

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212279Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multidisciplinary Review and Evaluation

Application Type	NDA (original submission, Type 1 - new molecular entity, 505(b)(2), associated IND 135463)
Application Number(s)	212279
Priority or Standard	Standard
Submit Date(s)	10/06/2018
Received Date(s)	10/09/2018
PDUFA Goal Date	8/9/2019 + 3 months extension = 11/9/2019
Division/Office	DMIP / ODE IV
Review Completion Date	11/4/2019
Established/Proper Name	(air polymer-type A) intrauterine foam
(Proposed) Trade Name	ExEm® Foam
Pharmacologic Class	Ultrasound contrast agent
Code Name	5071025
Applicant	GISKIT B.V.
Dosage Form	Foam; a single-dose kit containing one syringe with 5 mL clear gel [polymer-type A (hydroxyethyl cellulose), glycerin, and purified water], one syringe with 5 mL sterile purified water, and a coupling device to connect the two syringes
Applicant Proposed Dosing Regimen	Approximately 10 mL of ExEm® Foam is created by mixing 5 mL of clear gel and 5 mL of sterile purified water. Administer 2 to 3 mL of ExEm® Foam by intrauterine infusion. Repeat infusion of 2 to 3 mL of foam, as needed, to achieve visualization of the fallopian tubes.
Applicant Proposed Indication(s)/Population(s)	Assessment of fallopian tube patency in combination with ultrasound imaging in women with known or suspected infertility (b) (4)
Applicant Proposed SNOMED CT Indication Disease Term for Each Proposed Indication	85078005 Female infertility due to occlusion of fallopian tube
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	ExEm® Foam is an ultrasound contrast agent indicated for sonohysterosalpingography to assess fallopian tube patency in women with known or suspected infertility.
Recommended Dosing Regimen	2 to 3 mL of ExEm® Foam by intrauterine infusion using a 5-Fr or larger catheter. Dose may be repeated in 2 to 3 mL increments, as needed, to achieve visualization of the fallopian tubes. Maximum total dose is 10 mL.

Abbreviations: DMIP = Division of Medical Imaging Products; ODE IV = Office of Drug Evaluation IV; SNOMED CT = Systematized Nomenclature of Medicine—Clinical Terms; Fr = French gauge

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CDRH = Center for Devices and Radiological Health
DMEPA = Division of Medication Error Prevention and Analysis
DPMH = Division of Pediatric and Maternal Health
OCP = Office of Combination Products
OPDP = Office of Prescription Drug Promotion
OPQ = Office of Pharmaceutical Quality
OSE = Office of Surveillance and Epidemiology

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Signatures

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Glossary

2D	two-dimensional
3D	three-dimensional
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
BLA	biologics license application
CCIT	container closure integrity test
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CTFA	Cosmetic, Toiletry, and Fragrance Association
DBRUP	Division of Bone, Reproductive, and Urologic Products
DMEPA	Division of Medication Error Prevention and Analysis
EC	ethyl cellulose
FDA	Food and Drug Administration
Fr	French gauge
HEC	hydroxyethyl cellulose
HPC	hydroxypropyl cellulose
HDF	high-definition flow
GI	gastrointestinal
HPMC	hydroxypropyl methyl cellulose
HSG	hysterosalpingography
HyCoSy	hysterosalpingo-contrast sonography
HyFoSy	hysterosalpingo-foam sonography
ICH	International Conference on Harmonisation
IND	investigational new drug
IR	information request
ISO	International Organization of Standardization
IV	intravenous
LD ₅₀	median lethal dose
MC	methyl cellulose
NDA	new drug application
OCP	Office of Combination Products
PI	prescribing information
PID	pelvic inflammatory disease
PK	pharmacokinetics
sono-HSG	sonohysterosalpingography

1 Executive Summary

1.1. Product Introduction

ExEm Foam (air polymer-type A) intrauterine foam is an ultrasound contrast agent presented as a single-dose kit comprised of one 11-mL syringe containing 5 mL of clear gel [polymer-type A (hydroxyethyl cellulose), glycerin, and purified water], one 11-mL syringe containing 5 mL of sterile purified water, and a plastic coupling device that connects the two syringes. Air is also present within the syringes, such that when the components are mixed together, a foam is created (ExEm Foam). ExEm Foam is instilled into the uterus via a catheter under ultrasound imaging guidance to evaluate fallopian-tube patency. On ultrasound, the foam appears echogenic (white) when inside the fallopian tube. When the tube is patent, the foam will be seen traveling from the uterine cavity, through the tube, and spilling into the peritoneal cavity. The sterile gel is a 510(k)-cleared ultrasound coupling gel (b) (4)

1.2. Conclusions on Substantial Evidence of Effectiveness

Four adequate and well-controlled studies were submitted as primary sources of efficacy in this 505(b)(2) application. Although underlying patient-level or tube-level source data were not submitted for verification of the study results, the diagnostic performance of sonohysterosalpingography (sono-HSG) with ExEm Foam (hysterosalpingo-foam sonography [HyFoSy]) in all studies exceeded 50% using the lower bound of the 95% confidence intervals (CIs), with point estimates for sensitivity and specificity $\geq 80\%$. The studies varied in the types of instillation catheters and ultrasound imaging techniques used and in operator experience, reflective of clinical practice. While the two studies that evaluated the diagnostic performance of HyFoSy and sono-HSG with a saline-air mixture (hysterosalpingo-contrast sonography [HyCoSy]) were not designed to demonstrate superiority of HyFoSy over HyCoSy or noninferiority of HyFoSy to HyCoSy, in one study where patients received both HyCoSy and HyFoSy and were evaluated with the reference standard, the point estimates of both tests for sensitivity and specificity were generally similar.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Pathology leading to fallopian tube occlusion is a major cause of infertility in the United States. As a noninvasive, nonionizing imaging modality available at the point of care, ultrasound plays an important role in the diagnostic armamentarium for guiding infertile couples toward appropriate therapy. Yet fallopian tube patency is poorly evaluated on ultrasound without the use of contrast agents, and none currently marketed are approved for fallopian tube assessment. In this multidisciplinary review and evaluation authorized under Section 505(b)(2) of Federal Food, Drug, and Cosmetic Act, the review team relied on two reports published in the scientific literature to find that substantial evidence supports the effectiveness of ExEm Foam for assessment of fallopian tube patency in women with known or suspected infertility. Both reports demonstrate that in these patients, a high proportion of tubes were correctly identified as patent or occluded, using sonohysterosalpingography with ExEm Foam or equivalent and measured against laparoscopy with chromopertubation. For assessing safety, the review team also relied on data from FDA databases, reports on animal and other preclinical studies published in the scientific literature or owned by the Applicant, and the Applicant's reported experience marketing ExEm Foam outside the United States. Subsequent to labeling revisions, the review team finds that the benefit-risk of the product is favorable and recommends approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	• Infertility is the failure to achieve a clinical pregnancy after ≥12 months of regular unprotected sexual intercourse. • 15% of couples will not conceive during this time period. • In 20 to 30% of couples with infertility, the cause is a tubal abnormality.	• Tubal factors account for a proportion of the cases of infertility; an imaging test that can accurately diagnose tubal patency is needed for infertility work-up and subsequent management of infertility.
<u>Current Treatment Options</u>	• Laparoscopy with dye is the reference standard for determination of fallopian tube patency. • Imaging tests include sonohysterosalpingography (sono-HSG) with a saline and air mixture acting as a contrast agent (HyCoSy) and hysterosalpingography (HSG) with radiographic iodinated contrast.	• The reference standard is invasive and requires exposure to sedation or general anesthesia; the imaging tests are less invasive and do not require sedation/anesthesia. • HSG involves the use of an iodinated contrast agent that could result in a hypersensitivity reaction; the procedure also exposes the patient to radiation.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Benefit</u>	- Compared to HSG, sono-HSG with ExEm Foam (HyFoSy) does not expose the patient to radiation or iodinated radiographic contrast and it can be performed in the office setting. - ExEm Foam used in HyFoSy is postulated to be more stable and have a longer imaging half-life than the saline and air mixture used in HyCoSy; however, differences in stability and imaging half-life between the two ultrasound contrast agents have not been confirmed in clinical trials. - All efficacy studies submitted were from the literature; no patient-level or tube-level data sets were submitted. The studies evaluated the diagnostic performance of HyFoSy compared to the reference standard. - The definition of tubal patency indicated by peritoneal spillage of contrast agent was used in all studies submitted for efficacy except for one. - None of the efficacy studies were prospective studies designed to compare the diagnostic performance of HyFoSy to HSG. - The two efficacy studies that evaluated the diagnostic performance of both HyCoSy and HyFoSy were not designed to demonstrate superiority of HyFoSy over HyCoSy or noninferiority of HyFoSy to HyCoSy; in the one study where patients were evaluated with both HyCoSy and HyFoSy, the diagnostic performance of both tests was similar. - Studies varied in terms of ultrasound imaging techniques and instillation catheters used.	Despite variations in operator experience, ultrasound imaging techniques, and instillation catheters used (reflecting clinical sites' preferences), the sensitivity and specificity of HyFoSy was consistent across the studies and exceeded 60%.
<u>Risk and Risk Management</u>	- Adverse events reported in the literature and in the foreign postmarketing database are similar to those reported for HSG and HyCoSy and are likely related to the procedure itself and not to ExEm Foam. - Potential safety concern of scarring of the peritoneum or reproductive tract impacting fertility was not identified in the literature search. The pH of the foam is physiologic, and the osmolality of the foam is less than that of approved HSG imaging agents, where no such concern has been identified. - Although the studies utilized various catheters for instillation without incident, the Applicant did not provide performance testing data to confirm the physical compatibility of ExEm Foam with cleared HSG and sono-HSG catheters.	- Standard warnings and contraindications for HSG are applicable to HyFoSy and are included in the labeling. - The labeling will recommend usage of the foam with French gauge (Fr) 5 or larger catheters; one study reported resistance to instillation with use of a 5-Fr catheter. In the event of resistance to instillation, the label cautions against injecting forcefully and recommends using a larger catheter for instillation. - Catheter failure and breakage will be a focus of monitoring in the postmarket setting.

1.4. Patient Experience Data

Patient Experience Data Relevant to This Application (check all that apply)

☐ The patient experience data that were submitted as part of the application include:	Section of review where discussed, if applicable
☐ Clinical outcome assessment (COA) data, such as	
X Patient-reported outcome (PRO)	Section 8
☐ Observer-reported outcome (ObsRO)	
X Clinician-reported outcome (ClinRO)	Section 8
☐ Performance outcome (PerfO)	
☐ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐ Patient-focused drug development or other stakeholder meeting summary reports	
☐ Observational survey studies designed to capture patient experience data	
☐ Natural history studies	
☐ Patient preference studies (e.g., submitted studies or scientific publications)	
☐ Other: (Please specify):	
☐ Patient experience data that were not submitted in the application, but were considered in this review:	
☐ Input informed from participation in meetings with patient stakeholders	
☐ Patient-focused drug development or other stakeholder meeting summary reports	
☐ Observational survey studies designed to capture patient experience data	
☐ Other: (Please specify):	
☐ Patient-experience data were not submitted as part of this application.	

2 Therapeutic Context

2.1. Analysis of Condition

The World Health Organization (WHO) defines infertility as “a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse” (WHO 2019). It is estimated that 15% of couples will not conceive during this time period, and these couples may benefit from an infertility work-up (Lindsay and Vitrikas 2015). Primary infertility refers to infertility when the couple is never able to conceive; secondary infertility occurs when the couple is not able to conceive following a successful birth. Infertility may arise from female factors, male factors, or a combination of both, and the fertility work-up includes evaluation of both partners. In 20% to 30% of couples, infertility is caused by a tubal abnormality such as scarring from previous infection (Brigham and Women's Hospital 2019).

2.2. Analysis of Current Treatment Options

There are two tests that are widely used in the United States for the assessment of tubal patency: hysterosalpingography (HSG) and laparoscopy with chromopertubation. Chromopertubation is considered the reference standard exam. A dye such as methylene blue (an off-label use) is injected into the uterine cavity. Tubal patency demonstrated through contrast spillage from the fallopian tube fimbriae into the peritoneum is directly visualized with the laparoscope. HSG is an alternative and widely accepted procedure to laparoscopy with dye (Saunders et al. 2011). Tubal patency is established by visualization of radiographic contrast spillage into the peritoneum under fluoroscopy. Disadvantages of the procedure include radiation exposure and allergic reaction to the radiographic contrast agent. Omnipaque 240 and 300 (NDA 018956) and Lipiodol (NDA 009190) are approved contrast agents for HSG.

Sono-HSG evaluates fallopian tube patency with ultrasound. When contrast is used, the technique is referred to as hysterosalpingo-contrast sonography (HyCoSy). The contrast agent in HyCoSy can be variable, as in HSG. (b) (4)

No currently marketed ultrasound contrast agents have this indication. Alternatively, saline alone or a mixture of saline and air can be used as the contrast agent. Saline, acting as a negative contrast agent, appears black or anechoic within the uterine cavity and fallopian tubes. The air in the mixture increases the echogenicity of the saline in the fallopian tubes and peritoneum.

The saline and air mixture acts as a positive contrast agent with resultant improved visualization under ultrasound. Physicians may alternate instillation of air and saline to create this mixture or use cleared devices such as FemVue (K110288) and SonoFlow (K142545) to provide this mixture. However, some users may prefer a positive contrast imaging agent over a negative contrast imaging agent. It is postulated that due to potential greater stability of ExEm Foam as compared to the saline and air mixture, the foam might provide a longer imaging half-

life. However, testing has not been performed to demonstrate that ExEm Foam has a longer imaging half-life.

Gel-infusion sonography in the evaluation of fallopian tube patency has been described but appears uncommon in the United States per the Division of Bone, Reproductive, and Urologic Products (DBRUP) consultation.¹ The clear gel used in the kit [REDACTED] (b) (4) is cleared for gel infusion sonography, although it is cleared as a coupling agent, rather than as a contrast agent, for this use. Coupling agents are transmission media cleared for use for acoustically coupling the ultrasonic transducer to the body surface.

Within a given ultrasound imaging examination for fallopian tube patency, standard two-dimensional (2D) imaging can be performed to visualize the flow of contrast from the uterine cavity through the fallopian tubes and into the peritoneal cavity. Depending on the orientation of the fallopian tubes relative to the uterus, the operator may need to manipulate the ultrasound probe (transducer) to follow the course of the fallopian tubes and watch for peritoneal spillage of contrast.

Some ultrasound systems may be equipped with volumetric probes and software capable of three-dimensional (3D) imaging. With these systems, a volume of tissue can be acquired automatically without moving the transducer, allowing for easier assessment of contrast flow between the uterus, fallopian tubes, and peritoneal cavity, potentially on a single image.

¹ DBRUP consult June 23, 2017 in advance of July 17, 2017, pre-IND meeting.

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Table 1. Summary of Contrast Agents Relevant to Proposed Indication

Product Name	Relevant Indication	Dosing/ Administration (per labeling)	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
(b) (4)					
Omnipaque or Lipiodol	Fallopian tube patency evaluation with X-ray fluoroscopy	• Omnipaque: 15 to 20 mL • Lipiodol; inject in 2 mL increments		• Allergic reaction • Radiation exposure	Hexabrix approved for this use but not currently marketed
Methylene blue (or other dyes)	Unapproved indication for use in laparoscopy and dye procedure		Laparoscopy with intrauterine dye is reference standard test for fallopian tube patency		Off-label use
Saline/air mixture delivery devices (SonoFlow and FemVue)	Delivery of air and saline into uterus and fallopian tubes during sono-HSG			Maximum volume of 70 mL to be instilled due to risk of air embolism	

Abbreviation: sono-HSG, sonohysterosalpingography

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

ExEm Foam (air polymer-type A) intrauterine foam is an ultrasound contrast agent presented as a single-dose kit comprised of one 11-mL syringe containing 5 mL of a clear gel [polymer-type A (hydroxyethyl cellulose), glycerin, and purified water], one 11-mL syringe containing 5 mL of sterile purified water, and a plastic coupling device that connects the two syringes. The gel is a 510(k)-cleared ultrasound coupling gel (b) (4) for use in ultrasound imaging procedures. ExEm Foam is not approved or cleared for the evaluation of fallopian tube patency in the United States. It is marketed outside the United States as a device.

(b) (4)

On July 30, 2015, OCP concluded that ExEm Foam is a combination product, and that the foam is an ultrasound contrast agent, as it would “allow [an] image to provide information on whether the fallopian tubes are open or closed” on ultrasound. OCP determined that the primary mode of action is attributable to the contrast agent and the Center for Drug Evaluation and Research is the lead center for premarket review and regulation.

(b) (4)

(b) (4) FDA concluded that the foam produced by ExEm Foam is an ultrasound contrast agent and should be regulated as a drug by the Center for Drug Evaluation and Research. On July 16, 2017, a Type B pre-IND meeting (IND 135463) was held with the Applicant to discuss a 505(b)(2) NDA submission using literature for evidence of safety and efficacy. The Food and Drug Administration (FDA) provided advice on how the literature should be searched, including (1) the types of study designs that might provide substantial evidence of efficacy and (2) the types of safety concerns that may occur with use of the product that should be searched for in the literature. On February 28, 2018, the Applicant provided their proposed literature search protocol and statistical analysis plan. FDA provided responses on April 20, 2018, in a written-response-only format.

3.2. Summary of Resubmission/Submission Regulatory Activity

The following is an outline of the current review cycle:

- October 9, 2018: NDA received
- November 28, 2018: Clinical information request (IR) for financial disclosure information, statement of good clinical practice, and review of the use of the product or its components in pregnant or lactating women
- November 30, 2018: Division of Medication Error Prevention and Analysis (DMEPA) IR for comprehensive use-related risk analysis for the preparation of the product
- December 6, 2018: Applicant response to IRs November 28, 2018, and November 30, 2018, amendment 4
- December 21, 2018: Filing letter, including IRs
 - Clinical IR for:
 - Summary of 12 adverse events (AEs) reported in the pharmacovigilance database
 - Additional data from Ludwin study: subgroup analyses based on the two different definitions used for tubal patency or patient-level or tube-level data that would allow such subgroup analyses to be performed
 - Microbiology IR for:
 - Container closure integrity validation data
 - (b) (4) validation data
 - Bulk hold time study
 - Sterilization process validation for the coupling device
- December 28, 2018: Clinical IR regarding results of the Riganelli study, specifically clarification of whether the published results reflected patient-level data or tube-level data; discrepancy in the number of fallopian tubes used in the Applicant-generated analyses also noted
- January 15, 2019: Applicant submits updated prescribing information (PI) (b) (4) the submission also included information regarding use of the product in pregnant and lactating women, amendment 5
- January 16, 2019: Applicant submits updated Integrated Summary of Efficacy in response to clinical IR of December 28, 2018, amendment 6
- January 23, 2019: Combined clinical chemistry, manufacturing, and controls (CMC) Drug Product IR requesting product osmolality and comparison to physiologic osmolality and osmolality of other approved products
- January 25, 2019: Quality information amendment, included comparison of product pH to physiologic pH of the female reproductive tract, amendment 7
- January 25, 2019: Clinical IR requesting:
 - Additional information/underlying data available to support mixing instructions
 - Description of European Union reporting requirements for ExEm Foam and how AE reports are handled by the Applicant based on these requirements

- February 7, 2019: Clinical amendment, included updated integrated summary of safety and responses to filing IR and clinical IR for summary of the pharmacovigilance database and description of how complaints are handled, respectively, amendment 8
- February 26, 2019: CMC Drug Product IR in preparation for February 28, 2019 teleconference with Applicant; IR includes osmolality of the drug product, hydroxyethyl cellulose (HEC) specifications, and certificate of analyses for bulk water
- February 28, 2019: Teleconference with Applicant regarding CMC Drug Product issues
- March 4, 2019: CMC IR to include pH (6 to 7.5) in the water specification
- March 14, 2019: Response to CMC Drug Product and Microbiology IRs, amendment 11:
 - Microbiology response included information regarding the container closure integrity test (CCIT), bulk hold study, and (b) (4) validation data for one run of sterile purified water and one run of clear gel. A description of the coupling device sterilization process also included
 - CMC response included osmolality of the product
- March 28, 2019: CMC Microbiology IR requesting a CCIT study conducted with the proposed container closure system, two additional (b) (4) runs for the sterile purified water and clear gel, and the validation report for the coupling device sterilization process
- April 5, 2019: CMC Drug Product IR requesting three batches characterizing bubble size and distribution using Coulter analysis method
- April 5, 2019: Clinical IR (based on CDRH review consultation) requesting:
 - Additional information on the sizes, lengths, and types of catheters to be used with ExEm Foam
 - Comparison of the viscosity of the foam to approved agents used for HSG or sono-HSG
- April 15, 2019: CMC Microbiology IR response with CCIT study provided for a similar container closure; the Applicant proposes to provide the two additional validation runs of the (b) (4) process after NDA approval; summary of the coupling device sterilization process validation provided
- April 18, 2019: Microbiology IR regarding deficiencies related to:
 - Validation of container closure system; new CCIT study requested
 - (b) (4) process for sterile purified water and clear gel with request for data from two additional successful runs
- May 6, 2019: CMC Process IR: sterilization validation, packaging, stability results, bulk in-process testing, and executed packaging batch records and proposed commercial master batch records requested
- May 14, 2019: Teleconference with Applicant; Microbiology IR asking for summary of (b) (4) validation data
- May 16, 2019: Response to Microbiology IRs dated April 18, 2019, and May 14, 2019, amendment 14; in the response, a timeline of when the Applicant expects to provide outstanding responses to IRs was included (expected submission dates were in June and July 2019)
- May 16, 2019: Response to Clinical IR dated April 5, 2019; amendment 15

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- May 29, 2019: Response to CMC IRs dated February 26, March 4, and May 6, 2019; amendment 16
- June 7, 2019: Applicant submits draft CCIT protocol and CCI sensitivity protocol for FDA comment; amendment 17
- June 20, 2019: Applicant submits testing of size distribution, concentration, and ultrasound image quality when the foam is (1) made by mixing only 6 times, not the recommended 10, and (2) left to sit for 5 minutes prior to instillation; amendment 19
- July 3, 2019: Applicant response to CMC IRs of March 4, 2019; May 6, 2019; and May 20, 2019; amendment 20
- July 18, 2019: Teleconference with Applicant regarding timeline of submissions for outstanding CMC Drug Product, Processing, and Microbiology IRs
- July 23, 2019: Letter to Applicant regarding 3-month extension of the review clock based on the July 3, 2019 submission which constituted a major amendment to the NDA

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

The evidence of safety and efficacy relied on literature rather than on studies performed by the Applicant; therefore, no clinical sites were inspected.

