responds to the consult request from DMIP regarding ExEm Foam, a contrast agent intended to assess fallopian tube patency through intrauterine infusion in combination with ultrasound imaging in women with known or suspected infertility. ExEm Foam has been marketed outside the United States (e.g., the United Kingdom, Australia, and the Netherlands, etc.) as a diagnostic device by Giskit B.V. (hereafter referred to as the Applicant). Because gynecologists would be the end-user of this proposed product, DMIP asks DBRUP to assist with their review of clinical data included in the NDA.

2. Background:

The Applicant is proposing to market the ExEm Foam Kit for the purpose of assessing the patency of fallopian tubes in infertility patients using transvaginal ultrasound. The kit is composed of a 10mL syringe filled with 5mL of sterile ultrasound gel (b) (4) a second 10mL syringe containing 5mL of sterile purified water, and a coupling device to connect the two syringes. A foam is produced by vigorously pushing the contents of the syringes back and forth through the coupling devices connecting the syringes (see Figure A below). The final drug product, the “ExEm foam,” is composed of approximately (b) (4) % water, (b) (4) % glycerol, and (b) (4) % hydroxyethylcellulose. The foam, which is echogenic due to

the microbubbles of air created by the turbulence, is then instilled into the intrauterine cavity via a cervical catheter (b) (4) not included in the kit. Real-time ultrasound visualization of the foam filling the intrauterine cavity and entering the fallopian tubes is then noted. Tubal patency is ascertained by observing the foam traversing the fallopian tubes and spilling into the peritoneal cavity. The procedure is known as hysterosalpingo-foam sonography (HyFoSy).¹



Other techniques and mediums have been used to assess tubal patency. Hysterosalpingography (HSG) employs radiographic contrast dye instilled into the intrauterine cavity under fluoroscopic guidance to assess tubal patency. Tubal patency can also be evaluated laparoscopically with chromotubation where methylene blue is infused into the intrauterine cavity and spillage of dye from the fallopian tubes is observed under direct vision of the laparoscope.

Hysterosalpingo-contrast sonography (HyCoSy) uses contrast agents such as saline or radiopaque contrast to assess fallopian patency.^{2,3} This method is being used in the US;

¹ De Smit Medical Systems, Ltd. www.exemfoamkit.co.uk. ExEm Foam Kit Business Case – technical.

² American College of Obstetrics and Gynecology. Sonohysterography. Technology Assessment. August 2016;Number 12.

³ Rajesh H, Lim SL, Yu SL. Hysterosalpingo-foam sonography: patient selection and perspectives. *International Journal of Women's Health* 2017;9:23-32.

FDA-approved contrast agents for use in HSG include ethiodized oil (Lipiodol)⁴ and ioxaglate meglumine 39.3% and ioxaglate sodium 19.6% (Hexabrix).⁵ “HyFoSy” is a modification of tubal contrast sonography using the foam created from diluted (b) (4) gel as a hyperechogenic contrast agent.

The Applicant estimates that approximately (b) (4) ExEm Foam HyFoSy procedures have been performed worldwide. The postmarketing surveillance maintained by the Applicant has received 12 voluntary reports. Among these 12 reports, one pertained to a patient who developed salpingitis with tubal ovarian abscess post-procedure (file # 2016-03, received on May 26, 2016 by the Applicant) and another pertained to a patient who had pelvic inflammatory disease post-procedure (file #2016-02, received on February 3, 2016 by the Applicant).⁶

3. Consult Questions from DMIP and DBRUP Responses:

Consult Question #1: Do you agree with the sponsor’s response regarding the generalizability of the European clinical studies to the US population? See attached PIND 135463 Meeting Minutes dated August 15, 2017 – Annotated.

DBRUP response to Question #1:

We agree that there are no national or ethnic differences in the fundamental anatomy of the human female reproductive tract. Regardless of contrast agents used, we do not expect an inherent difference in imaging results in European and US women with infertility due to tubal factor. Therefore, the studies conducted in Europe can be generalized to the US population with tubal infertility. Whether the submitted studies are adequate to address efficacy and safety of use of ExEm Foam in US populations is a matter of review.