4.2. Product Quality

Review issues included the need for specifications for the drug product and components. These included size and concentration of the bubbles and pH, osmolality, viscosity, and of the drug and components.

From a process standpoint, (b) (4) validation, packaging, stability results, bulk in-process testing, and executed packaging batch records and proposed commercial master batch records were requested.

4.3. Clinical Microbiology

No clinical microbiology data are needed for this product and none were provided.

4.4. Devices and Companion Diagnostic Issues

The Division of Reproductive, Gastro-Renal, and Urologic Devices Obstetrics and Gynecology Devices Branch within the Office of Device Evaluation, CDRH was consulted regarding the compatibility of currently cleared catheters for sono-HSG or HSG with the ExEm Foam kit. The proposed kit does not include a catheter for instillation of the foam; the Applicant's proposed PI recommends a 5-Fr or larger catheter be used for foam instillation. The PI further instructs the user to use a larger catheter for instillation should resistance be encountered rather than instilling forcefully.

The original NDA submission did not provide a discussion of why ExEm Foam is compatible only with catheters of this size, although it was addressed by the Applicant subsequently in amendment 15. One study submitted for safety (Zizolfi et al. 2018) reported that the investigators had to dilute the foam as it was too viscous in its recommended formulation to pass through the 5-Fr catheter used in the study. Another study (Exacoustos et al. 2017) similarly used diluted ExEm Foam.

No other specifications for the catheter are included in the PI. Multiple versions of the kit are being marketed outside the United States, some of which include an instillation catheter. Per the Applicant, kits without the catheter included do not specify the sizes or types of catheters

that should be used with ExEm Foam.² Studies from the literature submitted for evidence of safety and efficacy used different sizes and types of catheters (i.e., Foley, balloon, and balloon-less). Table 2 summarizes the different catheters used.

Table 2. Summary of Catheters Used to Instill Foam in Published Studies

Type of Study	Study Identifier	Description of Catheter Used in Study to Administer Foam
Efficacy, Safety	Ludwin, <i>et al.</i> (Apr. 2017)	Disposable 5-Fr silicone catheter (Softinjector; RIMOS., Mirandola, Italy) with a balloon
Efficacy, Safety	Rosic, <i>et al.</i> (2018)	Cervical balloon-less catheter
Efficacy	Piccioni, <i>et al.</i> (2017)	5-French balloon-catheter
Efficacy, Safety	Riganelli, <i>et al.</i> (2018)	<i>Specific type of catheter used not disclosed by authors</i>
Efficacy, Safety	Dreyer, <i>et al.</i> (2015)	Cervical balloon-less catheter
Efficacy	Van Schoubroeck, <i>et al.</i> (2013)	2-mm [6-Fr] pediatric Foley's balloon catheter with stylet (Pediatric FolySil Catheter, Coloplast A/S, Humlebaek, Denmark)
Safety	Dreyer, <i>et al.</i> (2014)	Small cervical balloon-less catheter
Safety	Emanuel & Exalto, <i>et al.</i> (2012)	7-Fr Cervical balloon-less applicator (designed for Gel Instillation Sonography by GynaecologiQ BV, Delft, The Netherlands)
Safety	Exacoustos, <i>et al.</i> (2017)	5-Fr HyFoSy balloon catheter (PBN Medical, Stenlose, Denmark)
Safety	Exacoustos, <i>et al.</i> (2015)	5-Fr salpingographic balloon catheter
Safety	Ludwin, <i>et al.</i> (May/June 2017)	Sterile 5-Fr catheter (Softinjector; RIMOS., Mirandola, Italy)
Safety	Tanaka, <i>et al.</i> (2018)	Balloon catheter (Rocket HSG & Sonohystogram catheter with integral wire stylet (Rocket Medical plc, Washington, The UK))
Safety	Van Schoubroeck, <i>et al.</i> (2015)	2-mm [6-Fr] pediatric Foley's balloon catheter with stylet (Pediatric FolySil Catheter, Coloplast A/S, Humlebaek, Denmark)
Safety	Zizolfi, <i>et al.</i> (2018)	5-Fr salpingographic balloon catheter

Abbreviation: Fr, French gauge

² Amendment 15 dated May 16, 2019

Cleared HSG catheters are regulated as Class II devices under 21 CFR 884.4530 and typically are indicated for HSG, sono-HSG, or both.³ Physical compatibility of currently cleared catheters to the kit is dependent on the pressure and flow rates required for the procedure. The pressure and flow rates are themselves dependent on the viscosity of the imaging agent and diameter of the catheter lumen.

If higher pressure and flow rates are required for the HyFoSy procedure as compared to HSG or sono-HSG procedures, catheter malfunction such as failure and leakage may occur. Although the Applicant did not provide a comparison of the pressure and flow rates of HyFoSy to those encountered in HSG or sono-HSG to ensure physical compatibility of the catheters, the studies submitted for safety and efficacy did not report catheter failure. Leakage was reported occasionally; however, these instances were not attributed to issues with the catheter.

Comment: Postmarketing reports will be monitored for catheter issues.

CDRH consultation also discussed the impact the catheter may have on the distribution of bubbles in the foam prior to delivery to the uterus, which may affect imaging appearance and consequently, efficacy. For example, smaller-diameter catheters may have greater potential to disrupt the bubbles in the foam as compared to larger-diameter catheters. The studies used to establish efficacy used various sizes and types of catheters.

Comment: The labels for Omnipaque and Lipiodol do not specify the catheter to be used for instillation.

Based on the syringes used for the preparation of ExEm Foam, the CDRH consultant recommended that the labeling specify that the catheters have Luer connections.

Additional consultation from CDRH Office of Surveillance and Biometrics reported no relevant AEs from the cleared SonoFlow, FemVue, (b) (4) devices. Specifically, there were no AEs related to air embolism or peritoneal scarring.⁴

4.5. Human Factors

DMEPA provided a review of the labeling for areas of vulnerability that could lead to potential medication errors. The primary concern was the potential for incorrect preparation of the product leading to noninterpretable images and thus the need of a human factors validation study was evaluated.⁵

³ Office of Device Evaluation/Division of Reproductive, Gastro-Renal, and Urologic Devices/Obstetrics and Gynecology Devices Branch ICC190018 consult dated March 29, 2019.

⁴ CDRH/OSB ICCR2018-04180 and ICC 1900180 consults February 27, 2019, and March 27, 2019

⁵ DMEPA consult dated May 9, 2019

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The review team considered the clinical studies performed with the product, postmarketing experience with the use of the product outside the United States, and similarities between the product and currently marketed ultrasound contrast agents (Lumason) that require reconstitution prior to imaging. The Applicant also performed bench testing to evaluate ultrasound image quality when deviations in ultrasound preparation administration occurred.

The qualitative ultrasound images provided in the study reports were reviewed. There is no difference in the echogenicity of the foam between the various preparations that might affect the operator's ability to diagnose fallopian tube patency.

The main outcome of a noninterpretable image would be an additional test, HSG, which is already a routine imaging test performed for fallopian tube patency. A noninterpretable test would not result in a definitive management plan for infertility by a reproductive specialist.

The review team concluded that a human factor study was not needed and developed labeling recommendations to increase readability and prominence of important preparation information to enhance safe and effective use of the product.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

This NDA should be approved from a nonclinical perspective.

ExEm Foam is prepared from a clear gel and sterile purified water. The gel is composed of glycerol 85% (b) (4), HEC (b) (4), and purified water USP/EP (b) (4). Glycerol, a clear, viscous, water soluble polyhydric alcohol is present in ultrasound gel, vaginal moisturizers and lubricants, food additives, cosmetics, and personal health care products. HEC is a water soluble, modified cellulose polymer containing hydroxyethyl side chains commonly used in personal vaginal moisturizers and lubricants, lotions, oils, skin and hair care products. The safety of glycerol and HEC is well established by their widespread and long-term clinical use, which is well documented in the literature and made available by the Applicant to support this NDA.

The Applicant conducted biocompatibility safety studies on glycerol and HEC components of this product and no safety concern was reported. Based on available nonclinical pharmacology, pharmacokinetics (PK), toxicity, genotoxicity, reproductive and developmental toxicity, local tolerance, skin sensitization, and compatibility data on glycerol and HEC, there is no nonclinical safety concern with the use of ExEm Foam for the proposed indication and the new route of administration. However, because of lack of nonclinical safety studies involving intrauterine exposure of glycerol, HEC, or ExEm Foam, it was difficult to determine the risk of inflammatory reactions and the potential for scarring and adhesions in the uterus, tubes, and around the ovaries. The safety assessment of ExEm Foam following intrauterine exposure was therefore conducted using the following tools:

1. Search on FDA database for products containing glycerol or HEC for safety comparison to ExEm Foam
2. Applicant's literature search on possible ExEm Foam effects such as embolization, inflammation, scarring, and adhesion following intrauterine or intravaginal use
3. Search on available CDRH data on the clear gel and other products containing glycerol and HEC
4. Relevant CMC data including osmolality and pH of ExEm Foam

The information obtained from the FDA database on products containing glycerol and HEC yielded no safety signals and supported the safety information in the NDA. The analysis demonstrates that there are no safety concerns with the intended route of administration for ExEm Foam.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

No stand-alone safety pharmacology data were provided in this submission because there is no known direct or indirect pharmacological activity associated with glycerol and HEC. Glycerol and HEC are extensively used in cosmetics, personal care, and health care products. Glycerol is present endogenously as a result of dietary intake from plant and animal sources and a precursor for glycolysis/gluconeogenesis and synthesis of triacylglycerols. HEC is a modified cellulose. It is characterized by poor permeability across gastrointestinal (GI) epithelial mucosa. Glycerol is systemically absorbed following intrauterine exposure of ExEm Foam, though it does not significantly affect the basal fasting plasma glycerol. However, HEC demonstrates very low permeability across epithelial mucosa of the uterus and is expected to exhibit negligible effect following intrauterine administration.

The Applicant provided literature PK data on glycerol and HEC. The proposed route of administration for clear gel is intrauterine administration. However, these routes were not employed for glycerol or HEC in the nonclinical studies conducted in the available literature. The Applicant stated that nonclinical studies with oral administration are acceptable surrogates to characterize systemic toxicity potential with intrauterine administration. This statement is based on the similarity of the putative mechanisms of absorption across the GI and uterine mucosa for both compounds. The Applicant submitted PK data following oral administration of glycerol and HEC to assess the relevant PK parameters of ExEm Foam. The review team found that oral administration studies are not optimal surrogates for intrauterine and intravaginal administration studies, given that there is greater potential for absorption, irritation, inflammation, and epithelial cell damage in the uterus and vagina than in the GI tract.

5.4. ADME/PK

Table 3. Pharmacokinetic Characteristics

Type of Study	Major Findings
Absorption	<u>Glycerol</u> No reports of the intrauterine absorption of glycerol were found in the literature. Rapidly absorbed in human after oral administration. T_{max} approximately 1 to 1.5 hours (McEvoy 1993); T_{max} ranging from 1 to 2 hours reported in healthy human patients orally administered 1.2 g/kg glycerol (Sommer et al. 1993). Rat data suggest the intestinal absorption was saturable and mediated by a sodium-dependent, carrier-mediated transporter (Yuasa et al. 2003) (Kato et al. 2005). Similarly, in humans, glycerol uptake was enhanced by sodium-dependent transporter (Fujimoto et al. 2006). <u>HEC</u> No literature evidence of intrauterine absorption of HEC was found. Absorption of HEC was expected to be poor, similar to hydroxypropyl cellulose (HPC), its structural analog. Following oral administration of [^{14}C]HPC to rats, no radioactivity was detected in the blood and less than 3% was found in tissues or urine and up to 96.8% to 97.4% recovered in feces suggesting low oral absorption (Kitagawa et al. 1976).
Distribution	<u>Glycerol</u> Glycerol is distributed throughout tissue extracellular space (Becker et al. 2015). The distribution is associated with the location of glycerol kinase, its primary metabolizing enzyme and up to 80% of its activity is in the liver and 10% to 20% in the kidney (Frank et al. 1981). Following intraperitoneal administration in rats, [^{14}C]glycerol was retained in tissues and recovered in liver (approximately 30% to 32%) (Doerschuk 1951). Following intraperitoneal administration of [^{14}C]glycerol to rats, 5.9% of the radioactivity incorporated into lipids was found in liver, 0.26% and 0.16% in brain and kidney, respectively, and lesser percentages of lipids were found in spleen, heart, lung, stomach, mesenteric fat, testes, and small intestine (Gidez and Karnovsky 1954). Glycerol was rapidly distributed into red blood cells (Tourtellotte et al. 1972; Lin 1977). No data on plasma protein binding of glycerol was found in literature. Following an intravenous (IV) injection of [^{14}C]glycerol, there was rapid appearance of radioactivity measured in rat and rabbit fetal plasma within 2 minutes with specific activity of glycerol remaining the same in mother and fetus, suggesting placental transfer of glycerol in both species (Gilbert 1977). <u>HEC</u> No data on tissue or red blood cell distribution, plasma protein binding, or placental transfer of HEC was found in literature. However, data on tissue distribution of closely related analog [^{14}C]HPC demonstrated low levels in liver, kidney, and GI tract (0% to 0.25% following administration of single oral doses ranging from 250 mg/kg to 1.3 g/kg (CTFA 1968; Kitagawa et al. 1976).

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Type of Study	Major Findings
Metabolism	<u>Glycerol</u> Metabolic pathways of glycerol have been well elucidated in rats (Lin 1977; Frank et al. 1981). Systemically absorbed glycerol is initially phosphorylated to glycerol-3-phosphate by glycerol kinase. Up to 70% to 90% of glycerol-3-phosphate is subsequently oxidized to dihydroxyacetone phosphate by glycerol-3-phosphate dehydrogenase, and then isomerized to glyceraldehyde-3-phosphate. It can then proceed to either the gluconeogenesis or glycolysis pathways (Doerschuk 1951). The remaining 10% to 30% of glycerol-3-phosphate is esterified to free fatty acids as triglycerides. The triglycerides in the body can be catabolized to free glycerol and fatty acids (which subsequently undergo beta-oxidation). Administration of ExEm Foam is not expected to alter the endogenous metabolic equilibrium since the systemic glycerol absorption will not impact normal endogenous fasting levels after ExEm administration. <u>HEC</u> No reports on the metabolism of HEC, a modified cellulose, were found in the literature. However, the metabolism of unmodified cellulose is well characterized (Cummings 1984). Anaerobic microbes in the colon can produce cellulase enzymes that cleave the 1,4 β linkages to form shorter chain polysaccharides, which are further fermented into short-chain volatile fatty acids (e.g., acetate, propionate, butyrate), CO_2, CH_4, and H_2 (Chassard et al. 2005). Volatile fatty acids are further metabolized by known pathways for propionate to succinyl-CoA (tricarboxylic acid cycle); acetate is metabolized to acetyl-CoA; and butyrate is mostly metabolized to ketone bodies and CO_2 in the colonic epithelial cells. Available rat data on [^{14}C]-HPC (CTFA 1968; Kitagawa et al. 1976) demonstrate complete recovery of radioactivity in feces (>96%), which suggests minimal HPC metabolism and no volatile fatty acids formation
Excretion	<u>Glycerol</u> Data obtained from rats administered single doses of 26.3 mg [^{14}C]glycerol showed that only 0.95% to 1.5% of the dose was recovered in feces after 24 hours (Doerschuk 1951). Consistent with metabolism of glycerol to glyceraldehyde-3-phosphate, and subsequent oxidization to CO_2 by way of pyruvate, acetyl-CoA, and the tricarboxylic acid cycle, the main route of excretion was respiratory $^{14}\text{CO}_2$, accounting for 80% to 81% of the dose. The minor excretion of glycerol is responsible for urinary recovery of ^{14}C, which was only 6.1% to 6.2% of the dose, in keeping with reabsorption of glycerol reported in the kidney (Lin 1977). The percentage ^{14}C recovery was found as lipids in the carcass and liver, in agreement with glycerol-3-phosphate being an important intermediate in lipid synthesis and accounting for the remaining portion of excretion. Total ^{14}C recovery in these studies ranged from 96.0% to 96.8%. <u>HEC</u> There are no available data on the excretion of HEC in the literature. However, data on two studies involving oral administration of [^{14}C]HPC in rats showed that >96% radioactivity recovered was associated with feces; urine recovery ranged from 1.5% to 3.2% (CTFA 1968; Kitagawa et al. 1976). There was no radioactivity recovered in blood or as expired CO_2.

5.5. Toxicology

5.5.1. General Toxicology

Glycerol is extensively used in cosmetics and personal care products, food additives, and noncosmetic applications (Becker et al. 2015). HEC is used as humectant, binder, emulsion stabilizer, and film former in lotions, oils, bath products, eye make-up, skin care products, hair conditioners, hair dyes, and hair colors (Bergfeld et al. 2009). The Applicant conducted no toxicity studies on the safety of glycerol and HEC. However, safety data of glycerol and HEC available in published literature are provided to support the nonclinical safety of these compounds. The data are mostly from studies conducted before standardization of good laboratory practices and generally are not consistent with the standards described in current International Conference on Harmonization (ICH) or Organization for Economic Co-operation and Development guidance documents. Available safety data include single-dose, repeated-dose, genotoxicity, carcinogenicity, reproductive toxicity, local tolerability, skin irritation, and sensitization studies.

General Toxicology: Additional Studies

Single-dose toxicity on glycerol

Several single-dose toxicity studies were conducted with several routes using multiple species. Median lethal dose (LD₅₀) determinations were used in all the single-dose studies instead of no-observed-adverse-effect-level estimations, which could have allowed safety margins to be determined. The LD₅₀ values, however, showed that glycerol is well tolerated based on the large multiples of the exposure level when compared to the intended human dose. The oral route is more relevant for the intrauterine administration; summary data are shown in Table 4.

Table 4. Summary of LD₅₀ and Dose Multiples of Glycerol Dose in ExEm Foam Based on Oral Administration

Species	LD ₅₀	Dose Multiples to Calculated Human Glycerol Dose From ExEm Foam
Mouse	20.8 to 38 g/kg	272- to 497-fold
Rat	<24 to 27.5 g/kg	623- to 714-fold
Guinea pigs	7.75 to 11.5 g/kg	271- to 403-fold

Abbreviation: LD, lethal dose

Single-dose toxicity on HEC

Two single-dose toxicity studies were conducted with oral route in rats. The LD₅₀ values were also determined in the studies instead of no-observed-adverse-effect-level estimations, which would have allowed safety margins to be determined. Summary data are shown in Table 5.

Table 5. Single-Dose Toxicity Studies Conducted With Oral Route in Rats

Study Type (Reference)	Species	Study Design	Results
Single-dose toxicity (Smyth et al. 1947)	Rat (strain not provided)	Males (n=10) administered 8.7 g/kg	No adverse effects reported in a 14-day observation period postdosing.
LD ₅₀ determination following oral gavage (CTFA 1975)	Rat (albino)	n=4/group (sex not specified) 6.8, 10.3, 15.4, 23.1 g/kg doses employed	LD ₅₀ >23.1 g/kg. Adverse effects- hypoactivity, diarrhea at high dose, no deaths or adverse macroscopic pathology.

Abbreviation: LD, lethal dose

Table 6. Summary of LD₅₀ and Dose Multiples of HEC Dose in ExEm Foam Based on Oral Administration

Species	LD₅₀	Dose Multiples to Calculated Human Glycerol Dose From ExEm Foam
Rat	8.7 g/kg	1210-fold
Rat	>23.1 g/kg	
Guinea pig	7.75 to 11.5 g/kg	271- to 403-fold

Abbreviation: LD, lethal dose

Repeated-dose toxicity on glycerol

Several repeated-dose toxicity studies were conducted ranging from 3 days to 2 years in rats, 3 days to 50 days duration in dogs, and 30 to 40 days in rabbits and guinea pigs. The data showed that glycerol is well tolerated based on the large multiples of the exposure level in comparison with the intended human dose. The summary data obtained from studies conducted using oral route are shown in Table 7.

Table 7. Repeated-Dose Toxicity Studies Conducted Using Oral Route

Study Type (Reference)	Species	Study Design	Results
GI tolerability (Staples et al. 1967)	Rat (Charles River)	Females (n=10) Doses: 0, 2.9, 5.7, 12 g/kg and 1.9, 4.0, 6.3, 8.7 g/kg at 20%, 40%, 60%, or 80%	Dose-related increase in incidence of hyperemia, hemorrhage, and GI erosion.
General toxicity (44 days) (Fischer et al. 1949)	Rat (strain not specified)	Males (n=20/group) Doses: 0, 1%, 5%, 10%, 20% in water (0.115, 0.575, 1.15, 2.30 g/kg)	No treatment-related effects reported.
General toxicity (6 months) (Anderson et al. 1950)	Rat (strain not indicated)	Females (n=5/group) Doses: 0, 5% natural and synthetic glycerin in drinking water (6.7 g/kg/day for 6 months dose groups)	Generally, well tolerated. Mild calcified masses reported in kidney tubules in 3/5 rats administered natural and synthetic glycerol.
General toxicity (Hine et al. 1953)	Rat (Long Evans)	n=22/sex (n=26/controls) Doses: 3.1 to 3.5, 6.1 to 7.0, and 12 to 14 g/kg/day	No treatment-related effects reported.
GI tolerability (Staples et al. 1967)	Dog (mongrel)	Males, females (n=1/groups except high doses n=2) Doses: 2.9, 5.7, 12 g/kg	At 2.9 g/kg, no treatment-related effect reported. Stomach mucosa severely hyperemic with hemorrhage at 5.7 g/kg and 12 g/kg doses.
General toxicity (30 to 40 days) (Ostwald 1962)	Rabbit (species not specified)	Males (n=4) Doses: ~1.8 to 2.2 g/kg/day	No treatment-related effects reported. However, 15 to 30% hemolysis in 2 animals.

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Study Type (Reference)	Species	Study Design	Results
General toxicity (30 to 40 days) (Ostwald 1962)	Guinea pig	Males (n=10) Doses: ~3.4 to 5.0 g/kg/day	Death reported at highest dose. Evidence of anemia found in surviving animals, though no apparent treatment-related macroscopic pathology reported.

Abbreviations: GI, gastrointestinal

Most available data on toxicity studies (above) were conducted before standardization of good laboratory practice and current ICH recommendations and utilized parameters such as LD₅₀ that are no longer recommended. However, in a few studies (below), the no-observed-adverse-effect-levels were determined, and safety margins of 259 and 49.3 were estimated based on administration of 100% and 20% glycerol concentrations to dogs and rats, respectively, in the 3-day repeated-dose toxicity studies (Staples et al. 1967). None of these studies were conducted using the intrauterine route, as proposed for ExEm Foam.

Table 8. Summary of Dose Multiples of Glycerol Dose in ExEm Foam Based on Oral Administration

Species (Duration)	Identified Safe Dose(s)	Dose Multiples to Calculated Human Glycerol Dose From ExEm Foam
Rat (3 days)	1.9 g/kg/day	49.3-fold
Rat (44 days)	2.3 g/kg/day	59.7-fold
Rat (6 months)	6.7 g/kg/day	174-fold
Rat (2 years)	12 to 14 g/kg/day	311- to 364-fold
Dog (3 days)	2.9 g/kg/day	259-fold
Dog (50 weeks)	9 g/kg/day	80-fold
Rabbits (30 to 40 days)	1.8 to 2.2 g/kg/day	Well tolerated but adverse effects reported in 2 animals
Dog (3 days)	3.4 to 5.0 g/kg/day	Deaths and adverse effects reported at employed 119- to 175-fold

Repeated-dose toxicity on HEC

HEC repeated-dose toxicity studies have been conducted in the rat after oral administration (up to 2-year duration) as shown in Table 9.

Table 9. HEC Repeated-Dose Toxicity Studies in Rats After Oral Administration

Study Type (Reference)	Species	Study Design	Results
General toxicity (90 days) (CTFA 1961)	Rat (strain not specified)	n=10/sex/dose Doses: 0.20 to 0.23, 1.0 to 1.1, and 5.0 to 5.6 g/kg/day	No treatment-related effects reported.
General toxicity (2 years) (Smyth et al. 1947)	Rat (Wistar)	n=16/sex/dose Doses: 0.09, 0.41, and 2.31 g/kg/day	Mortality (48%) reported claimed not treatment related.

Table 10. Summary of Dose Multiples of HEC Dose in ExEm Foam Based on Oral Administration

Species (Duration)	Identified Safe Dose(s)	Dose Multiples to Calculated Human HEC Dose From ExEm Foam
Rat (90 days)	5.0 to 5.6 g/kg/day	695-fold (males) and 779-fold (females)
Rat (2 years)	2.31 g/kg/day	321-fold (treatment unrelated mortality reported)

5.5.2. Genetic Toxicology

5.5.2.1. Other Genetic Toxicity Studies

Genotoxicity Data on Glycerol

Available in vitro and in vivo genotoxicity data demonstrate that glycerol is nongenotoxic.

In vitro reverse mutation assay in bacterial cells (Ames)

Several Ames tests conducted using *S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538 strains at 0.2, 0.4, 0.6, 0.8, and 1.0 mg/plate in the presence and absence of metabolic activation (Doolittle et al. 1988) demonstrated that glycerol is nonmutagenic. Studies conducted at higher doses that exceed the ICH S2(R1) recommendations (see Table 11) also demonstrated that glycerol is nonmutagenic in the presence and absence of metabolic activation (Clark et al. 1979; Stolzenberg and Hine 1979; Haworth et al. 1983; Ishidate et al. 1984).

Table 11. Doses and Results of Glycerol Ames Test Studies

Study (Reference)	Concentration/Dose	Mutagenic Results
Ames (<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538) (Doolittle et al. 1988)	0.2, 0.4, 0.6, 0.8, 1.0 mg/plate	Negative
Ames (<i>S. typhimurium</i> TA92, TA94, TA98, TA100, TA1535, TA1537) (Ishidate et al. 1984)	Maximum of 50 mg/plate	Negative
Ames (<i>S. typhimurium</i> TA100) (Stolzenberg and Hine 1979)	9.2 and 92 mg/plate (+/-S9)	Negative
Ames (<i>S. typhimurium</i> TA98, TA100, TA1537, TA1538) (Clark et al. 1979)	Up to 10 mg/plate (+/-S9)	Negative
Ames (<i>S. typhimurium</i> TA98, TA100, TA1535, TA1537) (Haworth et al. 1983)	10 mg/plate	Negative

In vitro assays in mammalian cells

Chromosomal aberration tests in cultured Chinese hamster ovary cells treated with up to 1 mg/mL glycerol concentrations in the presence and absence of metabolic activation were negative (Ishidate et al. 1984; Doolittle et al. 1988). There was no increase in sister chromatid exchange (SCE) or mutation frequency in other assays (including the hypoxanthine-guanine phosphoribosyltransferase mutagenicity assay) that used various Chinese hamster ovary cell lines with a similar glycerol concentration range in the presence or absence of metabolic activation (Doolittle et al. 1988). There was no increase in [³H]methyl thymidine incorporation

into DNA associated with unscheduled DNA synthesis assay testing glycerol concentrations from 0.1 to 1.0 mg/mL (Doolittle et al. 1988).

Table 12. Doses and Results of Glycerol Mammalian Cell Studies

Study (Reference)	Concentration/Dose	Results
SCE using CHO cell line WBL (Doolittle et al. 1988)	0.2, 0.4, 0.6, 0.8, 1.0 mg/mL (+/-S9)	No increase in SCE frequency in presence or absence of rat S9
In vitro chromosomal aberration test using CHO cell line WBL (Doolittle et al. 1988)	0.1, 0.2, 0.4, 0.6, 0.8, 1.0 mg/mL (+/-S9)	No increase in number of structural chromosomal aberrations in presence or absence of rat S9
In vitro chromosomal aberration test using CHF cell line CHL (Ishidate et al. 1984)	Up to 1.0 mg/mL (metabolic activation system not used)	No increase in number of structural chromosomal aberrations
HGPRT gene mutation assay using CHO (K1-BH4 cell line) (Doolittle et al. 1988)	0.1, 0.2, 0.4, 0.6, 0.8, 1.0 mg/mL (+/-S9)	No increase in mutation frequency in presence or absence of rat S9
Unscheduled DNA synthesis using rat hepatocytes (Doolittle et al. 1988)	0.1, 0.25, 0.5, 0.75, 1.0 mg/mL	No increase in [³ H]methyl thymidine incorporation into DNA associated with unscheduled DNA synthesis

Abbreviations: CHF, Chinese hamster fibroblast; CHO, Chinese hamster ovary; HGPRT, hypoxanthine-guanine phosphoribosyltransferase; SCE, sister chromatid exchange

In vivo assays in mammalian cells

No statistically significant increase of chromosomal structural aberrations (2.2%) and gaps (1.6%) versus concurrent controls was reported in an in vivo chromosomal aberration study in rats given a single IP dose of 1 g/kg glycerol (Bariliak and Kozachuk 1985). Data from a dominant lethal gene assay conducted in untreated females mated to male rats given single doses of 0.01, 0.1, and 1.0 g/kg glycerol demonstrated no statistically significant decreases in implantation sites, percentage of fetal loss, and percentage of live fetuses.

Table 13. Doses and Results of Glycerol In Vivo Mammal Studies

Study (Reference)	Concentration/Dose	Results
In vivo chromosomal aberration in rats (Bariliak and Kozachuk 1985)	10 male rats dosed at 1 g/kg glycerol; after 2 days, the rats were sacrificed and cytogenic analysis performed in 50 metaphases	Nonstatistically significant 2.2% increase in structural aberrations and 1.6% gaps vs. concurrent controls
Dominant lethal assay (Bariliak and Kozachuk 1985)	Male rats given 0.01, 0.1, 1 g/kg glycerol mated to untreated females (n=10 to 11/dose group)	Nonstatistically significant decrease in implantation sites, percentage fetal loss, and percentage live fetuses reduced at high dose; no fetal anomalies seen at high dose; no significant postimplantation deaths

Genotoxicity Data on HEC

There is lack of genotoxicity studies for HEC in the literature. However, there is information on several studies on the genotoxicity of structurally similar cellulose analogs (e.g., methyl cellulose [MC]), carboxymethyl cellulose, ethyl cellulose [EC]). These analogs tested negative in in vitro bacterial reverse mutation assays, several in vitro mammalian systems including host-mediated assay, chromosomal aberration study, mouse lymphoma L5178Y TK+/- assay, and

several in vivo mammalian systems (e.g., micronucleus test, host-mediated assay, dominant lethal assays, and chromosomal aberration tests). Thus, this class of compound is not genotoxic.

In vitro nonmammalian assays

Ames test conducted on MC at up to 50 µg/plate with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, evaluated in the presence and absence of metabolic activation was negative (Blevins and Taylor 1982). Similarly, carboxymethyl cellulose was negative in *S. typhimurium* strains TA98 and TA100 in the presence and absence of metabolic activation, and also negative in *E. Coli* WP-2 in the absence of metabolic activation (Sugimura 1976). In addition, EC tested at several concentrations up to 5 mg/plate demonstrated no mutagenic activity in the bacterial reverse mutation test in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, *E. Coli* strain WP2uvrA/PkM101 (CM891) with and without metabolic activation (DeMerlis et al. 2005).

In vitro mammalian assays

MC at a concentration of 100 mg/mL was evaluated for mutagenicity in an in vitro host-mediated and chromosomal aberration study (Litton Bionetics 1974; Bergfeld et al. 2009) and showed no increase in mutant or recombinant frequency using *S. typhimurium* TA1530 and G-46 strains. In an in vitro chromosomal aberration study involving human tissue culture cells exposed to concentrations up to 800 µg/mL, no significant structural aberrations were reported in anaphase chromosomes (Litton Bionetics 1974). EC was tested for mutagenic potential in the mouse lymphoma assay (L5178Y TK+/- cells) in the presence and absence of S9 metabolic activation (DeMerlis et al. 2005) and no significant increase in mutation frequency was reported.

In vivo mammalian assays

In a host-mediated study involving mice administered 5 g/kg, MC demonstrated no significant increase in mutant or recombinant frequencies using *Saccharomyces* D3 (Litton Bionetics 1974; Bergfeld et al. 2009). Data obtained from an in vivo chromosomal aberration study involving rats orally administered single doses of MC orally up to 5 g/kg showed no significant structural aberrations in bone marrow metaphase chromosomes (Litton Bionetics 1974; Bergfeld et al. 2009). MC also demonstrates nonmutagenic effect in a dominant lethal assay in male rats dosed up to 5 g/kg and mated to untreated females (Litton Bionetics 1974; Bergfeld et al. 2009). In an in vivo micronucleus test, EC (tested as the excipient Surelease, which contained 25% EC) failed to cause any chromosome damage or bone marrow cell toxicity when orally administered by gavage to mice at doses of 0.5, 1.0, and 2.0 g/kg (DeMerlis et al. 2005).

5.5.3. Carcinogenicity

No carcinogenicity studies have been conducted with glycerol. Literature data from a 2-year study in Long Evans rats given up to 20% glycerol in the diet showed no treatment-related increase in tumor incidence (Hine et al. 1953). A tumor-promoting activity was reported in male ddY mice administered 5% glycerol in drinking water following a single subcutaneous dose of 10

mg/kg 4-nitroquinolone 1-oxide (4NQO) at durations ranging from 4 weeks to 25 weeks (Inayama 1986; Inayama et al. 1986; Nagahara 1987). However, no tumors were reported with glycerol itself in studies involving 25-week dosing period using this model. Similarly, no carcinogenicity studies have been reported with HEC.

No treatment-related increase in tumors was found in a 2-year HEC general toxicity repeated-dose study in rats (Smyth et al. 1947). Furthermore, no treatment-related tumor effects were reported following longer-term administration studies involving three structurally related, modified cellulose analogs: methyl ethyl cellulose, carboxymethyl cellulose (McElligott and Hurst 1968), and hydroxypropyl methyl cellulose (HPMC) (McCollister et al. 1973). These data suggest a lack of carcinogenicity in this class of compounds. Thus, available literature evidence shows that glycerol is not carcinogenic though it could demonstrate minimal carcinogenicity potential when administered with other compounds. No evidence of any carcinogenicity has been attributed to HEC and its analogs in studies involving longer-term administration of 2 years duration.

5.5.4. Reproductive and Developmental Toxicology

Glycerol

There are available data on studies conducted to evaluate the effects of glycerol on fertility, embryo-fetal development, and pre/postnatal development in mice, rats, and rabbits. The data suggest that glycerol did not have any adverse effect on embryo-fetal development or pre/postnatal development. Table 14 shows that there was no suppression of spermatogenesis in males after oral administration of glycerol while suppression of spermatogenesis was reported after intratesticular injection. However, intratesticular route is not relevant to the intended intrauterine exposure for ExEm Foam. There also were no reported adverse treatment-related effects on fertility in a two-generation rat study.

Table 14. Glycerol Reproductive and Developmental Toxicology Studies

Study Type (Reference)	Species	Study Design	Results
Male fertility (Wiebe et al. 1989)	Squirrel monkey	Single intratesticular administration of saline or 200 to 300 μ L of up to 49% glycerol performed in males (n=10/group); animals evaluated for 22 months postinjection.	There was treatment-related suppression of spermatogenesis; azoospermia in most animals with little or no change in either serum gonadotropins or testicular steroids.
Embryo-fetal toxicity (Food and Drug Research Laboratories 1974a)	CD-1 mouse	Females (n=19 to 23 successfully mated per group) orally dosed 0, 12.8, 59.4, 276, and 1,280 mg/kg on GD6-15; Cesarean-section on GD17; assessment of implantation/resorption sites, live/dead fetuses.	No treatment-related effects on maternal or fetal survival. Based on glycerol exposure in ExEm Foam, 1,280 mg/kg dose employed gave a safety margin of 17 (BSA). Visceral and skeletal anomalies did not differ from controls at any dose level.

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Study Type (Reference)	Species	Study Design	Results
Embryo-fetal toxicity (Food and Drug Research Laboratories 1974c)	Wistar rat	Females (n=21 to 24 successfully mated per group) orally dosed 0, 13.1, 60.8, 282, and 1,310 mg/kg on GD6-15; Caesarean-section on GD20; assessment of implantation/resorption sites, live/dead fetuses.	No treatment-related effects on maternal or fetal survival. Based on glycerol exposure in ExEm Foam, 1,310 mg/kg dose employed gave a safety margin of 34 (BSA).
Embryo-fetal toxicity (Food and Drug Research Laboratories 1974b)	Dutch-Belted rabbit	Females artificially inseminated (n=11 to 14 per group) orally dosed 0, 11.8, 54.8, 254.5, and 1,180 mg/kg on GD6-18; Caesarean-section on GD29; assessment of <i>corpora lutea</i> , implantation/resorption sites, live/dead fetuses.	No treatment-related effects on maternal or fetal survival. Based on glycerol exposure in ExEm Foam, 1,180 mg/kg dose employed gave a safety margin of 61 (BSA).
Two-generation study (Wegener 1953)	Rat (strain not provided)	Rats (n=10/sex) orally dosed 2 g/kg/day 8 weeks before mating; female dosing continued to weaning and F1 (n=10/sex) continued to mating.	No effects on reproductive efficiency of F0, growth, fertility, and reproductive performance of F1 generation; no treatment-related effects on histopathology in tissues of F1 and F2 generations; no treatment-related effects on onset of estrus cycle and weight and microscopy of endocrine organs for both F1 and F2. Based on glycerol exposure in ExEm Foam, 2 g/kg dose employed gave a safety margin of 52 (BSA).

Abbreviations: BSA, body surface area; GD, gestation day

HEC

Available data on absorption of HEC suggest very low oral/intrauterine systemic absorption attributable to its poor permeability across epithelial membranes. Thus, it is unlikely HEC will pose any serious reproductive toxicity risk. The Applicant found no stand-alone fertility studies conducted on HEC in the literature. No adverse effects on reproductive organ weights and microscopic pathology were reported during the repeated-dose toxicity studies on HEC as reviewed above. This suggests lack of any HEC treatment effects on fertility. Data obtained on orally administered structurally related, modified cellulose compounds showed no reproductive or developmental toxicity potential.

Table 15. HEC Reproductive and Developmental Toxicology Studies

Study Type (Reference)	Species	Study Design	Results
Fertility/embryo-fetal toxicity (Hoshi et al. 1985)	Sprague Dawley rat	Males (n=25/group) orally dosed with 0, 0.625, 1.25, and 2.5 g/kg HPMC from 60 days before pairing until the completion of mating, while females (n=22 to 25/group) received same HPMC doses from 14 days prior to mating up to GD7. Pregnant females sacrificed on GD21 and all fetuses examined for abnormalities.	No abnormality in mating or fertility in HPMC-treated rats. No HPMC-treatment-related external, internal, or skeletal malformations in the fetuses. No adverse effects on mating, fertilization, implantation, or early embryonic development reported.
Embryo-fetal development (Guttner et al. 1981)	Mouse	Mice (n=11 to 13/group) given 0, 1%, or 4% HEC in 10 mL/kg (HEC doses of 0, 100, and 400 mg/kg) by IP injection on GD3-7 or GD8-12. Cesarean-section on GD19.	Increased fetal resorption at both doses on GD3-7; 18.7% and 43.8% resorptions for 100 and 400 mg/kg doses, respectively, as against 8.3% and 5.1% for saline and sesame oil controls, respectively. Increased weights of surviving fetuses in 400 mg/kg group on GD3-7; this same group had 10.2% and 10.5% gross visceral and skeletal deformities, respectively, compared to 1.98% and 1.96% for saline control; 1.39% and 8.57% for sesame oil control; and 4.65% and 9.76% for 100 mg/kg HEC group.
Embryo-fetal development (Kitagawa et al. 1978b)	Wistar rat	Pregnant Wistar rats (n=21 to 24/dose group for Cesarean-section group and n=12 to 15/dose group for the spontaneous-delivery group) given oral HPC doses of 0, 0.2, 1.0, and 5.0 g/kg on GD7-17. Cesarean-section on GD21; assessment of <i>corpora lutea</i> , implantations, live/dead fetuses, and resorbed embryos. The fetuses' evaluation was done and pups in spontaneous delivery groups on PND28 and examined for behavioral/neurological effects on PND35 while the F1 generation was monitored through sexual maturity and mating.	No treatment-related effects on maternal toxicity, fetal toxicity, teratogenicity, development of the skeleton, and reproductive ability of the F1 generation reported.
Embryo-fetal development (Kitagawa et al. 1978a)	Himalayan Rabbits	Rabbits (n=11 to 12/dose group) given oral doses HPC at 0, 0.2, 1.0, and 5.0 g/kg on GD6-18 doses. Cesarean-section on GD29; assessment of <i>corpora lutea</i> , implantations, live/dead fetuses, and resorbed embryos. Viable fetuses evaluated for body weight, and visceral and skeletal anomalies.	No treatment-related effects on maternal toxicity, embryo or fetal toxicity, or visceral or skeletal malformations of the fetuses reported.