Consult Question #2: There are variations in the definitions of tubal patency and occlusion that were used in the clinical studies and in the prescribing information. For example, in section 2.3 of the PI (Imaging Guidance), the following definitions are provided: “(b) (4) a tube is (b) (4) classified as occluded if (b) (4) ExEm Foam (b) (4) is not observed to pass from the tube (b) (4) the tubal lumen (b) (4) distended (b) (4) contrast flow (b) (4) observed in the intramural or isthmic part of the tube. (b) (4) ”

a. Is peritoneal spillage needed to confirm tubal patency of (b) (4)

⁴ Lipiodol label https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/009190s024lbl.pdf.

⁵ Hexabrix label https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018905s0251lbl.pdf.

⁶ Complaint Summary Record, page 2 of 4, submitted on February 7, 2019.

DBRUP response to Question #2:

By convention of clinical practice and according to multiple literary references, we consider documentation of peritoneal spillage as the only evidence adequate to establish tubal patency.^{3,7,8,9,10,11,12} [REDACTED] (b) (4)

[REDACTED]. In addition, if there is no spillage of contrast into the peritoneal cavity visualized, then additional studies should be performed to determine tubal patency.

Consult Question #3: Do you agree with the sponsor's assessment of risks of false positive (occlusion) and false negative (patent) diagnoses outlined in section 2.5.5.2 (Clinical Overview)? Specifically:

- a. The consequence of a false positive (occlusion) in a patient undergoing fertility work-up would be repeat exam (to rule out tubal spasm) or confirmation with laparoscopy with dye?***

DBRUP response to Question #3a:

If the HyFoSy procedure using ExEm Foam fails to show tubal patency when the tubes are actually patent, the patient may be advised to undergo assisted reproductive technologies, such as in vitro fertilization (IVF); she would incur inherent risks of ovarian hyperstimulation and, in rare cases, other serious adverse events. This scenario could represent a significant burden for the patient.

Therefore, if occlusion is seen, it would be reasonable to first repeat the HyFoSy to assess tubal patency or perform HSG, before resorting to laparoscopy and chromotubation.

- b. The consequence of a false negative (patency) in a patient undergoing fertility work-up would be delay in discussion of fertility treatment options?***

⁷ American Society for Reproductive Medicine. Diagnostic Evaluation of the Infertile Female: a Committee Opinion June 2015;103:Number 6.

⁸ Hamed HO, Shahin AY, Elsamman AM. Hysterosalpingo-Contrast Sonography Versus Radiographic Hysterosalpingography in the Evaluation of Tubal Patency. International Journal of Gynecology and Obstetrics 2009;105:215-217.

⁹ Panchal S, Nagori C. Imaging Techniques for Assessment of Tubal Status. Journal of Human Reproductive Sciences 2014;7:2-12.

¹⁰ Piccioni, M, et al. Sonohysterosalpingography: Comparison of Foam and Saline Solution. J Clin Ultrasound 2017;45(2):67-71.

¹¹ Riganelli L, et. al. Ultrasonography Reappraisal of Tubal Patency in Assisted Reproduction Technology Patients: Comparison Between 2D and 3D-Sonohysterosalpingography. A Pilot Study. Minerva Ginecol 2018;70(2):123-128.

¹² Van Schoubroeck D et. al. Pain During Fallopian-Tube Patency Testing by Hysterosalpingo-foam Sonography. Ultrasound Obstet Gynecol 2015;45:346-350.

DBRUP response to Question #3b:

If HyFoSy procedure using ExEm Foam is interpreted to showed tubal patency when the tubes are not patent, the patient could potentially undergo cycles of medical treatment (e.g., ovulation induction agent with clomiphene, intrauterine insemination, etc.) without the prospect of benefit. Importantly, for women in their reproductive years, fertility declines over time and the sooner therapy is started, the better the chances of pregnancy. A false negative result may lead to more than a delay in discussing treatment options; in fact, it may lead to a delay in starting appropriate therapy for tubal factor infertility, and in turn, achieving a pregnancy. This delay in establishing an accurate diagnosis adversely impacts the desired outcome.

c.