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Study Type (Reference)	Species	Study Design	Results
Embryo-fetal development (Cappon et al. 2003)	New Zealand white rabbits	Groups of 18 to 20 rabbits given oral doses 0, 0.05, 0.15, 0.625, or 2.5 g/kg HPMC (acetate/succinate salt) from GD7-19. Cesarean-section on GD29; assessment of <i>corpora lutea</i> , implantation sites, pre/postimplantation loss, early/late resorptions, viable fetuses, fetal weights, and external, visceral, and skeletal findings.	No treatment-related effects reported on any of these developmental toxicity endpoints.
Prenatal and postnatal development (Hoshi et al. 1985)	Sprague Dawley rat	Pregnant rats (n=24 to 26/dose group) given HPMC oral doses at 0, 0.625, 1.25 and 2.5 g/kg doses from GD17 to PND21. At birth, the pup was examined for body weight and external abnormalities. After weaning, groups of 36 to 43 males and females were sacrificed, and tissues and organs examined macroscopically and histologically. Rat group (10/sex) was examined at 8 weeks of age for behavioral and motor endpoints. Another group of F1 males and females (n=25/sex) was allowed to develop to sexual maturity and mated; development of F2 generation was observed until weaning.	No treatment-related findings in postnatal growth and differentiation, behavior, and reproductive ability of F1 generation reported. Elevated liver weights in F1 generation at weaning statistically significant for males but not for females. Liver effect not considered treatment related.

Abbreviations: GD, gestation day; HEC, hydroxyethyl cellulose; HPMC, hydroxypropyl methyl cellulose; PND, postnatal day

5.5.5. Other Toxicology Studies

Local Tolerance

There is a lack of literature data on local tolerance studies for glycerol and HEC. However, in a published paper, it was found that 2.8% HEC in water is noncytotoxic to cervical HeLa cells in a 24-hr incubation at 37°C in 5% CO₂ (Cunha et al. 2014). The Applicant provided a summary of FDA 510(k) clearance for marketed vaginal moisturizer/personal lubricant products in which glycerol and HEC are ingredients. In all the products, vaginal irritation studies were conducted in rabbits. The rabbit studies involved intravaginal application of the product once daily for approximately 5 days and following sacrificing, the entire vagina excised, examined, and scored for discharge, edema, and erythema. Histological examinations of the tissue were performed and found that all the products containing glycerol and/or HEC were reported to be nonirritating (data for Intimol™ were not specified). However, the Applicant did not provide the concentrations or amounts of glycerol and HEC components in these products. Therefore, it was not possible to compare to the glycerol and HEC exposure expected from ExEm Foam administration.

Dermal Irritation

Glycerol

Dermal irritation of glycerol has been evaluated in a number of studies conducted in rabbits and guinea pigs.

In a rabbit dermal irritation study conducted with glycerol (Weil and Scala 1971), glycerol was found to be nonirritating. Glycerol was applied (amounts not specified) to a 1"x1" shaved area on the backs of the animals, which was then occluded with a patch. Another similar study involving natural or synthetic glycerol applied to the shaved backs of female albino rabbits (Hine et al. 1953) also found no evidence of irritation. A modified Draize test was employed in another study in rabbits where 0.5 mL of a glycerol/water mixture was applied to the backs of female New Zealand rabbits, with skin evaluated 24 and 72 hours after application (Clark et al. 1979). The product was also found to be nonirritating. In guinea pig study, intradermal injection of 0.1 mL glycerol was administered to the abdominal region of guinea pig. Irritation was scored after 4 hours, 24 hours, and 1 week after injection (Latven and Molitor 1939). Glycerol was found to be minimally irritating (graded 1 on a scale of 0 to 4).

HEC

In a repeat-insult patch test (Elder 1986) HEC at 5% and 100% concentrations was found to be nonirritating. Skin irritation tests in male albino rabbits were also conducted on HEC (2%), and modified cellulose analogs structurally related to HEC (HPC, 2%; and, MC, 2%) (Guillot et al. 1981). Each solution (0.5 mL) was applied on two patch areas: the right (scarified) and left (intact) flanks of male albino rabbits (6 per group). Patches exposed to HEC, HPC, and MC were occluded for 23 hours, removed, and readings (scale of 0 to 8) taken 1 hour and 48 hours later.

All patches were nonirritant and the primary irritation indices for HEC, HPC, and MC ranged from 0.04 to 0.21 (max =8).

Sensitization

Glycerol

The sensitization potential of glycerol was evaluated following intradermal injection of 0.1 mL of 0.1% glycerol solution (natural or synthetic) in male guinea pigs every other day for a total of 10 injections. This was followed by injection of 0.05 mL of the glycerol solution adjacent to a sensitizing area following a 2-week treatment-free period (Hine et al. 1953). Glycerol demonstrated no sensitization potential under the conditions of this test.

HEC

There were no reports on evaluation of the sensitization potential of HEC found in the literature. However, there is literature evidence that the sensitization potential of HPMC has been evaluated. The Magnusson-Kligman guinea pig maximization test was conducted to evaluate sensitization of HPMC (CTFA 1980). The test involved administration of three intradermal injections into the shaven shoulder of 0.1 mL of 50% complete Freund's adjuvant in saline, 0.1 mL of 1% HPMC in saline, and 0.1 mL of 1% HPMC in 50% complete Freund's adjuvant in saline. At the completion of the testing, sensitization reactions were scored at 24 and 48 hours after patch removal and indicated no sensitization potential. Furthermore, HPMC was evaluated for sensitization in Hartley albino guinea pigs (n=10 males per group) using a modified Maguire method (CTFA 1978). Similarly, no responses were reported in this testing with HPMC.

Biocompatibility Studies

The Applicant conducted the following compatibility studies on clear gel:

- Genotoxicity (ISO-10993-3)
- Cytotoxicity (ISO-10993-5)
- Skin irritation (ISO-10993-10)
- Sensitization (ISO-10993-10)
- Acute systemic toxicity (ISO-10993-11)

Genotoxicity (ISO-10993-3)

The Applicant conducted Ames and mouse lymphoma assays to evaluate the genotoxicity of the clear gel. The Ames test was conducted using *S. typhimurium* strains TA97, TA98, TA100, TA102, and TA 1535, with and without metabolic activation (S9), that were exposed to (b) (4) g/mL clear gel extracted with (b) (4). There was no positive mutagenic response observed in any of the tester strains evaluated. The mouse lymphoma assay was conducted by incubating concentrations of the gel (0.1 g/mL, 0.2 g/mL, 0.5 g/mL, and 1.0 g/mL) with cultured mouse lymphoma cells (L5178Y TK+/- 3.7.2C) for 3 hours at 37°C in 5% CO₂ in the presence/absence of S9 fraction for 3 hours. The cells were subcultured to

determine cytotoxicity (relative cloning efficiency). The treated cultures were maintained for 14 days and the mutation frequency determined. There was no treatment-related effect on cloning efficiency or mutation frequency in the presence or absence of metabolic activation (S9), suggesting that extracts of clear gel were not genotoxic.

Cytotoxicity (ISO-10993-5)

L-929 cells were cultured to form a subconfluent monolayer. Serial dilutions (100%, 66%, 44%, 30%, 20%) of clear gel extract were exposed to the L-929 cells for 24 hours in a humidified incubator in 5% CO₂ at 37°C. A qualitative scoring by microscopy performed revealed no cellular damage. No inhibition of cell growth at any of the clear gel extract dilutions in comparison with the negative control (extract of silicone rubber) was reported. This data suggest lack of any cytotoxic effect under conditions of this assay.

Skin irritation (ISO-10993-10)

The skin irritation potential of polar and nonpolar extracts of clear gel was evaluated using male and female albino rabbits. The extracts (0.5 mL) were exposed for 4 hours to shaved areas of the rabbit's back (n=3 per group) using nonocclusive patches. The skin reaction was graded at 1, 24, and 48 hours from the end of the 4-hour challenge exposure and the primary irritation index was determined. Results showed that the primary irritation indices for both extracts were 0 suggesting that clear gel had no skin irritation potential based on this assay.

Sensitization (ISO-10993-10)

The sensitization potential of polar and nonpolar clear gel extracts was evaluated using guinea pigs (Dunkin Hartley strain). The exposed the polar and nonpolar extracts (0.5 mL) to shaved areas of the guinea pig's flank (n=10 per group) for 6 hours using nonocclusive patches on three occasions separated by 7 days (induction period). Fifteen days following the last application of the induction phase, 0.5 mL of the polar and nonpolar extracts were applied in a similar fashion for 6 hours (challenge phase). The skin reaction was graded at 2, 24, and 48 hours from the end of the 6-hour challenge exposure. Results demonstrate that both extracts were Grade 1, suggesting that clear gel was not a sensitizing agent in this assay.

Acute systemic toxicity (ISO-10993-11)

The acute toxicity of polar and nonpolar clear gel extracts was evaluated in mice (n=5 per group) administered 50 mL/kg via the tail vein and clinically observed at 4, 24, 48, and 72 hours postdosing. Results showed no treatment-related adverse effects on clinical signs or body weights suggesting that no acute toxicity effect is reported to the clear gel extracts at the employed dose.

Nonclinical gaps and resolution: The Applicant assumed studies conducted using oral route as an acceptable surrogate route to characterize systemic toxicity based on the putative mechanism of absorption across the GI and uterine mucosa for both compounds. This assumption would not work for intrauterine and intravaginal routes though mucous membranes are the moist layer of semipermeable tissue lining the mouth, nose, eyes, uterus and anus.

These tissues do not have the protective layer found on the surface of the outer skin; mucous membranes can be damaged, irritated and penetrated by synthetic chemicals much more easily. However, rectal and vaginal absorption is many times greater than oral absorption (Thomas 2007). Uterine absorption is equally expected to be much greater than oral absorption. This explains why despite the use of glycerol and HEC in many medications such as nose and eye drops and cosmetics products, the oral route might not be an acceptable surrogate for intrauterine administration of ExEm Foam.

According to the Applicant, “[Applicant] did not conduct or identify nonclinical safety studies conducted by intrauterine administration for glycerol or HEC.” Thus, the Applicant did not evaluate the potential for ExEm Foam to cause inflammatory reactions resulting in scarring or adhesions in the uterus/tubes and around ovary. A lack of nonclinical safety data on intrauterine administration of ExEm Foam therefore creates a gap in the nonclinical testing of this product.

The gap in the nonclinical testing is addressed by review of the following evidence to evaluate the safety of intrauterine exposure of ExEm Foam:

1. Applicant’s literature search on possible ExEm Foam effects, such as causing embolization, inflammations, or scarring/adhesion following intrauterine/intravaginal use
2. Search on FDA database for products containing glycerol or HEC for safety comparison to ExEm Foam
3. Search on available CDRH data on clear gel and other products containing glycerol and HEC
4. Relevant CMC data on osmolality and pH of ExEm Foam

Applicant’s literature search on possible ExEm Foam effects, such as causing embolization, inflammations, scarring/adhesion following intrauterine use

Gaps in preclinical testing were discussed at the pre-NDA meeting held on August 15, 2017. The Division of Medical Imaging Products agreed with Applicant’s plan to search the literature for (1) procedure-related events such as embolization or intravasation, infection, and sterility (infertility), and (2) potential for ExEm Foam to cause inflammatory reactions resulting in scarring or adhesions in the uterus, tubes, or around the ovaries. The Applicant included the literature search in the clinical section of the submission (see Section 8.2.5) on FDA database for products containing glycerol or HEC for safety comparison to ExEm Foam.

Data on composition of products containing glycerol and HEC were sought in the FDA databases, which include (1) Inactive Ingredient Search of Approved Drug Products (FDA 2019a) and (2) Mercado (FDA 2019b) to determine how the concentrations of the glycerol and HEC components compare with ExEm Foam. An additional search was conducted on commonly used intrauterine products to compare their glycerol and HEC composition with that of ExEm Foam. Data obtained on glycerol (CAS 56815) as an inactive ingredient from the Inactive Ingredient Search for Approved Drug Products gave 20 total preparations, mostly parenteral, nasal, oral, and epidural preparations, and no intrauterine preparations were found. Lack of required information on intrauterine route of administration renders the data search not so helpful.

Glycerin is the commercially available purer form of glycerol; glycerin contains 95% glycerol. The search on glycerin was then conducted and several gel products containing varying compositions of glycerin administered via uterine routes were found during the search. The search gave 122 pharmaceutical formulations, which were mostly oral, parenteral, ophthalmic, topical, vaginal, and rectal preparations with no uterine preparations. Out of these formulations, the closest to the desired uterine preparations found were the five glycerin preparations administered via vaginal route.

In the formulations found, glycerin was employed at the following concentrations in the following intravaginally formulated products: cream, emulsion, sustained release (17% weight/weight), emulsion cream (5% weight/weight), gel (concentration not provided), insert (22 mg), and suppository (227.9 mg). Comparative safety analysis of these preparations and the glycerol component of ExEm Foam containing (b) (4) % weight/weight suggests that ExEm Foam is relatively safer following intravaginal administration than all the above-listed formulations based on a shorter duration of exposure to ExEm Foam.

The search conducted on HEC gave 36 preparations, which were mostly oral, ophthalmic with only one nasal preparation; none was an intrauterine preparation. The concentration of the oral preparation was not provided while concentrations in ophthalmic preparations was up to 1.6%. Based on the relatively small surface area of the eye exposed to the preparation in comparison to the surface area of the intrauterine tissue, no safety concern was envisaged following the exposure of 1.585% HEC content of ExEm Foam when administered via intrauterine route.

A search conducted on “glycerol and uterine” using Mercado (FDA 2019b) gave 582 related drug applications. In all applications found, glycerol was compounded with other compounds either as active or inactive ingredients. The search on “glycerin and uterine” gave 1,306 related drug applications. Similarly, in all the preparations, glycerin was either an active or inactive ingredient, and the intrauterine route only was employed in less than 10 drug applications, mostly in the form of intrauterine devices. Concentrations of glycerol in the intrauterine devices were higher than the glycerol content in ExEm Foam. Most applications were indicated for topical applications to tissues with a smaller surface area, such as nasal or eye topical applications. Compared to these applications, ExEm Foam is intended for a larger surface area and a more limited diagnostic use. Therefore, the glycerol in ExEm Foam is relatively safer than in many applications involving intrauterine administrations found in the search.

Results of a search conducted on “hydroxyethyl cellulose and uterine” using Mercado (FDA 2019b) gave 319 related applications. In most drug applications found, HEC was mostly an inactive ingredient, used at much higher concentrations than in ExEm Foam.

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ExEm Foam (air polymer-type A intrauterine foam)

Based on the searches conducted on the intrauterine preparations of glycerol and HEC—major components of ExEm Foam—in the FDA’s Inactive Ingredient Search for Approved Drug Products and Mercado platforms, and the safety assessment performed on the preparations in comparison to ExEm Foam, there are no safety concerns with the intrauterine administration on ExEm Foam. The data obtained from the above databases will suffice for nonclinical safety studies on intrauterine administration for glycerol or HEC.

Furthermore, glycerol and HEC are components of several over-the-counter products commonly administered intravaginally. For example, AVVA (Benzalkonium Chloride) Gel™ is formulated with allantoin, carbomer, glycerin, HEC, sodium hydroxide, and water. The inclusion of glycerin and HEC, components of ExEm Foam in AVVA also supports the safety of ExEm Foam. However, concentrations of all inactive agents, including glycerin and HEC, were not included, and therefore no inference could be drawn in terms of comparison between safety of these ingredients in AVVA and components of ExEm Foam.

Search on available CDRH data on clear gel and other products containing glycerol and HEC

Data on the clear gel in the kit is sufficient since the gel is diluted with water in a ratio of 1:1 to produce ExEm Foam. Therefore, a search on CDRH documentation on clear gel was conducted to obtain safety information on potential inflammatory reactions, such as scarring or adhesions in uterus, tubes, or the ovaries following intrauterine exposure of clear gel. (b) (4)

(b) (4)

The biocompatibility data provided safety information of the product when administered intraperitoneally, intravenously, and topically for various safety and toxicity studies. None of the studies involve intrauterine administration of the product. Even the closed-patch sensitization test conducted in guinea pig skin cannot be extrapolated for intrauterine exposure. Likewise, the lack of skin irritation reported in the rabbit does not establish lack of any potential inflammatory reactions such as scarring or adhesions in uterus, tubes or the ovaries following intrauterine exposure. However, intravaginal irritation test was conducted on I-D Glide lubricant, another product containing glycerin regulated by CDRH. I-D Glide is produced by Westridge Laboratories, Inc. The ingredients of the product include purified water (b) (4), glycerin (b) (4), propylene glycol (b) (4), cellulose polymer (b) (4), PEG 90m (b) (4), and other additives including EDTA (b) (4). The intravaginal irritation test conducted on six healthy adult New Zealand white albino rabbits (2 to 3 kg) was negative. These data could serve as a surrogate for intravaginal irritation test in ExEm Foam. The study indicates that at a relatively high concentration of glycerin/glycerol ((b) (4) %) in the I-D Glide there is no intravaginal irritation in the treated rabbits. The study concluded that no irritation was reported at such a relatively high concentration of (b) (4) % glycerin and (b) (4) % glycerol.

Information obtained from available products containing glycerol/glycerin discussed above further justifies the safety of much lower concentrations of the components of ExEm Foam. The information is not required or used to establish safety of intrauterine exposure of ExEm Foam.

Relevant CMC data on osmolality and pH of ExEm Foam

The osmolality and pH of ExEm Foam were compared with those of marketed intravaginal products. The pH value of ExEm Foam should align with the physiological pH of the uterine lining, fallopian tube lining, and peritoneal cavity. WHO recommends for these lubricants a pH of 4.5 and an osmolality below 1,200 mOsm/kg. The values for ExEm Foam are 462 mOsm/kg and pH of 6.0 to 7.5. The pH of the clear gel aligns with the physiologic pH of the uterus, suggesting no safety issues with the exposed uterus, ovary, and fallopian tubes body regions. There is no safety concern over the osmolality of ExEm Foam, which is only 462 mOsm/kg compared to 2,000 to 6,000 mOsm/kg for most lubricants applied intravaginally.

The safety assessment of ExEm Foam relied on:

1. Search on FDA database for products containing glycerol or HEC for safety signals
2. Applicant's literature search on possible ExEm Foam adverse effects, such as embolization, inflammation, scarring, and adhesion following intrauterine use
3. Search on available CDRH data on clear gel and other products containing glycerol and HEC
4. Formulation, osmolality, and pH of ExEm Foam

The totality of the data and other information suggests that ExEm Foam is safe for intrauterine administration from a nonclinical perspective.

6 Clinical Pharmacology

6.1. Executive Summary

No clinical pharmacology studies have been conducted by the Applicant.

ExEm Foam is composed of 5 mL clear gel, containing glycerol and HEC. When the gel is mixed with an equal amount of sterile purified water, the viscosity of the gel is decreased, and air bubbles are introduced into the gel, creating an echogenic contrast agent. The product has no pharmacological activity; it is a foam that can flow through patent fallopian tubes, which is visible on ultrasound.

Assuming that a full 10 mL of ExEm Foam is administered and all the glycerol is absorbed, the normal fasting endogenous glycerol plasma levels would not be affected. According to the Applicant, no literature data are found on absorption of HEC. However, due to the apparent poor permeability of HEC across GI epithelial mucosa, HEC would be expected to exhibit very low permeability across the epithelial mucosa of the uterus, and, consequently, produce negligible HEC systemic exposure (see also Sections 0 and 6.3 for details of ADME). Therefore, there is likely a very low exposure to HEC from the intrauterine application of ExEm Foam.

6.2. Summary of Clinical Pharmacology Assessment

Several studies demonstrate the diagnostic efficacy of ExEm Foam in assessing tubal patency. One of the large studies, which included assessment of more than 250 fallopian tubes, assessed multiple ultrasound techniques used in conjunction with ExEm Foam and established tubal patency status using a recognized gold standard. See Section 8 for review of clinical studies.

6.2.1. Pharmacology and Clinical PK

No PK studies were conducted by the Applicant. No clinically significant drug interactions are expected or known.

6.2.2. General Dosing and Therapeutic Individualization

ExEm Foam is prepared using two syringes, one containing 5 mL of clear gel, and the other containing 5 mL of sterile purified water, in two 11-mL piston syringes. The syringes are connected with a coupling device. To prepare ExEm Foam, the syringes are depressed at least 10 times to dilute the gel and create small bubbles. As the gel and water are pushed through small openings in the syringes, turbulence causes local pressure drops, resulting in air dissolving in the gel and yielding the air-containing ExEm Foam that is stable for several minutes. The resulting foam is then infused into the uterine cavity via a standard catheter.

A total of 2 to 3 mL of ExEm Foam is administered for ultrasonography. Infusion of 2 to 3 mL of foam can be repeated, as needed, to achieve visualization of the fallopian tubes. The dosing is acceptable based on the clinical experience.

Therapeutic Individualization

There is no therapeutic individualization of ExEm Foam. The product is not intended for use in pediatric patients. In addition, ExEm Foam has not been studied in geriatric patients. The product is not for use in postmenopausal women.

The use of ExEm Foam is contraindicated in pregnant patients. A pregnancy test should be performed before the tubal patency test is performed.

6.3. Comprehensive Clinical Pharmacology Review

No clinical pharmacology studies were performed by the Applicant. The Applicant used literature data to describe the absorption, distribution, metabolism, and excretion (ADME) of ExEm Foam. The clear gel contains glycerol 85% and HEC in sterile purified water (see Table 16).

Table 16. Quantitative Composition of Clear Gel

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

Abbreviations: EP, European Pharmacopoeia; NF, National Formulary; USP, United States Pharmacopeia; w/w, weight/weight

ExEm Foam is prepared immediately prior to use in the health care setting, when 5 mL of gel is mixed with an equal amount of sterile purified water through the adapter device that connects the two syringes, to yield approximately 10 mL of foam (see Table 17).

Table 17. 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) (4)

Abbreviation: HEC, hydroxyethyl cellulose

6.4. General Pharmacology and Pharmacokinetic Characteristics

ExEm Foam has no known direct or indirect pharmacological activity.

Glycerol PK Characteristics

See Section 5.4 for discussion of animal studies on glycerol ADME.

Glycerol is rapidly and completely absorbed after oral administration, with an estimated T_{max} of approximately 1 to 2 hours. In rats, intestinal absorption of glycerol is saturable and mediated by a sodium-dependent, carrier-mediated transporter. A similar mechanism appears operable in humans, as a sodium-dependent transporter also enhanced glycerol uptake in a human colon cancer cell line.

As the potential systemic absorption of glycerol is not predicted to impact normal endogenous fasting plasma levels of glycerol after performing an ExEm Foam ultrasound procedure, the endogenous glycerol metabolic equilibrium associated with glycerol is not expected to be altered, and procedure-related drug interactions would not be expected.

HEC PK Characteristics

See Section 5.4 for discussion of animal studies on HEC ADME.

Based on this apparent poor permeability across GI epithelial mucosa, it is expected HEC would exhibit negligible permeability across epithelial mucosae of the fallopian tube and uterus. No reports of tissue distribution, metabolism, and excretion of HEC were located in the literature.

The PK of HEC was assumed to be represented by the PK of HPC, a structurally similar, modified cellulose polymer analog of HEC. See Section 5.4 for discussion of animal studies on HPC ADME.

6.4.1. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The ultrasound signal is created by the ExEm Foam bubbles. See Section 8 for review of clinical studies.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is appropriate for the general patient population for which the indication is being sought. See Section 6.2.2 of this review for details on dosing.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. No intrinsic factors were identified to affect the performance of the product.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The product will be administered via an intrauterine catheter and therefore no effect of food is expected.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 18. Clinical Trials Relevant to This NDA

Trial Design (Reference)	Study Endpoints	Patients Enrolled	Study Population	Centers/ Countries
<i>Controlled Studies to Support Efficacy and Safety</i>				
2D-HyFoSy or 3D-HyFoSy vs. laparoscopy and dye (patients randomly assigned to 2D or 3D imaging with HyFoSy) (Riganelli et al. 2018)	Sensitivity and specificity of HyFoSy	50; 25 per group	History of infertility	1 site
2D-HyCoSy, 2D/3D-HyFoSy, and 2D/3D-HDF-HyFoSy vs. laparoscopy and dye (patients received all procedures) (Ludwin et al. 2017a)	Accuracy of HyFoSy and HyCoSy	132	History of infertility	3 sites (same investigators), 1 country
HyFoSy vs. laparoscopy and dye (van Schoubroeck et al. 2013)	Agreement of HyFoSy to laparoscopy and dye	20	History of subfertility	1 site
HyFoSy or HyCoSy vs. laparoscopy and dye (patients randomly assigned to either HyFoSy or HyCoSy) (Piccioni et al. 2017)	Sensitivity and specificity of HyFoSy and HyCoSy	18 in HyFoSy arm; 19 in HyCoSy arm	History of primary infertility	1 site
Assessment of pain with HyFoSy vs. HSG (patients randomly assigned to either HyFoSy or HSG). Injection pressures controlled by anesthesia infusion pump (Dreyer et al. 2014)	Median pain scores	19 in HyFoSy arm; 20 in HSG arm	History of infertility	1 site
<i>Studies to Support Safety</i>				
Assessment of pain with HyFoSy as compared to HyCoSy and the effect of painkillers on pain scores; additional AEs reported (Ludwin et al. 2017b)	Median pain scores and percentage of patients with moderate to severe pain	300: 175 women received analgesics; 125 women received no analgesics	History of infertility	1 site
Assessment of pain with HyFoSy as compared to transvaginal ultrasound, pap smear, or blood draw; all patients premedicated (van Schoubroeck et al. 2015)	Median pain scores	216	Women referred for tubal patency evaluation	1 site
<i>Other Studies Pertinent to Review of Efficacy or Safety</i>				
HyFoSy vs. HSG in the confirmation of tubal occlusion (patients underwent both procedures) (Rosic et al. 2018)	Accuracy of HyFoSy (HSG used as reference standard)	90 (86 completed study procedures)	History of Essure device placement for sterilization	1 site
HyFoSy vs. HSG in the confirmation of tubal occlusion (patients underwent both procedures) (Dreyer et al. 2015)	Accuracy of HyFoSy (HSG used as reference standard)	26	History of Essure device placement for hydrosalpinx	1 site

Abbreviations: HDF, high-definition flow; HSG, hysterosalpingography; HyCoSy, hysterosalpingo-contrast sonography; HyFoSy, hysterosalpingo-foam sonography; NDA = new drug application

7.2. Review Strategy

Efficacy

Four studies included in the first section of Table 18 were used for primary evidence of efficacy (van Schoubroeck et al. 2013; Ludwin et al. 2017a; Piccioni et al. 2017; Riganelli et al. 2018). In these studies, HyFoSy was performed in women with infertility or subfertility and compared to the reference standard, laparoscopy and dye. Diagnostic performance results (i.e., sensitivity and specificity) were reported or derived from 2x2 tables generated by the Applicant based on the publications. The Riganelli study compared the diagnostic performance of HyFoSy using 2D and 3D imaging techniques. Two studies (Ludwin et al. 2017a; Piccioni et al. 2017) compared the diagnostic performance of HyFoSy to HyCoSy, an alternative ultrasound test for tubal patency.

The reference standard (laparoscopy and dye) uses the presence or absence of peritoneal spillage of the contrast agent to define a patent or an occluded tube, respectively. There was some variability in the ultrasound definitions used for patent and occluded; therefore, these definitions are reported for each study below. For both the reference standard and the ultrasound imaging tests, positive results refer to occluded tubes and negative results refer to patent tubes.

Two studies (Dreyer et al. 2015; Rosic et al. 2018) were considered supportive. These two studies provided diagnostic performance results that were complementary to the four primary studies above. The women who were evaluated in these two studies underwent tubal occlusion with the Essure device for either sterilization (Rosic et al. 2018) or treatment of hydrosalpinx (Dreyer et al. 2015). Therefore, these women were highly likely to have tubal occlusion on HyFoSy as compared to the women above being evaluated for infertility. For example, the Ludwin paper estimated a 6% tubal occlusion rate for its sample size estimation. The papers by Rosic and Dreyer have limited generalizability due to the differences between the studied populations and the proposed target population. Therefore, these papers were treated as supportive sources of efficacy.

Safety

The primary sources of clinical evidence for safety came from published literature reporting ExEm Foam kit use and the pharmacovigilance database from the foreign postmarketing experience. These sources were augmented by comparisons of the product to the approved contrast agents for HSG (chemical profile) and cleared devices for HyCoSy using saline and air (safety profile). The safety profile of (b) (4) (clear gel) in the context of use as a coupling agent was also evaluated. For both the safety and efficacy analyses, although p-values were reported in the published literature as part of the studies' results, the review team considered these p-values nominal and they were not considered during the review.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Studies Used to Support Efficacy

8.1.1. Riganelli et al. (2018)

8.1.1.1. Study Design

“Ultrasonography Reappraisal of Tubal Patency in Assisted Reproduction Technology Patients: Comparison Between 2D- and 3D-Sonohysterosalpingography. A Pilot Study” (Riganelli et al. 2018) was a prospective study of 50 infertile women, previously evaluated with laparoscopy, who were randomly assigned to either 2D-HyFoSy (Group 1) or 3D-HyFoSy (Group 2) imaging evaluation. Results of HyFoSy were compared to laparoscopy with dye as the reference standard.

Ultrasound Imaging Readers/Performers

The ultrasound operator performing and interpreting HyFoSy was the same for all procedures and the individual was blinded to the laparoscopy results.

ExEm Foam Instillation

20 mL of ExEm Foam was prepared by mixing 10 mL of clear gel and 10 mL of sterile purified water as per product instructions. These volumes are twice those of the product proposed for marketing in the United States. However, the ratio of gel to water (1:1) and the mixing process to create the foam are the same. The catheter used for instillation was not specified.

Ultrasound Imaging Technique

In Group 2, 3D evaluation was performed twice: real-time during foam instillation and postprocedure using 3D reconstructions.

8.1.1.2. Study Endpoints

The study reported sensitivity and specificity of HyFoSy for each imaging test (2D-HyFoSy or 3D-HyFoSy). The publication also reported the false positive rate, false negative rate, positive predictive value, and negative predictive value.

Definition of Patent Tube on HyFoSy

Passage of contrast along the length of the tube until its (peritoneal) spread at adnexal level.

Definition of Occluded Tube on HyFoSy

No (peritoneal) spread of the contrast medium and contrast is seen within the course of the tube only partially, even after repeated instillation of foam.

The above definitions were used to define negative and positive imaging results on a tube-level, and when compared to the results of the reference standard, were used for the calculation of sensitivity and specificity. The length of the procedure was also reported for each group.

8.1.1.3. Statistical Analysis

Data from the two HyFoSy imaging groups were compared using the Student’s *t*-test for continuous data analysis while the Fisher’s Exact Test was used for categorical data. A *p*-value less than 0.1 was considered statistically significant.

Comment: In general, a p-value less than 0.05 in a two-sided test is the threshold for concluding statistical significance.

8.1.1.4. Study Results

Compliance With Good Clinical Practice

This study was performed at Sapienza University of Rome, Italy. The Hospital Ethical Committee approved the study and written informed consent was obtained from all patients prior to enrollment.

Financial Disclosure

The publication states that the authors “certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.” See Section 13.2 for the Applicant’s financial disclosure statement.

Patient Disposition

Fifty-four patients were considered eligible. Four were excluded; two were excluded due to tight cervical stenoses and two did not sign the informed consent form. Fifty patients were therefore enrolled and randomly allocated to the two groups (2D-HyFoSy or 3D-HyFoSy).

Table 19. Patient Demographics (Riganelli et al. 2018)

	All N.=50 (range)	2D-HyFoSy * N.=25 (range)	3D-HyFoSy † N.=25 (range)	1
Median age, years	34.5 (33-36)	34 (33-35)	35 (33-36)	
Median BMI ‡ (kg/m²)	24.1 (23.9-27.9)	23.7.1 (23.9-28.3)	24.9 (23.9-27.9)	
Months of infertility, median	27.6 (16-42)	28.2 (16-42)	26.9 (12-42)	
Cause of infertility				
Endometriosis	7 (14%)	3 (12%)	4 (16%)	
Previous PID §	16 (32%)	9 (36%)	7 (28%)	
CUA ¶	3 (6%)	1 (4%)	2 (8%)	
Others #	24 (48%)	13 (52%)	11 (44%)	

*2D-sonohysterosalpingography; †3D-sonohysterosalpingography; ‡Body Mass Index; §pelvic inflammatory disease; ¶congenital anomalies; #others: endocrine dysfunction, Asherman, endometrial polyps, submucosal mioma idiopathic.

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

All women had to (1) have at least 12 months of infertility, (2) have previous diagnostic laparoscopy elsewhere, (3) be referred to the site's assisted reproductive treatment unit between October 2015 and December 2016, and (4) be scheduled for the assisted reproductive treatment program.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

No concomitant medications such as analgesics or antibiotics were reported.

Efficacy Results: Primary Endpoint

The publication reported measures of diagnostic performance as shown in the Table 20.

Table 20. Diagnostic Performance Results (Riganelli et al. 2018)

	Sensitivity (%)	Specificity (%)	FP (%)*	FN (%)* †	PPV (%) ‡	NPV (%) §
2D-(HyFoSy) ¶	80	92	8	20	81.08	91.42
3D-(HyFoSy) ¶	98	91.4	8.6	2	83.29	98
Lap and dye #	100	100	0	0	100	100

*False positive rate; †false negative rate; ‡positive predictive values;
§negative predictive values; ¶sonohysterosalpingography; #laparoscopy with chromoperturbation.

However, it is unclear from the publication whether the analyses were performed on a tube-level or on a patient-level; sensitivity and specificity were not defined. A clinical IR was submitted December 28, 2018, for this information. The Applicant contacted the study authors to answer the IR but did not receive a response. Based on the statistical team's review, results presented in the paper are suspected to be tube-level.

Data Quality and Integrity

The data quality and integrity were not verifiable as this was a published study and raw data were not submitted for review.

Efficacy Results: Secondary and Other Relevant Endpoints

The mean time of the 3D-HyFoSy procedure was 5 minutes compared to 7.5 minutes for the 2D-HyFoSy procedure.

8.1.2. Ludwin et al. (2017a)

8.1.2.1. Study Design

“Accuracy of Hysterosalpingo-Foam Sonography in Comparison to Hysterosalpingo-Contrast Sonography With Air/Saline and to Laparoscopy With Dye” (Ludwin et al. 2017a) was a prospective, observational study that included sexually active women between the ages of 21 to 40 years who had a medical history of infertility without prior evaluation for tubal patency. Each patient underwent the following sequence of procedures in the ultrasound imaging room:

- Standard 2D ultrasound of the pelvic organs
- 3D ultrasound of the uterus
- 3D-saline-infusion-sonohysterography to assess the uterine cavity for anomalies
- 2D-air/saline-HyCoSy
- 2D/3D-HyFoSy
- 2D/3D-high-definition flow (HDF) Doppler enhancement-HyFoSy (2D/3D-HDF-HyFoSy)

On the following day, patients underwent laparoscopy with dye for evaluation of tubal patency.

Ultrasound Imaging Readers/Performers

Three investigators evaluated tubal patency with ultrasound. All were specialists in gynecology and obstetrics, “with 12 to 15 years [of] experience in 2D ultrasound imaging and HyCoSy and 7 to 10 years of experience in 3D imaging.” The publication did not state the investigators’ experience with HyFoSy. Each investigator performed one of the tubal patency procedures for a given patient: 2D air/saline-HyCoSy, 2D/3D-HyFoSy, or 2D/3D-HDF-HyFoSy. The procedure performed was decided by a randomization program. Each investigator was blinded to the results of the other investigators’ findings.

Reference Standard Readers/Performers

Two different investigators (i.e., not the ultrasound readers) evaluated tubal patency with laparoscopy and dye. They were blinded to the results of the ultrasound imaging examinations at the start of the procedure. Once their initial assessment of the patency of the tubes was complete, the operating room nurse read out the results of the ultrasound imaging procedures so that the investigators could further interrogate the fallopian tubes as needed.

ExEm Foam Instillation

ExEm Foam was prepared as per manufacturer’s instructions and was instilled via a 5-Fr silicone catheter with balloon.

Ultrasound Imaging Technique

During administration of the foam, tubal patency was evaluated real-time with 2D ultrasound. The 3D ultrasound volume acquisitions were also acquired during the procedure and were only utilized during the procedure to aid in diagnosis of fallopian tube patency. The 3D acquisitions were not evaluated postprocedure for the determination of fallopian tube patency. High Definition Flow Doppler was used to visualize flow of contrast through the fallopian tubes.

8.1.2.2. Study Endpoints

Diagnostic accuracy of 2D/3D-HyFoSy and 2D/3D-HDF-HyFoSy in evaluating tubal patency as compared to laparoscopy and dye as the reference standard.

Definition of Patent Tube on HyFoSy and HyCoSy

- Contrast flow observed to pass from the tube into the peritoneal cavity
OR
- Contrast flow observed in either the intramural or isthmic part of the tube for (a) 10 seconds and/or (b) during 3D volume acquisition without any sign of hydrosalpinx and in the presence of peritoneal spillage

Definition of Occluded Tube on HyFoSy and HyCoSy

- Contrast not observed to pass from the tube into the abdominal cavity
OR
- Tubal lumen distended with flow visualized in the intramural or isthmic part of the tube

The above definitions were used to define negative and positive imaging results on a tube-level, which when compared to the results of the reference standard were used for the calculation of diagnostic accuracy.

Comment: HSG and laparoscopy with dye use presence or absence of peritoneal spillage to diagnose the presence of a patent or occluded tube, respectively. The investigators used additional definitions for tubal patency and occlusion beyond these definitive criteria. For example, they considered that flow only within a portion of the visualized tube would be sufficient for diagnosis of fallopian tube patency. Unlike laparoscopy with dye, contrast flow within the entire length of the tubes can be directly visualized under fluoroscopy during HSG when patent, however, definitive diagnosis of tubal patency with HSG remains dependent on visualization of peritoneal spillage.

The authors did not record which criterion was used to diagnose tubal patency or occlusion for each individual tube. Allowance of the second definition of tubal patency (flow within the tube for 10 seconds without seeing peritoneal spillage) would result in a greater likelihood of calling a tube patent, thereby decreasing sensitivity (by increasing false negatives) and increasing specificity (by increasing true negatives).

8.1.2.3. Statistical Analysis

Sample-size calculation was based on the sensitivity of 2D/3D-HDF-HyFoSy, with expected sensitivity of 99% and a disease prevalence of tubal occlusion of 6%. Required sample size was calculated to be 254 tubes or 127 patients assuming two tubes for each patient.

The study compared the diagnostic accuracy of and the concordance between the three ultrasound imaging procedures: 2D-air/saline-HyCoSy, 2D/3D-HyFoSy, and 2D/3D-HDF-HyFoSy. McNemar's test was used to compare all the diagnostic methods. Data were presented in a contingency table, with p-values for comparing the methods' diagnostic accuracy (ACC). Agreement between each test was evaluated using the kappa (κ) statistic, proportion of agreement, positive percent agreement and negative percent agreement. The κ -value was interpreted in terms of the strength of agreement as follows: poor, 0.20; fair, 0.21 to 0.40; moderate, 0.41 to 0.60; good, 0.61 to 0.80; and very good, 0.81 to 1.00.

8.1.2.4. Study Results

Compliance With Good Clinical Practice

This study was performed in Krakow, Poland, at three sites with the same investigators: an academic medical center, a private hospital, and a private medical center. The study was approved by the local bioethics committee. All patients had to provide written informed consent for eligibility.

Financial Disclosure

The publication states that (1) no external funding was given for this study and (2) the authors had no conflicts of interest to disclose.

Patient Disposition

Considered for enrollment were 169 eligible patients; 144 met inclusion/exclusion criteria. Two patients had missing results, six were lost to follow-up, and three withdrew consent. Data from 132 patients with 259 tubes were used for calculating diagnostic accuracy.

Comment: One patient or two tubes are unaccounted for in the publication flowchart of patient disposition.

Table 21. Patient Demographics (Ludwin et al. 2017a)

Variable	Value
Age (y)	32.3 ± 4.3, 32.0 [29–35]
Weight (kg)	61.7 ± 11.9, 59 (55–65)
Height (cm)	166.6 ± 5.7, 167 [163–170]
Infertility	
Primary/secondary	103 (78)/29 (22)
Duration (y)	2.6 ± 1.8, 2 [1.5–3.0]
Additional pathological findings	
Myomas	5 (3.8)
Submucosal	1 (0.8)
Endometrial polyps	5 (3.8)
Congenital uterine anomalies by ASRM ^c	12 (9.1)
Unicomuante uterus	2 (1.5)
Septate uterus	5 (3.8)
Arcuate uterus	5 (3.8)
Endometriosis	4 (3)
Benign ovarian cysts	6 (4.6)

^aN = 132.