[Redacted] (b) (4)

DBRUP response to Question #3c:

[Redacted] (b) (4)

Consult Question #4: The company states

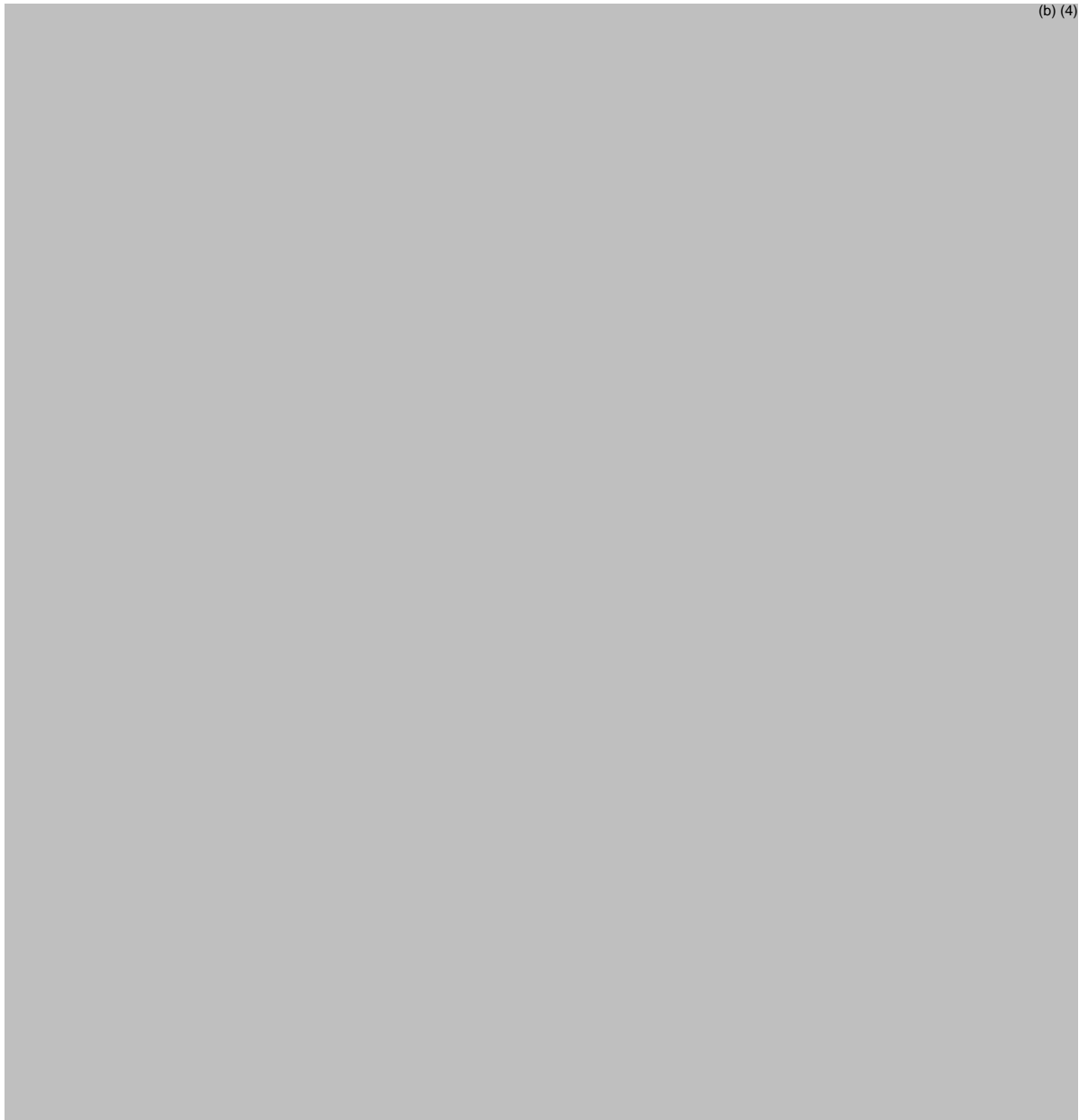
[Redacted] (b) (4)

DBRUP response to Question #4:

No. We do not agree. Data submitted in the NDA pertain only to the diagnostic reliability for tubal status (i.e., occluded or patent). [Redacted] (b) (4)

[Redacted]

[Redacted] (b) (4)



Consult Question #6: Enclosed are the (b) (4) Prescribing Information – do you have any comments regarding wording?

DBRUP response to Question #6:

We provide our initial recommendations for ExEm Foam labeling below. We are available to assist with your labeling review and discussion with the Applicant.