^bData reported as number (%) or mean ± standard deviation, and median [lower-upper quartile].

^cASRM classification with supplemented morfometric criteria (Ludwin and Ludwin, 2015; Ludwin et al., 2015).

ASRM, American Society of Reproductive Medicine.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Patients were given an effervescent tablet of paracetamol and codeine phosphate diluted in water 1 hour prior to the ultrasound imaging procedures for pain prophylaxis.

Efficacy Results: Primary Endpoint

The publication provided cross-tabulation of the ultrasound imaging modalities compared to laparoscopy and dye and provided the overall accuracy, defined as the proportion of true test results, for each modality. An occluded fallopian tube was defined as a positive result.

Table 22. Cross-Tabulation of Ultrasound Imaging Results Compared to Reference Standard (Ludwin et al. 2017a)

2D-air/saline-HyCoSy	Laparoscopy		
ACC = 84.2%			
	Abnormal	Normal	Total
Abnormal	14	32	46
Normal	1	204	205
Inconclusive	3	5	8
Total	18	241	259
2D/3D-HyFoSy			
ACC = 91.9%			
	Abnormal	Normal	Total
Abnormal	13	14	27
Normal	2	225	227
Inconclusive	3	2	5
Total	18	197	259
2D/3D-HDF-HyFoSy			
ACC = 95.8%			
	Abnormal	Normal	Total
Abnormal	17	7	24
Normal	1	231	232
Inconclusive	0	3	3
Total	18	241	259

^aMcNemar test for data with conclusive results.

ACC, accuracy; air/saline-HyCoSy, air/saline hysterosalpingo-contrast sonography; 2D/3D-HyFoSy, 2D/3D hysterosalpingo-foam sonography; 2D/3D-HDF-HyFoSy, 2D/3D-high-definition flow hysterosalpingo-foam sonography.

Diagnostic accuracy measures were provided, including and excluding inconclusive results as shown in Table 23. In the first row, inconclusive results are excluded. In the second row, inconclusive results are treated as occluded, and in the third row, inconclusive results are treated as patent.

Multidisciplinary Review and Evaluation NDA 212279
ExEm Foam (air polymer-type A intrauterine foam)

Table 23. Measures of Diagnostic Performance (Ludwin et al. 2017a)

Inconclusive results	Accuracy (%)	κ	Sensitivity	Specificity	PPV ^b	NPV ^c	LR+ ^d	LR- ^e
<i>Air/saline-HyCoSy</i>								
ex. ^f	86.80	0.40 (0.25–56)	93% (68–99)	86% (81–91)	30% (18–46)	99.5% (97–100)	6.9 (4.9–9.8)	0.08 (0.01–0.5)
occ. ^g	85.33	0.41 (0.27–0.55)	94% (73–100)	85% (79–89)	31% (20–46)	99.5% (97–100)	6.2 (4.5–8.5)	0.07 (0.01–0.4)
pat. ^h	86.10	0.37 (0.22–0.53)	78% (52–94)	87% (82–91)	30% (18–46)	98% (95–99)	5.9 (3.9–8.8)	0.26 (0.1–0.6)
<i>2D/3D-HyFoSy</i>								
ex. ^f	93.70	0.59 (0.41–0.77)	87% (60–98)	94% (90–97)	48% (29–68)	99% (97–100)	14.8 (8.6–25.6)	0.14 (0.04–0.5)
occ. ^g	92.06	0.60 (0.44–0.77)	89% (65–99)	93% (89–96)	50% (32–68)	99% (97–100)	13.4 (8.1–22.1)	0.12 (0.03–0.4)
pat. ^h	91.59	0.54 (0.36–0.72)	72.22 (47–90)	94% (90–97)	48% (29–68)	98 (95–99)	12.4 (6.9–22.3)	0.3 (0.1–0.6)
<i>2D/3D-HDF-HyFoSy</i>								
ex. ^f	96.88	0.79 (0.65–0.93)	94% (73–100)	97% (94–99)	71% (49–88)	99.6% (98–100)	32.1 (15.3–67.2)	0.06 (0.01–0.4)
occ. ^g	95.75	0.73 (0.58–0.88)	94% (73–100)	96% (93–98)	63% (42–81%)	99.6% (98–100)	22.8 (12.3–42.2)	0.06 (0.01–0.4)
pat. ^h	96.91	0.79 (0.65–0.93)	94% (73–100%)	97% (94–99)	71% (49–87%)	99.6% (98–100)	32.5 (15.5–68)	0.06 (0.01–0.4)

^aN = 259 (tubes).

^bPositive predictive value.

^cNegative predictive value.

^dPositive-likelihood ratio.

^eNegative-likelihood ratio, 95% CIs are presented in parentheses.

^fInconclusive results excluded.

^gInconclusive results = occluded.

^hInconclusive results = patent.

Data Quality and Integrity

The data was not verifiable as this was a published study without data submission. Submission of patient-level or tube-level data was encouraged in previous communications to the Applicant prior to the NDA submission. In addition, such data were requested in the filing letter for the Ludwin study (with primary intent to perform subgroup analyses of diagnostic accuracy using the varying definitions of tubal patency). In the response to the clinical IR made in the 74-day filing letter received February 4, 2019, the Applicant stated that such subgroup analyses would not be possible, as the authors of the Ludwin paper did not record whether each tubal diagnosis relied on peritoneal spillage or visualization of contrast flow for more than 10 seconds. There is one unaccounted patient included in the patient disposition flowchart (261 tubes reported on chart; 259 tubes reported in the text).

Efficacy Results: Secondary and Other Relevant Endpoints

See Table 23 above for agreement results (kappa) for each ultrasound modality with the reference standard.

8.1.3. Van Schoubroeck et al. (2013)

8.1.3.1. Study Design

“The Use of a New Gel Foam for the Evaluation of Tubal Patency” (van Schoubroeck et al. 2013) was a nonrandomized, observational, academic and single-center study of 20 women (40 fallopian tubes) evaluated for subfertility and scheduled for laparoscopy with dye or chromopertubation. The patients were imaged first with HyFoSy and then proceeded to laparoscopy with chromopertubation with methylene blue.

Comment: Subfertility (and how it differs from infertility) was not defined.

Ultrasound Imaging Readers/Performers

Number and expertise of readers were not specified.

Reference Standard Readers/Performers

Surgeon was not blinded to HyFoSy results.

ExEm Foam Instillation

ExEm Foam was prepared as per manufacturer’s instructions. As in the Riganelli study, the kit used contained double the amount of gel and water (10 mL each) than the to-be-marketed United States kit. A 2-mm pediatric Foley balloon catheter with stylet was used.

Ultrasound Imaging Technique

2D static images, 2D clips, and 3D volumes were obtained in the study. The publication did not state how or if the 3D volumes were used in determining tubal patency; study results were not separated by diagnoses made by 2D or 3D imaging, as in the Riganelli study.

8.1.3.2. Study Endpoints

The primary endpoint was agreement of HyFoSy as compared to laparoscopy with chromopertubation.

Definition of Patent Tube on HyFoSy

A patent tube must demonstrate all of the following:

- Continuous forward flow for at least 15 seconds visualized in the proximal part of the tube
- Contrast seen over the whole length of the tube
- Tubal lumen did not distend
- Peritoneal spillage was visualized around the ovaries or in the pouch of Douglas

The above definition was used to define a positive or negative imaging result on a tube-level, which when compared to the result of the reference standard, was used for the calculation of agreement.

8.1.3.3. Study Results

Compliance With Good Clinical Practice

This study took place at University Hospitals Leuven, Belgium. The publication states that the study was approved by the hospital's Ethics Committee and written informed consent was obtained.

Financial Disclosure

Not included in the publication; publication is included in the Applicant's 3454 form where option 2 was selected (certifying no financial arrangement, proprietary interest, or significant payments).

Patient Disposition

All 20 patients completed the HyFoSy and laparoscopy procedures.

Demographic Characteristics

Median (range) age:	30 (23 to 40) years
Median (range) parity:	0 (0 to 3)
Median (range) gravidity:	0 (0 to 3)
Primary infertility:	n=14 patients
Secondary infertility:	n=6 patients

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Women on oral contraceptives: n=3

Efficacy Results: Primary Endpoint

Agreement between HyFoSy diagnoses and laparoscopy with chromopertubation diagnoses was 100%. The Applicant provided the following table of tube-level data in the integrated summary of effectiveness.

Table 24. Tube-Level Data Comparing HyFoSy to Laparoscopy (van Schoubroeck et al. 2013)

		2D/3D HyFoSy	
		Patent	Non-Patent
Laparoscopy	Patent	TN=36	FP=0
	Non-Patent	FN=0	TP=4

Abbreviation: HyFoSy, hysterosalpingo-foam sonography

The statistical reviewer confirmed the results of the Applicant's agreement test by using Kappa statistics. The statistical reviewer also calculated sensitivity and specificity, which were 100% (95% CI: 73% to 100%) and 100% (95% CI: 90% to 100%), respectively.

Efficacy Results: Secondary and Other Relevant Endpoints

Four of the 20 patients received HSGs previously. In one patient, HSG could not be performed (failed), but HyFoSy could be performed, showing patency of both tubes consistent with laparoscopy findings. In two other cases, HSG incorrectly diagnosed a tube as blocked, whereas HyFoSy correctly identified a tube as patent.

Table 25. Tube-Level Data Comparing HyFoSy to HSG and Laparoscopy (van Schoubroeck et al. 2013)

Case	Fallopian tube	HSG	HyFoSy	Lps chromo
1	left	patent	patent	patent
	right	patent	patent	patent
2	left	failed ¹	patent	patent
	right	failed ¹	patent	patent
3	left	blocked	blocked	blocked
	right	blocked	patent	patent
4	left	patent	patent	patent
	right	blocked	patent	patent

¹ Technical failure

Abbreviations: HSG, hysterosalpingography; HyFoSy, hysterosalpingo-foam sonography; Lps chromo, laparoscopic chromoperturbation

Source: Table 1. Overview of the four patients who underwent X-ray HSG, HyFoSy and laparoscopic chromoperturbation

8.1.4. Piccioni et al. (2017)

8.1.4.1. Study Design

Women with at least 2 years of primary infertility scheduled for laparoscopy with dye were prospectively enrolled in the study, “Sonohysterosalpinography: Comparison of Foam and Saline Solution” (Piccioni et al. 2017). The women were randomized into one of two groups for imaging evaluation (HyFoSy or HyCoSy). The aim of the study was to compare HyFoSy to HyCoSy in assessing tubal patency in women undergoing laparoscopy with dye.

Ultrasound Imaging Readers/Performers

An experienced sonographer performed all sono-HSG exams.

Reference Standard Readers/Performers

Number of surgeons and blinding were not specified.

ExEm Foam Instillation

Foam was prepared with 10 mL of clear gel, 10 mL of sterile purified water, (and air) as per manufacturer’s instructions. A cervical balloon-less applicator was used to instill the foam. For HyCoSy exams, a 5-Fr balloon catheter was used for instillation of the saline-air mixture.

Ultrasound Imaging Technique

B-mode scanning and color Doppler techniques were used. A volumetric endovaginal probe was used; however, the paper does not describe whether 3D imaging was obtained and/or reviewed.

8.1.4.2. Study Endpoints

Sensitivity and specificity of the ultrasound imaging modality (HyFoSy or HyCoSy) using laparoscopy and dye as the reference standard.

Definition of Patent Tube on HyCoSy or HyFoSy

Spillage of saline solution or foam from the fimbria as indicated by fluid flow surrounding the ovary and its collection in the pelvis on B-mode imaging. On power Doppler, two criteria were used to detect tubal patency: steady color Doppler signal in a segment of tube indicating flow and detection of spillage from the fimbria end.

Definition of Occluded Tube on HyCoSy and HyFoSy

Absence of peritoneal spillage.

The above definitions were used to determine negative and positive imaging results on a tube-level, which when compared to the results of the reference standard were used for the calculation of sensitivity and specificity.

8.1.4.3. Study Results

Compliance With Good Clinical Practice

This study took place at Sapienza University of Rome, Italy. The publication states that the Hospital Ethical Committee approved the protocol and written informed consent was obtained from all patients.

Financial Disclosure

Financial disclosure information was not included in the publication. This publication is included in the Applicant's 3454 form where option 2 was selected (certifying no financial arrangement, proprietary interest, or significant payments).

Patient Disposition

Thirty-seven women were evaluated; it is not specified how many were originally enrolled and if any patients withdrew or could not have their ultrasound exams completed due to pain or technical reasons.

Demographic Characteristics

Eighteen women underwent HyFoSy and 19 women underwent HyCoSy. Their demographics are shown in Table 26.

Table 26. Patient Demographics (Piccioni et al. 2017)
Clinical Data of Patients Undergoing Sonohysterosalpingog-
raphy with Foam (HyFoSy) and Saline Solution (HyCoSy)

Clinical Data	Results	
	HyFoSy	HyCoSy
No. of patients	18	19
	Mean (min-max)	
Age (years)	34 (33–35)	34 (33–36)
BMI (kg/m ²)	26.1 (23.9–28.3)	25.9 (23.9–27.9)
Months of infertility	28.8 (16–42)	26.4 (12–42)
	Patients (%)	
Causes of infertility		
Endometriosis	11 (61.1%)	11 (57.9%)
Previous PID	3 (16.7%)	4 (21%)
Unexplained infertility	4 (22.2%)	4 (21.1%)

Abbreviations: BMI, body mass index; HyCoSy, sonohysterosalpingography with saline solution instillation; HyFoSy, sonohysterosalpingography with foam instillation; PID, pelvic inflammatory disease.

Efficacy Results: Primary Endpoint

The publication reported patient-level diagnostic performance results, as shown in Table 27.

Table 27. Patient-Level Diagnostic Performance Results (Piccioni et al. 2017)
Comparison of the Results of Sonohysterosalpingography with Foam Instillation (HyFoSy) and Sonohysterosalpingography
with Saline Solution Instillation (HyCoSy) with Laparoscopic Findings

	No. of Patient	Tubal Patency	Tubal Occlusion	Sensitivity	Specificity	Overall Accuracy
Results of dye test in HyFoSy group	18	11	7	—	—	—
HyFoSy	18	10	7	87.5%	100%	94.4%
Results of dye test in HyCoSy group	19	11	8			
HyCoSy	19	6	5	50%	66.6%	57.9%

The Applicant provided a 2x2 table comparing the ultrasound imaging modality results to the laparoscopy results at a tube-level based on the results section of the manuscript (see Table 28).

Table 28. Tube-Level Data Comparing HyFoSy or HyCoSy to Laparoscopy (Piccioni et al. 2017)

		HyFoSy	
		Patent	Non-Patent
Laparoscopy	Patent	TN=20	FP=0
	Non-Patent	FN=2	TP =14

		HyCoSy	
		Patent	Non-Patent
Laparoscopy	Patent	TN=12	FP=6
	Non-Patent	FN=10	TP =10

Abbreviations: HyCoSy, hysterosalpingo-contrast sonography; HyFoSy, hysterosalpingo-foam sonography

The 95% CIs for sensitivity and specificity of HyFoSy calculated by the statistics reviewer were 87.50% (95% CI: 62% to 99%) and 100% (95% CI: 83% to 100%), respectively.

The 95% CIs for sensitivity and specificity of HyCoSy calculated by the statistics reviewer were 50% (95% CI: 28% to 72%) and 66.6% (95% CI: 45% to 88%), respectively.

Efficacy Results: Secondary and Other Relevant Endpoints

Agreement of HyFoSy with laparoscopy findings was reported as 94.4% (95% CI: 72.4% to 99.9%). Agreement of HyCoSy with laparoscopy findings was reported as 57.8% (95% CI: 36.2% to 76.9%).

8.1.5. Rosic et al. (2018)

8.1.5.1. Study Design

“Use of Hysterosalpingo-Foam Sonography for Assessment of the Efficacy of Essure Hysteroscopic Sterilization” (Rosic et al. 2018) was a prospective, nonrandomized, single-center study of 86 patients who underwent tubal occlusion with Essure device placement as a means of sterilization/contraception. To confirm tubal occlusion, each patient underwent both HyFoSy and HSG (the confirmatory test in this clinical setting) 12 weeks after the procedure.

Ultrasound Imaging Readers/Performers

A single sonographer performed all HyFoSy examinations. The exams were performed prior to HSG.

Reference Standard Readers/Performers

A gynecologist not involved in the performance of the HyFoSy procedure performed the HSG procedure. The images were read by a radiologist who was blinded to the results of HyFoSy.

ExEm Foam Instillation

10 mL of clear gel was mixed with 10 mL of sterile purified water to create 20 mL of foam. The foam was instilled into the uterine cavity through a cervical balloonless catheter.

Ultrasound Imaging Technique

2D transvaginal ultrasound imaging

8.1.5.2. Study Endpoints

The primary endpoint was the accuracy of HyFoSy for the confirmation of tubal occlusion after Essure placement using HSG as a reference standard. The secondary endpoint was the correlation between the position of the micro-inserts on (noncontrast) 2D transvaginal ultrasound imaging and tubal occlusion on HSG.

Definition of Patent Tube on HyFoSy

Leakage of foam into the tube past the insert and into the peritoneal cavity.

This definition was used to define a positive imaging test, which when compared to the reference standard was used to calculate accuracy.

Comment: The definitions of a patent tube and occluded tube at HSG were not defined but are assumed to be complementary to the HyFoSy definition of a patent tube.

8.1.5.3. Statistical Analysis

The differences in continuous data were tested for significance by the Wilcoxon signed rank test. $P < 0.05$ was considered statistically significant.

8.1.5.4. Study Results

Compliance With Good Clinical Practice

The study took place at University Medical Center Maribor, Slovenia. The study was approved by the National Medical Ethics Committee and written consent was obtained from all patients.

Financial Disclosure

Not included in the publication. See Section 13.2 for the Applicant's financial disclosure statement.

Patient Disposition

There were 90 patients enrolled in the study, 86 of whom completed all imaging procedures. Of the four patients who did not, one had vasovagal syncope with HyFoSy, one declined HSG, one had contrast leakage with HSG, and the last withdrew consent.

Demographic Characteristics

The mean age of the patients evaluated was 40.1 years, with range between 35 to 47 years. Mean parity was 1.9 births, with range between 0 and 4 births.

Efficacy Results: Primary Endpoint

The accuracy as well as sensitivity and specificity of HyFoSy (using HSG as the reference standard) with the 95% CIs and the associated numbers of true positive, true negative, false positive, and false negative findings are presented in Table 29.

Table 29. Tube-Level Diagnostic Performance Results (Rosic et al. 2018)

Variable	HyFoSy vs HSG (n = 170 fallopian tubes)
True-positive, n	159
True-negative, n	6
False-positive, n	5
False-negative, n	0
Prevalence of tubal occlusion, %	93.5 (89–97)
Sensitivity, %	100.0 (97–100)
Specificity, %	54.6 (23–83)
Positive predictive value, %	97.0 (93–99)
Negative predictive value, %	100.0 (42–100)
Accuracy, %	97.1 (93–99)

Abbreviations: HSG, hysterosalpingography; HyFoSy, hysterosalpingo-foam sonography

This study reported the lowest specificity out of all the studies submitted for efficacy.

Efficacy Results: Secondary and Other Relevant Endpoints

The concordance rate between a satisfactory micro-insert position and tubal occlusion and an unsatisfactory position and tubal patency was 83.5% (95% CI, 77% to 89%).

8.1.6. Dreyer et al. (2015)

Study Design

“Diagnostic Accuracy of Hysterosalpingo-Foam-Sonography to Confirm Tubal Occlusion After Essure® Placement as Treatment for Hydrosalpinges” (Dreyer et al. 2015) was a prospective study designed to evaluate HyFoSy as a confirmatory test for proximal tubal occlusion following Essure device placement for treatment of hydrosalpinx. All women in the study underwent HyFoSy followed by HSG 12 weeks after Essure placement.

Ultrasound and Reference Standard Imaging Readers/Performers

All HyFoSy and HSG procedures were performed by two physicians experienced with both tests. HSG readers were not blinded to the HyFoSy results.

ExEm Foam Instillation

A cervical balloon-less catheter was used to instill approximately 5 mL of foam created by 10 mL of gel mixed with 10 mL of sterile purified water.

Ultrasound Imaging Technique

Not specified.

8.1.6.1. Study Endpoints

The primary outcome was accuracy and was “measured by the sum of the true positives and true negatives divided by the sum of the true positives, true negatives, false positives, and false negatives.” Sensitivity (defined as the true occluded rate), specificity (defined as the true patency rate), positive predictive value, and negative predictive value were also reported.

The definitions of a patent and an occluded tube diagnosed by HyFoSy (on which to establish true positive, true negative, etc. cases) were not defined in the paper.

8.1.6.2. Statistical Analysis

Differences in continuous data were tested for significance using a Wilcoxon signed rank test. A $p\text{-value} < 0.05$ indicated statistically significant differences, and all values were calculated using a two-tailed significance level. The authors also calculated sensitivity, specificity, positive predictive value and negative predictive value with their corresponding 95% CIs. Statistical analyses were conducted to assess agreement between HyFoSy and HSG.

8.1.6.3. Study Results

Compliance With Good Clinical Practice

The study was performed at VU University Medical Center, Amsterdam, The Netherlands. The study was conducted under Institutional Review Board approval. All women gave informed consent.

Financial Disclosure

IQ Medical Ventures provided the clear gel for the HyFoSy procedures. The paper states “IQ Medical Ventures had no role in study design, data collection and analyses, decision to publish, or preparation of the manuscript.” Dr. Emanuel (one of the inventors and owners of the patent for ExEm Foam and who owns a (b)(4)% share in Giskit B.V., a subsidiary of IQ Medical Ventures) provided his assistance by teaching the procedure to the study investigators.

Patient Disposition

Twenty-six women underwent Essure device placement between March 2011 and May 2014. A total of 38 Essure devices were placed for hydrosalpinges (14 women with unilateral hydrosalpinx and 12 women with bilateral hydrosalpinges).

Demographic Characteristics

Demographic characteristics of the women are shown in Table 30.

Table 30. Patient Demographics (Dreyer et al. 2015)

n = 26	
Age (years)	33.5 (IQR 29.1–37.8)
Para	
Nulliparous	23/26 (88.5%)
Multiparous	3/26 (11.5%)
Treatment	
Unilateral Essure® placement	14/26 (53.8%)
Bilateral Essure® placement	12/26 (46.2%)

IQR = interquartile range.

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

All women were premedicated with naproxen 500 mg, the evening before and 2 hours before the tests.

Efficacy Results: Primary Endpoint

The Applicant provided a 2x2 table of the tube-level results based on the results described in the publication (see Table 31).

Table 31. Tube-Level Data Comparing HyFoSy to HSG (Dreyer et al. 2015)

		HyFoSy	
		Patent	Non-Patent
X-Ray HSG	Patent	TN=4	FP=0
	Non-Patent	FN=1	TP=33

Abbreviations: FN, false negative; FP, false positive; HSG, hysterosalpingography; HyFoSy, hysterosalpingo-foam sonography, TN, true negative; TP, true positive

The tube-level diagnostic performance of HyFoSy using HSG as a reference standard is reported in Table 32.

Table 32. Tube-Level Diagnostic Performance Results (Dreyer et al. 2015)

Primary outcome	HyFoSy (n = 38 tubes)	HSG (n = 38 tubes)
Proximal occlusion after Essure® placement (Conceptus Inc.)		
Sensitivity	97.1% (95% CI 84.6% to 99.5%)	NA
Specificity	100.0% (95% CI 40.2% to 100.0%)	NA
Positive predictive value	100.0% (95% CI 89.3% to 100.0%)	NA
Negative predictive value	80.0% (95% CI 28.8% to 96.7%)	NA
Accuracy	97.4% (95% CI 92.3% to 100.0%)	NA

Abbreviations: CI, confidence interval; HSG, hysterosalpingography; HyFoSy, hysterosalpingo-foam sonography; NA, not applicable

Efficacy Results: Secondary and Other Relevant Endpoints

The HyFoSy procedure took less time than the HSG procedure. There was no statistical difference in the volumes of contrast medium used in the two procedures.

Table 33. Secondary Endpoint Results (Dreyer et al. 2015)

Secondary outcome	HyFoSy (n = 26 women)	HSG (n = 26 women)
VAS pain scores (cm)	2.0 (IQR 0.2 to 2.9)	5.1 (IQR 3.0 to 7.0)
Procedure time (min)	5.5 (IQR 4.0 to 7.0)	9.5 (IQR 8.0 to 11.8)
Volume of used contrast medium (ml)	3.5 (IQR 2.3 to 7.9)	4.0 (IQR 3.0 to 4.9)

Abbreviations: HSG, hysterosalpingography; HyFoSy, hysterosalpingo-foam sonography; IQR, interquartile range; NS, not specified; VAS, visual analog scale

8.1.7. Assessment of Efficacy Across Studies

Due to differences in study design, the results of the four studies treated as primary sources of evidence were not pooled together for analysis. However, the results of the different studies are compiled together in this section to enable assessment of efficacy across studies.

Primary Endpoints

A total of 435 fallopian tubes from 220 patients were evaluated in the assessment of HyFoSy's diagnostic performance for the proposed target population/indication. The 95% CIs were either generated by the statistical reviewer (van Schoubroeck et al. 2013; Piccioni et al. 2017) or reported (Ludwin et al. 2017a).

Table 34. Summary of Tube-Level Diagnostic Performance of HyFoSy Compared to Laparoscopy With Dye From Literature

Study	Number of Patients/Tubes	Ultrasound Technique	Sensitivity (95% CI)	Specificity (95% CI)
Riganelli	25 patients 50 tubes ^a	2D-HyFoSy	80% ^b	92% ^b
Piccioni	18 patients 36 tubes	2D (±3D) HyFoSy	87.5% (62% to 99%)	100% (83% to 100%)
Riganelli	25 patients 50 tubes ^a	3D-HyFoSy	98% ^b	91.4% ^b
van Schoubroeck (2013)	20 patients 40 tubes	2D/3D-HyFoSy	100% (73% to 100%)	100% (90% to 100%)

Study	Number of Patients/Tubes	Ultrasound Technique	Sensitivity (95% CI)	Specificity (95% CI)
Ludwin	132 patients 259 tubes	2D/3D-HyFoSy	89% (65% to 99%) ^c	93% (89% to 96%) ^c
Ludwin	132 patients 259 tubes	2D/3D-HDF Doppler-HyFoSy	94% (73% to 100%) ^c	96% (94% to 99%) ^c
Total number of patients/tubes	220 patients 435 tubes			

^a Number of tubes not specified in paper, number of tubes here is given with the assumption of two tubes per patient (no congenital anomalies)

^b Measures of diagnostic performance given in paper were not specified as either tube-level or patient-level, assumed tube-level here

^c Measures of diagnostic performance treating inconclusive results as occluded

Abbreviations: CI, confidence interval; HDF, high-definition flow; HyFoSy, hysterosalpingo-foam sonography

These studies differ in ultrasound technique (e.g., use of 2D versus 3D imaging), catheter used to instill foam, and definitions used to diagnose tubal patency (Ludwin et al. 2017a). Despite these differences, the diagnostic performance of HyFoSy using laparoscopy and dye as a reference standard is overall consistent, performing better than chance, with the lower bound of the 95% CI exceeding 60%. In studies that used advanced imaging techniques beyond 2D imaging such as 3D imaging or HDF Doppler (Ludwin et al. 2017a; Riganelli et al. 2018), the point estimates for diagnostic performance for sensitivity ranged from 87.5% to 100%.

Secondary and Other Endpoints

Two studies (Ludwin et al. 2017a; Piccioni et al. 2017) compared the diagnostic performance of HyFoSy to HyCoSy. The performance estimates are shown in Table 35. In each study, the 95% CIs around the point estimates for HyFoSy to HyCoSy overlap and are consistent with similar performance of the two ultrasound techniques.

Table 35. Summary of Tube-Level Diagnostic Performance of HyFoSy and HyCoSy From Literature

Study	Number of Patients/Tubes	Ultrasound Technique	Sensitivity (95% CI)	Specificity (95% CI)
Piccioni	18 patients 36 tubes	2D (±3D) HyFoSy	87.5% (62% to 99%)	100% (83% to 100%)
Piccioni	19 patients 38 tubes	HyCoSy	50% (28% to 72%)	67% (45% to 88%)
Ludwin	132 patients 259 tubes	2D/3D-HyFoSy	89% (65% to 99%) ^a	93% (89% to 96%) ^a
Ludwin	132 patients 259 tubes	2D/3D-HDF Doppler HyFoSy	94% (73% to 100%) ^a	96% (94% to 99%) ^a
Ludwin	132 patients 259 tubes	HyCoSy	94% (73% to 100%) ^a	85% (79% to 89%) ^a

^a Measures of diagnostic performance treating inconclusive results as occluded

Abbreviations: CI, confidence interval; HDF, high-definition flow; HyCoSy, hysterosalpingo-contrast sonography; HyFoSy, hysterosalpingo-foam sonography

Additional Efficacy Considerations

Multiple different types and sizes of catheters were used in the studies submitted for efficacy, suggesting that the above results demonstrating efficacy are generalizable to clinical practice regardless of the catheter used. No instances of catheter failure (breakage) were reported.

Furthermore, although most studies used an (b) (4) ExEm Foam that contained twice the amount of gel and water, the ratio of gel to water remains identical to that present in the proposed kit for marketing in the United States. Therefore, diagnostic performance is expected to be the same in the postmarketing setting.

8.1.8. Integrated Assessment of Effectiveness

Although the studies varied in terms of operator experience and catheters, kits, and ultrasound imaging modalities used, the sensitivity and specificity of HyFoSy exceeded 60% (using the lower bounds of the 95% CIs) in all 4 primary studies evaluated for efficacy, with point estimates for sensitivity and specificity being at least 80%. Furthermore, this overall consistency in light of such clinical practice variations suggests that the expected diagnostic performance in the post approval setting will likely be similar.

8.2. Review of Safety

8.2.1. Safety Review Approach

The following sources of clinical evidence of safety were evaluated:

- Published studies reporting ExEm Foam use
- The pharmacovigilance database from the foreign postmarketing experience
- Comparisons to the approved contrast agents for HSG
- Safety profile of cleared devices for HyCoSy using saline and air
- Safety profile of (b) (4) (clear gel) in the context of use as a coupling agent

8.2.2. Review of the Safety Database

Overall Exposure

Based on the literature searches for safety and/or efficacy, 1,616 patients in 14 studies were evaluated with ExEm Foam (see Table 36). In 12 out of the 14 studies (1,434 patients), a foam that was equal parts clear gel and sterile purified water was used. The two other studies, one evaluating 50 patients (Zizolfi et al. 2018) and one evaluating 132 patients (Exacoustos et al. 2017), were included in the integrated summary of safety. The investigators from these two studies reported using diluted foam in their investigations to achieve easy passage of the foam through 5-Fr catheters.

Of the 12 studies using the proposed formulation, two evaluated HyFoSy in the context of proximal tubal occlusion via Essure device (Dreyer et al. 2015), (Rosic et al. 2018), as described above. These two studies evaluated a total of 112 patients. The remaining 10 studies evaluated 1,322 patients for tubal patency in patients with history of infertility and used the proposed formulation of ExEm Foam.

Table 36. Summary of Published Studies Submitted for Safety

	Study Design (Reference)	N	Medication	Comment(s)
1	Prospective study of the feasibility of HyFoSy as an office tubal patency test (Emanuel et al. 2012)	73	None	
2	Prospective study assessing diagnostic performance of HyFoSy using laparoscopy with chromopertubation as a reference standard (van Schoubroeck et al. 2013)	20	HyFoSy performed under general anesthesia prior to laparoscopy with chromopertubation	• Efficacy study only, did not report AEs
3	Prospective assessment of pain from HyFoSy compared to HSG (Dreyer et al. 2014)	19	None	• Two arms: HyFoSy and HSG • Anesthesia pump used to instill foam to control pressure
4	Prospective assessment of pain from HyFoSy compared to HSG (Dreyer et al. 2015)	26	500 mg Naproxen night before and 2 hours before tests	• Patients received HyFoSy followed by HSG • Women status post Essure device
5	Retrospective: Questionnaire sent to patient asking for fertility post procedure (Exacoustos et al. 2015)	294		• Only 157 patients provided follow-up, no immediate AEs reported
6	Prospective assessment of pain from HyFoSy compared to preceding transvaginal ultrasound (van Schoubroeck et al. 2015)	216	400 mg Ibuprofen	• Patients received transvaginal ultrasound followed by HyFoSy
7	Prospective study assessing diagnostic performance of HyFoSy compared to HyCoSy using laparoscopy as a reference standard (Piccioni et al. 2017)	18	None	• Patients randomized to either HyFoSy or HyCoSy • Efficacy study only; did not report AEs
8	Prospective study evaluating feasibility of automated 3D-HyFoSy (Exacoustos et al. 2017)	132	Oral azithromycin 1 g	• Pain assessments and AEs reported • Diluted foam
9	Prospective assessment of pain from HyFoSy compared to HyCoSy (Ludwin et al. 2017b)	300	175/300 patients received codeine and paracetamol	• Patients received HyCoSy followed by HyFoSy • Pain tracked for 24 hours
10	Prospective study assessing diagnostic performance of HyFoSy using laparoscopy with dye as a reference standard (Ludwin et al. 2017a)	132	Codeine and paracetamol	• Efficacy study with AEs reported
11	Prospective study assessing diagnostic performance of 2D- and 3D-HyFoSy using laparoscopy and dye as a reference standard (Riganelli et al. 2018)	50	None	• Efficacy study with pain assessment and AEs reported

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Study Design (Reference)	N	Medication	Comment(s)
12 Prospective assessment of diagnostic performance of HyFoSy using HSG as a reference standard (Rosic et al. 2018)	86	None	• Patients received HyFoSy followed by HSG. • Women status post Essure device
13 Retrospective: Questionnaire sent to physician asking for fertility, side effects, or complications post procedure (Tanaka et al. 2018)	200	None	• Immediate AEs reported for all patients, longer-term follow-up only in 155 patients
14 Prospective assessment of pain from HyFoSy compared to HSG (Zizolfi et al. 2018)	50	None	• Patients received HyFoSy followed by HSG. • Diluted foam

Abbreviations: AE, adverse event; HSG, hysterosalpingography; HyCoSy, hysterosalpingo-contrast sonography; HyFoSy, hysterosalpingo-foam sonography

ExEm Foam is marketed in the European Union and other countries. The Applicant estimates approximately (b) (4) exposures based on the number of units sold and submitted a summary of AEs from their pharmacovigilance database, described below.

Adequacy of Safety Database

AE reporting in the literature was variable. As indicated in Table 36 above, some studies (those performed to evaluate the diagnostic performance of HyFoSy) did not address AEs in their publications. Others as part of their prospective study design had formal assessments of pain using visual analog scales, sometimes comparing pain ratings from HyFoSy to pain ratings from another procedure such as HSG or HyCoSy. Use of pain medication and antibiotic prophylaxis was variable in the studies, reflective of clinical practice. Most patients were observed for AEs for a short time immediately after the HyFoSy procedure; only one study of 300 patients evaluated patients 24 hours after the procedure for pain (Ludwin et al. 2017b). Combined with the foreign postmarketing exposure, the size of the safety database is adequate.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Patient-level data were not provided from any of the published studies; submission quality is limited to quality of AE reporting in the published studies and the Applicant's postmarketing database.

8.2.4. Safety Results

Deaths

No deaths were reported in the literature.

Serious Adverse Events

No serious AEs were reported in the literature.

Dropouts and/or Discontinuations Due to Adverse Effects

In one study, it was reported that the HyFoSy procedure was abandoned in two women due to significant discomfort or vasovagal reaction (Tanaka et al. 2018). The other studies did not report early termination of the HyFoSy procedure due to adverse events.

Significant Adverse Events

Significant AEs requiring hospitalization were not reported in the literature studies. However, the foreign postmarketing database contains a report of tubo-ovarian abscess, a serious AE.

Treatment-Emergent Adverse Events and Adverse Reactions*Pain*

The most common safety assessment performed in the studies was for pain as measured by a visual analog scale with pain ratings either between 1 to 10 or 0 to 10. Several studies compared the pain related to HyFoSy to the pain related to another diagnostic test, such as HyCoSy, transvaginal ultrasound, or HSG. In most studies, the patients received both HyFoSy and the diagnostic comparator, and the order of examinations was fixed. If the diagnostic comparator was transvaginal ultrasound or HyCoSy, those exams were performed prior to HyFoSy in the same clinic visit. If the diagnostic comparator was HSG, HyFoSy was performed prior to HSG. In general, the studies found that HyFoSy had lower pain scores compared to HSG or transvaginal ultrasound.

Comment: The order of interventions was fixed for logistical reasons; therefore, the pain assessments for an examination may be biased by the order in which the examinations were performed. In general, the first tubal patency examination had lower pain ratings than the second tubal patency examination.

Table 37. Summary of Published Studies With Pain Assessments

Study (Author/Year)	N	Comparator	Premedication	Pain Score Results	Comment
1 (Dreyer et al. 2014)	19	HSG, patients enrolled to either HyFoSy or HSG arm	None	Median score HyFoSy: 1.7 Median score HSG: 3.7	Anesthesia pump used to instill foam to control pressure
2 (Dreyer et al. 2015)	26	HSG, patients underwent HyFoSy followed by HSG	500 mg naproxen night before and 2 hours before tests	Median score HyFoSy: 2.0 Median score HSG: 5.1	
3 (van Schoubroeck et al. 2015)	216	Transvaginal ultrasound, performed prior to HyFoSy	400 mg ibuprofen	Median score HyFoSy: 3.6 Median score transvaginal ultrasound: 1.5	
4 (Exacoustos et al. 2017)	132	None	None	Mean score during HyFoSy: 5.4 Mean score after HyFoSy: 4.2	Diluted foam
5 (Ludwin et al. 2017b)	300	HyCoSy, patients underwent HyCoSy followed by HyFoSy	175/300 patients received codeine and paracetamol	Median (mean) score HyFoSy: 2.0 (2.5) Median (mean) score HyCoSy: 2.0 (1.9) % of HyFoSy exams reported with moderate to severe pain: 25% % of HyCoSy exams reported with moderate to severe pain: 10%	Pain tracked for 24 hours

Study (Author/Year)	N	Comparator	Premedication	Pain Score Results	Comment
6 (Riganelli et al. 2018)	50	Pain scores of 2D- and 3D-HyFoSy	None	Mean score 3D imaging: 3.8 Mean score 2D imaging: 4.8	
7 (Tanaka et al. 2018)	200	None	None	2/200 patients complained of severe discomfort or vasovagal episode leading to discontinuation	
8 (Zizolfi et al. 2018)	50	HSG, patients underwent HyFoSy followed by HSG	None	Mean score HyFoSy: 1.6±2.5 Mean score HSG: 4±2.95	Diluted foam

Abbreviations: HSG, hysterosalpingography; HyCoSy, hysterosalpingo-contrast sonography; HyFoSy, hysterosalpingo-foam sonography

One study randomized patients to either HyFoSy or HSG (N=19 for HyFoSy and N=20 for HSG) (Dreyer et al. 2014). To further control for differences in instillation pressure related to the operator instilling the agent, an anesthesia pump was used to instill the contrast agent. The median visual analog scale score for HyFoSy was 1.7 while the median visual analog scale score for HSG was 3.7.

Vasovagal reactions

Other than pain, the most common AE reported during HyFoSy was vasovagal reaction.

Table 38. Patients With Vasovagal Reactions in HyFoSy Studies

Study	Total Number of Patients	Number of Patients With Vasovagal Reactions (%)
Emanuel et al. ^a	73	5 (6.8)
Exacoustos et al. ^b	132	2 (1.5)
Ludwin et al. ^c	300	3 (1.0)
Rosic	86	1 (1.2)
Tanaka	213	2 (0.9)

^a Emanuel MH, van Vliet M, Weber M, Exalto N, 2012, First experiences with hysterosalpingo-foam sonography (HyFoSy) for office tubal patency testing, Human Reproduction, 27(1): 114-117

^b Exacoustos C, T berio F, Szabolcs B, Romeo V, Romanini E, Zupi E, 2015, Can tubal flushing with hysterosalpingo-foam sonography (HyFoSy) media increase women's chances of pregnancy?, Journal of Minimally Invasive Gynecology, 22:S238

^c Ludwin I, Martins WP, Nasti CO, Ludwin A, 2017, Pain Intensity During Ultrasound Assessment of Uterine Cavity and Tubal Patency With and Without Painkillers: Prospective Observational Study, Journal of Minimally Invasive Surgery, 24(4):599-608

8.2.5. Analysis of Submission-Specific Safety Issues

Inflammation Related to ExEm Foam Resulting in Scarring of Female Reproductive Tract Impacting Fertility

No literature reports of adhesions, scarring, or inflammation of the fallopian tubes, uterus, or ovaries as a result of exposure to the foam or its components, HEC or glycerol, were found.

(b) (4)

(b) (4)

Biocompatibility testing for the gel was included with the NDA submission and included acute systemic toxicity, cytotoxicity, and sensitization.

(b) (4)

To address the potential for inflammation or scarring of the fallopian tubes and uterus related to ExEm Foam use, the Applicant was asked to compare the pH and osmolality of the foam to the pH and osmolality of the female reproductive tract. In response, the Applicant submitted SDN 7 (1.11.1 Quality Information Amendment January 25, 2019) where the pH range of the product was (b) (4) 6.0 to 7.5. This range was chosen based on animal studies where the pH in the uterus and the fallopian tubes was between 7.22 to 7.94 (Ng et al. 2018).