Recommendations for the Prescribing Information (PI)

1. Delete the term [REDACTED] (b) (4) throughout the PI; this term is not a recognized clinical term used in the US.
2. Add the instruction [REDACTED] (b) (4) to **Section 2 Dosage and Administration** and Delete it from **Section 5 Warnings and Precautions**.
3. Revise **Section 2.3 Imaging Guidance** to delete [REDACTED] (b) (4)
4. Delete all statements [REDACTED] (b) (4)
5. Add the following to **Section 4 Contraindications**:
 - Vaginal bleeding
 - Acute pelvic inflammatory disease (PID), acute cervicitis, vaginitis, or other lower genital tract infections (even if patient is receiving antibiotic therapy)
 - Known or suspected uterine or cervical neoplasia
 - Within 30 days of curettage or conization.
6. Delete the statement [REDACTED] (b) (4) from **Section 5 Warnings and Precautions**. In these clinical scenarios, the risks from the ExEm Foam HyFoSy procedure outweigh any therapeutic benefit. The drug/procedure should be contraindicated in these clinical situations.

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/

JENNIFER W LAWRENCE
03/08/2019 10:47:42 AM

CHRISTINA Y CHANG
03/08/2019 10:52:27 AM

AUDREY L GASSMAN
03/08/2019 10:58:35 AM

Date: November 6, 2018

To: Marc Neubauer, ICCR Lead Reviewer, Office of Health Technology 3,
Marc.Neubauer@fda.hhs.gov

From: M. Isabel Tejero del Rio, Office of Health Technology 3,
Isabel.Tejero@fda.hhs.gov

Applicant/Licensure: GISKIT B.V.

Submission (Type & Number): NDA 212279

Combination Product Name: ExEm Foam

Combination Product

Intended Use: Ultrasound contrast

Device Constituent (Type): Prefilled syringe

CTS ICCR Number: ICC1800897

Sharepoint ICCR Number: ICCR2018-03902

ICCR Instruction (ICCR Form): Evaluate compliance with 21 CFR part 820

Pre-Approval Facility N/A

Inspection: N/A

CDRH/OC Recommendation: No compliance review or facility inspections will be necessary for this product as currently described

The Office of Technology 3 at CDRH received a consult request from CDER to evaluate the regulatory requirements under 21 CFR part 820 and PAI for application NDA 212279. A review of the information provided was conducted from a device compliance perspective.

The intended use of ExEm Foam is as an ultrasound contrast imaging product that can be infused into the Fallopian tubes to aid in assessing tubal patency.

ExEm® Foam is a water-soluble ultrasound imaging agent prepared by mixing (b) (4) Gel and (b) (4) Water immediately prior to use with a single-use kit. It is composed of glycerol and hydroxyethyl cellulose (HEC) in purified water. The product will be delivered as a kit, which consists of the following components:

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Devices and Radiological Health

Office of Health Technology 3, Division C (Pilot)

- (1) Sterile 11-mL syringe containing 5 mL of (b) (4) Gel
- (1) Sterile 11-mL syringe containing 5 mL of (b) (4) Water
- (1) Sterile coupling device
- (1) Prescribing Information (PI) (b) (4)

The foam will be prepared in-office by a medical professional immediately prior to use by mixing (b) (4) Gel (b) (4) with an equal amount of purified water diluent ((b) (4) Water).

CDRH conducted a risk-based assessment of the device constituent part and has determined that does not need to conduct a compliance evaluation of the application unless changes to the delivery system or user population are made that need a re-evaluation of our decision.

This assessment pertains exclusively to the Compliance Review:

- Desk review of 21 CFR 820 call-outs, and
- Evaluation of manufacturing facilities to determine the need for inspections associated with this application.

The decision for not conducting a device compliance review for this application is independent from the technical review of the device constituent part done by our pre-market colleagues.

However, the applicant is still responsible to ensure their product is compliant with all applicable regulatory requirements and is ready to provide proof of compliance during inspection if requested. Thus, we recommend the applicant follows FDA's [guidance](#) for the current good manufacturing practice requirements under 21 CFR part 820.

 Digitally signed by Maria
Isabel Tejero Del Rio -S
Date: 2018.11.06 11:36:24
-05'00'

M. Isabel Tejero del Rio

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/

ANIKA A LALMANSINGH

11/07/2018

Uploaded on behalf of Marc Neubauer, ICCR Lead Reviewer, Office of Health Technology 3