The calculated osmolality for the foam is 462 mOsm/kg (SDN 11, 1.11.1 Quality Information Amendment, submitted March 14, 2019). For reference, Omnipaque 240 and 300, which are approved contrast agents for HSG have osmolalities of 520 and 672 mOsm/kg. The Applicant stated that (b) (4) has been placed inside the uterus for gel infusion sonography (not as a coupling agent but as an imaging agent). No AEs of uterine scarring or inflammation have been reported to FDA stemming from such use.

Infection

The risk of infection related to HSG is 1% (Lee 2019). In the pain assessment study by Ludwin of 300 patients evaluated with both saline-air HyCoSy and HyFoSy, one AE of adnexitis (0.3%) and one AE of fever (0.3%) were reported (Ludwin et al. 2017b). The remainder of the submitted literature papers did not report infection or infection-related AEs. Usage of antibiotic prophylaxis was variable in the studies.

As described in Section 8.2.7, two postprocedure infection-related complications were reported to the Applicant. One was pelvic inflammatory disease (PID) and the other salpingitis with tubo-ovarian abscess. The Applicant stated that 2.5% of patients undergoing HSG develop PID but did not provide a reference for this figure. Tubo-ovarian abscess is a serious complication particularly in the infertile woman, and the optimal treatment may require surgery.

The 2015 American Institute of Ultrasound In Medicine Practice Parameter for the Performance of Sonohysterography contraindicates the procedure in women with pelvic infection or unexplained pelvic tenderness which could indicate PID. The practice parameter does not specifically recommend testing for infection prior to the examination and states only that antibiotic prophylaxis may be considered.

The PI for Lipiodol includes several comments about PID and endocervicitis. Use of the contrast agent in HSG in acute PID or endocervicitis is contraindicated. Exclusion of these conditions prior to the procedure is recommended. Exacerbation of PID is included in the postmarketing adverse reactions section. The Omnipaque label does not address specific contraindications for HSG.

Procedure-Related Embolization or Contrast Intravasation

The prevalence of contrast agent intravasation during HSG has been reported to be 0.4% to 6.9% (Bhoil et al. 2016). This complication is the result of “backflow of injected contrast into the adjoining vessels.” The contrast passes from the uterine cavity to the myometrial veins and eventually into the pelvic veins and inferior vena cava. Conditions that increase endometrial vascularity and permeability are predisposing risk factors for contrast intravasation. Contrast intravasation may result in complications such as pulmonary embolization. Patients may present with coughing or dyspnea. The risk of pulmonary embolization related to intravasation of Lipiodol is included in its PI.

There were no reports in the literature or complaints in the Applicant database of HyFoSy procedure-related intravasation or embolization or symptoms consistent with such complications. However, the ultrasound imager may not easily visualize the occurrence of foam intravasation, as the imaging plane of the uterus and fallopian tubes will likely be in a different plane than the pelvic and myometrial veins. Therefore, to specifically evaluate for this complication when the patient is asymptomatic, the imager would have to (1) move the probe towards these veins and (2) recognize the presence of echogenic material within the veins (which are normally anechoic). This is in contrast to HSG, where the entire pelvis is imaged in a single field-of-view during the procedure. As a result, opacification of the pelvic and myometrial veins by contrast is immediately visible when contrast intravasation occurs on HSG.

The risk related to foam intravasation and embolization was further assessed by evaluating the consequences of intravasation and embolization of IV air, HEC, and glycerol at the volumes used in creating the foam.

The labeling for CDRH-cleared devices that mix saline and air for sono-HSG/HyCoSy, FemVue (K110288) and SonoFlow (K142545), address the risk of air embolism. The FemVue label includes the following warning: “CAUTION: In order to minimize the risk of air embolism, do not exceed delivery of six (6) filled syringe volumes to the patient. Air embolism has not been reported with saline-air contrast volumes below 70 mL” (FemVue 2019). In contrast, the maximum volume of the foam is 10 mL, of which air is a very small component given that the foam is composed of 5 mL of clear gel and 5 mL of sterile purified water. Further, a review of the AEs reported to the FDA related to use of the FemVue and SonoFlow devices revealed no complaints related to intravasation or embolization. A review article on vascular air embolism classifies volumes of acute air embolism <0.5 mL/kg as small and often well tolerated (Mirski et al. 2007).

There is preclinical evidence demonstrating the safety of IV glycerol and HEC. Glycerol is also used as an inactive ingredient in FDA-approved products for IV administration as per the FDA Inactive Ingredient Database.

8.2.6. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Several studies excluded women with history of gynecologic cancer (Exacoustos et al. 2017; Ludwin et al. 2017a; Ludwin et al. 2017b; Piccioni et al. 2017; Riganelli et al. 2018). ExEm Foam is contraindicated in women with known or suspected reproductive tract malignancy due to risk of retrograde/peritoneal spread of tumor.

Long-term complications from HyFoSy related to tumor development or carcinogenicity have not been reported or assessed clinically. See Section 5.5 for additional information.

Human Reproduction and Pregnancy

ExEm Foam is contraindicated for use in sono-HSG due to risk of fetal harm. Several studies confirmed that the patients enrolled in the study were not pregnant prior to HyFoSy and/or scheduled the procedure during the proliferative phase of the menstrual cycle to minimize chance of pregnancy during HyFoSy. The studies did not assess risk of fetal harm related to the procedure. The Division of Pediatric and Maternal Health also performed a literature search of the PubMed, Embase, Micromedex, TERIS, Reprotox, and Briggs databases to find additional relevant articles not cited by the Applicant.⁶ No additional relevant articles were retrieved. See Section 5.5 for additional information.

⁶ DPMH consult for NDA 212279 April 16, 2019.

Pediatrics and Assessment of Effects on Growth

No studies were performed in pediatric patients. The safety and effectiveness of ExEm Foam have not been established in pediatric patients.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The product will be instilled into the uterus by the health care provider, most likely a gynecologist, radiologist, or medical staff under the provider's supervision. As the Applicant states, unnecessarily large volumes of foam may result in increased pain or vasovagal incidents, the provider will therefore instill only the amount of foam needed to achieve adequate evaluation of tubal patency. The total volume of foam to be used will be less than 10 mL. The median volume of foam used in the procedure was 3.5 mL (Dreyer et al. 2015). There is no potential for overdose or drug abuse.

8.2.7. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The product is approved in Europe and other countries as a medical device and is patient to the regulatory oversight of the European Union authorities. MedDev 2.12-1 requires "maintenance of a vigilance system for collecting and assessing information on potential incidents involving device malfunctions or injuries." Events requiring reporting include those that relate to "malfunction or deterioration in the characteristics and/or performance of its product, as well as any inadequacy in the labeling or the instructions for use which, directly, or indirectly, might have led to the death of a patient, or user, or of other persons, or to a serious deterioration in the state of health." Serious deterioration in the state of health includes:

- Life-threatening illness
- Permanent disability
- Condition requiring medical or surgical intervention to prevent life-threatening illness or permanent disability
- Any indirect harm as a consequence of the use of an in vitro fertilization/assisted reproductive treatment device
- Fetal distress, fetal death, or any congenital anomaly or birth defect

In addition to MedDev 2.12-1, the Applicant's surveillance and reporting system must comply with ISO-13485 (Medical devices—Quality management systems—Requirements for regulatory purposes). Per the International Organization of Standardization (ISO) website, this is as "an internationally agreed standard that sets out the requirements for a quality management system specific to the medical devices industry" (ISO 2016). The Applicant undergoes routine regulatory audits to assess postmarketing safety compliance during renewal of ISO-13485 certifications.

The Applicant estimates based on the number of units sold that (b) (4) HyFoSy procedures have been performed in the postmarket setting. The Applicant reviewed their complaint files and reports 12 complaints since commercial launch in 2010, of which none were considered serious AEs by the Applicant. The majority of events reported were pain and vasovagal episodes, side effects related to the sono-HSG procedure rather than directly related to ExEm Foam. In 2015, the volume of ExEm Foam produced by the kit was reduced from 20 mL to 10 mL as a lower volume was found to be sufficient for evaluating tubal patency. The Applicant postulates that larger volumes of instilled foam may increase the incidence of pain and vasovagal reactions.

The Applicant submitted a Complaint Summary Record, which is summarized in Table 39.

Table 39. Foreign Postmarketing Complaint Summary Record

	Date of Receipt	Description	Assessment by Applicant	Action
1	08-11-2011	Pain/vasovagal reaction	AEs related to the volume of foam	Reduced maximum foam volume to 10 mL
2	03-13-2012			
3	02-20-2014	Abdominal pain	AEs procedure-related, not unique to the foam	
4	06-29-2014			
5	09-12-2014			
6	02-03-2016	PID	AEs procedure-related, not unique to the foam. Applicant states 2.5% of patients undergoing HSG develop PID	
7	05-26-2016	Salpingitis with tubo-ovarian abscess		
8	11-24-2016	Mild redness/face rash 4 days after the procedure	Allergic reaction, not related to foam or its components.	<i>Comment: No information regarding concomitant medications such as antibiotics or analgesics</i>
9	12-08-2016	Abdominal pain	AE procedure-related, not unique to foam	
10	05-29-2017	Pain with inflation of balloon catheter	AE procedure-related, not unique to foam	
11	06-06-2017	Dysrhythmia 1 day after procedure	Unrelated to foam	
12	10-30-2017	Faint/collapse for a few seconds during procedure	AE procedure-related, not unique to foam	
13	07-09-2018	Vasovagal reaction (several patients)	AE procedure-related, not unique to foam	

Abbreviations: AE, adverse event; HSG, hysterosalpingography; PID, pelvic inflammatory disease

As the Applicant did not view any of these complaints as meeting criteria for a serious incident that was unexpected with relationship to the product, these AEs were not reported to the regulatory authorities.

8.2.8. Integrated Assessment of Safety

Based on the foreign postmarketing experience and the experience in the literature, it is expected that patients who undergo HyFoSy will experience symptoms related to the procedure itself such as pain, vasovagal reaction, and spotting. The incidence of infections is expected to be rare and likely within the range seen with HSG and HyCoSy. The product will be contraindicated in women with known or suspected genital tract infection or inflammation and in women who have had a gynecologic procedure within the last 30 days to minimize the risk of postprocedure gynecologic infection. An adverse reaction related to ExEm Foam itself or its components is unlikely. Peritoneal or reproductive tract scarring is not expected. The literature search does not show evidence of a risk of scarring. The pH of the female reproductive tract is comparable to the pH of ExEm Foam. The product has a lower osmolality compared to other approved agents for HSG, and it is intended for one-time use. Regardless, the potential for scarring will be monitored in the postmarket setting.

8.3. Statistical Issues

This application is based on published medical literature. Except for (Ludwin et al. 2017a), which studied 132 patients (259 tubes), the study sample size was generally small (18 to 25 patients with 36 to 50 tubes). Diagnostic performance on sensitivity and specificity were prespecified in some studies (Ludwin et al. 2017a; Piccioni et al. 2017), whereas two studies (van Schoubroeck et al. 2013; Riganelli et al. 2018) lacked such prespecification. It is unclear whether the analysis results of the Riganelli et al. study (2018) were performed on a tube-level or on a patient-level; sensitivity and specificity were not defined. Based on the statistical team's review, results presented in the paper are suspected to be on a tube-level.

8.4. Conclusions and Recommendations

The benefit risk of ExEm Foam is favorable. The diagnostic performance of HyFoSy is in comparison to the reference standard is acceptable. Based on the literature and the foreign postmarketing experience, the product does not appear to pose additional concerns of safety beyond the risks already expected with sono-HSG or HSG.

9 Advisory Committee Meeting and Other External Consultations

This NDA was not taken to FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for the class, and there were no controversial issues that would benefit from advisory committee discussion.

10 Pediatrics

No studies were performed in pediatric patients. The Applicant submitted a waiver for pediatric studies. The safety and effectiveness of ExEm Foam have not been established in pediatric patients. However, pediatric use of HyFoSy is not expected.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

The following is a high-level review of major changes to the PI, presented by section.

Product Title Applicant Proposed: ExEm Foam, (b) (4)	Agreed-Upon Language: ExEm Foam (air polymer-type A) intrauterine foam
Justification: The supplicant did not propose a nonproprietary name. The OPQ reviewer worked with the Applicant to establish the chemical name, dosage form, and ROA. The nonproprietary nomenclature was based on the model for ultrasound contrast agents where the chemical name is comprised of the components of the bubble [gas, shell]. Therefore, the template for the established name was [chemical name][route][dosage form].	
Indications and Usage (1) Applicant Proposed: ExEm® Foam is indicated for (b) (4) in women with known or suspected infertility (b) (4).	Agreed-Upon Language: ExEm® Foam is indicated for <u>sonohysterosalpingography</u> to assess fallopian tube patency in women with known or suspected infertility.
Justification: (b) (4) is not a diagnostic term in the United States. Reworded for clarity and to align with the wording of other diagnostic agents.	
Dosage and Administration (2) The entire section was edited. Outlining detailed changes is outside the scope of this summary. The major changes and their justifications were: • (b) (4) 2 DOSAGE AND ADMINISTRATION. Detailed preparation instructions (b) (4). • Removed (b) (4). Retained succinct administration instructions pertinent to the drug. • Removed (b) (4). • Instillation of the foam was recommended with a 5-Fr catheter as these were used in the clinical studies. • Imaging Guidance (2.4) was changed to reflect the data in the clinical studies and the convention of current clinical practice in the United States. The Applicant proposed to expand the definition of a patent tube to include the finding of a thin bright line (visualizing foam in the tube) (b) (4). Based on the clinical evidence, the review team agreed that documentation of peritoneal spillage is the only finding adequate to establish tubal patency. Likewise, the absence of peritoneal spillage suggests the presence of an occluded tube. See Section 8.1.1.2 for details.	

Dosage Forms and Strengths (3) Applicant Proposed: (b) (4)	Agreed-Upon Language: Intrauterine Foam, single-dose kit containing: • Syringe A: one syringe with 5 mL clear gel [polymer-type A (hydroxyethyl cellulose), glycerin, and purified water] • Syringe B: one syringe with 5 mL sterile purified water • One Combifix® Adaptor (coupling device) When prepared as directed, ExEm Foam will contain more than 10,000 to 127,000 bubbles per mL.
Justification: (b) (4) FDA recommended labeling the contents of the kit to clearly depict the contents of each syringe. They are alternatively named Syringe A and B. The concentration of bubbles in the reconstituted product was required and placed in 3 DOSAGE AND STRENGTHS, similar to labeling for other ultrasound contrast agents. One might argue that this could be placed only in the product quality section (11 DESCRIPTION); however, it remains important for the end user, is critical to imaging, and is congruent with previous labeling decisions with similar products.	
Contraindications (4) Applicant Proposed: (b) (4)	Agreed-Upon Language: ExEm Foam is contraindicated for use in: • Pregnancy <i>[see Warnings and Precautions (5.1)]</i> • Patients with known or suspected lower genital tract inflammation or infection <i>[see Warnings and Precautions (5.2)]</i>. • Patients who have had a gynecologic procedure within the last 30 days <i>[see Warnings and Precautions (5.2)]</i>. • Patients with vaginal bleeding – Due to the risk of intravasation of ExEm Foam as a result of exposure of the endometrial vessels during bleeding, and – Due to the potential risk of endometriosis as a result of seeding the peritoneum with endometrial tissue. • Patients with known or suspected reproductive tract neoplasia due to the risk of peritoneal spread of neoplasm
Justification: The main mechanism of the contraindication is the procedure: HSG with intrauterine infusion of the medication. Therefore, the review team maintained the contraindication for pregnancy and added contraindications related to the procedure. The procedure should not be done in patients who are pregnant, have a genital tract infection, are within 30 days of a gynecologic procedure, have active vaginal bleeding, and known or suspected gynecologic tract neoplasm, due to the risks described above. According to 21 CFR 201.57(a)(9), a contraindication is not based on a theoretical risk. Therefore, the contraindication (b) (4)	

Warnings and Precautions (5) Applicant Proposed: (b) (4)	Agreed-Upon Language: 5.1 Risk for Fetal Harm ExEm Foam is contraindicated for use in pregnancy due to the potential risk of fetal harm 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) [see <i>Contraindications (4)</i>]. 5.2 Risk for Post-Procedure Gynecologic Infections There is a risk of post-procedure gynecological infections when ExEm Foam is used in sonohysterosalpingography. ExEm Foam is contraindicated for use in patients with known or suspected genital tract inflammation or infections (e.g., pelvic inflammatory disease (PID) or suspected sexually transmitted disease) even if the patient is receiving antimicrobial therapy. ExEm Foam is contraindicated in patients who have had a gynecologic procedure within the past 30 days (e.g., curettage or conization) due to the risk of post-procedure infections [see <i>Contraindications (4)</i> and <i>Adverse Reactions (6.2)</i>].
Justification: The warnings were restated in the “risk-mitigation” format. Typically, the risk from the contraindications may be included as a warning; however, not all of the contraindications were included as warnings. (b) (4) were omitted because (b) (4). Although there were risks associated with the contraindication, there were no mitigation steps other than not performing the sono-HSG procedure. The contraindication captured this message. For the pregnancy contraindication, there are mitigation steps pertinent to the risk of fetal harm; therefore, the warning about it was included. The contraindications not to use with known or suspected gynecologic infection or after recent gynecologic procedure were made into a warning: Risk for Post-Procedure Gynecologic Infections. Although the only mitigation is to not perform the sono-HSG procedure, a warning was included because infection is a known adverse reaction post sono-HSG; therefore, it is a true risk rather than a potential risk based on the procedure.	
Adverse Reactions (6) The Applicant proposed (b) (4) The adverse reactions section was reorganized to focus on the adverse reactions from the efficacy trials included in 14 CLINICAL STUDIES, as well as the foreign postmarketing experience.	
(b) (4)	
Use in Special Populations (8) Labeling Sections 8.1 Pregnancy, 8.2 Lactation, and 8.3 Females and Males of Reproductive Potential were reworded to comply with PLLR. Section 8.3 was further edited to remove (b) (4) Section 8.4 Pediatric Use was updated to comply with 21 CFR 201.57(c)(9)(iv). (b) (4)	

Description (11) The entire section was edited to comply with 21 CFR 201.57(c)(12). ExEm Foam (air polymer-type A) is intrauterine foam provided as a kit. The content of the kit, including the product quality attributes, were included in the labeling. The product quality of the reconstituted foam was also detailed.	
Clinical Studies (14) Applicant Proposed: The applicant proposed (b) (4) (b) (4) Ludwin Study, Riganelli Study, (b) (4) (b) (4)	Agreed-Upon Labeling: Study A (Riganelli Study) Study B (Ludwin Study) (b) (4)
Justification: The review team kept the two studies that assessed the performance of sono-HSG with ExEm Foam for the diagnosis of tubal patency in women with infertility using laparoscopy with chromopertubation as the reference standard. (b) (4) (b) (4) The Riganelli study was renamed "Study A" and described first. Since the data were taken from the literature and could not be independently verified, the review team described the performance as "tubes that were correctly identified as occluded" and "tubes that were correctly identified as patent." The Ludwin study was renamed "Study B." It was ordered second (b) (4) (b) (4) The same rationale applies for the review team's preference to summarize the results of Study B in general terms: "The performance estimates in Study B were numerically similar to those reported in Study A." (b) (4)	
How Supplied/Storage and Handling (16) The How Supplied portion of Section 16 was updated to reflect the team's thinking regarding naming of the kit components. Storage and handling information proposed in 2 DOSAGE AND ADMINISTRATION was moved to the appropriate section of the PI.	

12 Office Director (or Designated Signatory Authority) Comments

The Office Director concurs with the interpretation of the data by the review team and agrees with the recommendation to approve the drug.

13 Appendices

13.1. References

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13.2. Financial Disclosure

In a response to clinical IR received December 6, 2018, for financial disclosure information, the Applicant submitted Form 3454 and provided the following information:

- Dr. Niek Exalto and Dr. Mark Hans Emanuel are the inventors of ExEm Foam and hold the patents. These physicians each hold (b) (4)% ownership in Giskit B.V. There was one submitted publication from Drs. Exalto and Emanuel (Emanuel et al. 2012) submitted in the NDA for safety. However, the Applicant does not consider this publication as a covered study for two reasons: (1) it is not being used to support the product's efficacy and (2) the number of patients included in the study do not constitute a significant proportion of the Applicant's literature safety database (4.6%, or 73 of the 1,578 patients).
- The Applicant excluded a publication by C. Exacoustos (Exacoustos et al. 2015) as a covered study because it was a poster presentation with limited contribution to the safety and efficacy of the product.
- Otherwise, option 2 was checked on Form 3454: "As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study; had no proprietary interest in this product or significant equity interest in the sponsor of the covered study; and was not the recipient of significant payments of other sorts."

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/s/

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