

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203684Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: September 2, 2014

Reviewer(s): Amarilys Vega, M.D., M.P.H, Medical Officer
Division of Risk Management (DRISK)

Team Leader: Doris Auth, Pharm.D, Team Leader
DRISK

Division Director: Cynthia LaCivita, Pharm.D, Acting Director
DRISK

Subject: Evaluation of need for a REMS

Drug Name(s): Sulfur hexafluoride lipid microsphere
(kit for preparation of injectable suspension)

Therapeutic Class: Ultrasound contrast media (ATC class: V08DA)

Dosage and Route: 25 mg sterile, non-pyrogenic lyophilized powder in a
(b) (4)-sealed vial

Application Type/Number: NDA 203684

Submission Number: Resubmission Class 2; Sequence No. 0023 (21)

Applicant/sponsor: Bracco Diagnostics Inc.

OSE RCM #: 2014-850

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that should not be released to the public**

1 INTRODUCTION

This review documents the Division of Risk Management's (DRISK) evaluation of whether a Risk Evaluation and Mitigation Strategy (REMS) is necessary for sulfur hexafluoride lipid microsphere for injection (NDA 203684).

Bracco Diagnostics is seeking approval of sulfur hexafluoride lipid microsphere for injection for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

DRISK reviewed the applications for sulfur hexafluoride lipid microsphere for injection submitted to FDA on December 21, 2011 (original application) and May 5, 2013 (class 2 resubmission) and determined that a REMS was not required to manage the serious risks associated to this product (i.e., serious cardiopulmonary reactions). See DRISK reviews dated August 21, 2012 and October 24, 2013.¹

A complete response (CR) letter was issued on November 27, 2013. The CR letter cited manufacturing facilities deficiencies. A class 2 resubmission was received by FDA on April 11, 2014 including the Applicant's response to the deficiencies identified in the CR letter, revised labeling, and a safety update.

Bracco Diagnostics did not include a REMS or risk management plan in this resubmission.

The proprietary name, Lumason[®], was approved by FDA on November 4, 2013.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Amarilys Vega MD, MPH: DRISK Reviews, dated August 21, 2012 and October 24, 2013.
- Lumason, resubmission cover letter, April 11, 2014.
- Lumason proposed label, April 11, 2014.
- Lumason safety update, dated February 25, 2014.
- Scheldon Kress, MD: Lumason, medical officer's resubmission safety review, Division of Medical Imaging Products, June 10, 2014.

3 RESULTS OF REVIEW

Lumason is associated with serious life-threatening anaphylactic and anaphylactoid reactions which occur infrequently (1 in 10,000 exposures). The data included in the safety update did not show any significant increase in the incidence of Lumason-related serious life-threatening events.

¹ Amarilys Vega, MD, MPH: DRISK Review for sulfur hexafluoride lipid microsphere for injection (NDA 203684), dated August 21, 2012 and October 24, 2013.

4 CONCLUSIONS AND RECOMMENDATIONS

Data included in the April 11, 2014 submission did not change the known safety profile of Lumason. DRISK's original recommendation that a REMS is not required to manage the serious risks associated to sulfur hexafluoride lipid microsphere for injection remains unchanged.

Please contact DRISK if you have any questions.

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/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Management Options Review-Addendum

Date: 10/24/2013

Reviewer(s): Amarilys Vega, M.D., M.P.H, Medical Officer
Division of Risk Management (DRISK)

Team Leader: Cynthia LaCivita, Pharm.D., Team Leader
DRISK

Division Director: Claudia Manzo, Pharm.D, Director
DRISK

Drug Name(s): Sulfur hexafluoride lipid microsphere
(kit for preparation of injectable suspension)

Therapeutic Class: Ultrasound contrast media (ATC class: V08DA)

Dosage and Route: 25 mg sterile, non-pyrogenic lyophilized powder in a
(b) (4)-sealed vial

Application Type/Number: NDA 203684

Submission Number: ORIG-1 Resubmission/Class 2; Sequence No. 0017

Applicant/sponsor: Bracco Diagnostics Inc.

OSE RCM #: 2013-2099

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1 INTRODUCTION

This document is an addendum to DRISK's August 21, 2012 review of the Sponsor's proposed risk management approach for sulfur hexafluoride lipid microsphere for injection (NDA 203684).¹ In this addendum, DRISK documents its evaluation of Bracco Diagnostics Inc. resubmission of their risk management approach for sulfur hexafluoride lipid microsphere received on May 31, 2013.

Sulfur hexafluoride lipid microsphere for injection is proposed for use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation.

The initial application for sulfur hexafluoride received a complete response letter dated October 19, 2012 due to manufacturing facility- and product quality-related issues.² The primary safety concerns with sulfur hexafluoride involved anaphylactoid type reactions and serious cardiovascular events occurring immediately after product administration. Definity and Optison, other contrast agents approved in the US for echocardiography, also have a risk for cardiopulmonary reactions, which is managed through labeling (a boxed warning for serious cardiovascular events) and routine pharmacovigilance.

The proprietary names SonoVue and (b) (4) were deemed unacceptable by the Division of Medication Error Prevention and Analysis (DMEPA). On September 13, 2013 Bracco submitted a new proprietary name, Lumason, which is currently under review by DMEPA.³

2 REVIEW FINDINGS AND RECOMMENDATIONS

The submission from May 2013 addressed the deficiencies listed in the complete response letter from October 2012 and did not document additional changes to the safety profile of sulfur hexafluoride. Bracco included in the proposed label a boxed warning similar to that included in Definity and Optison labels.

DRISK's recommendation to manage the risks associated to sulfur hexafluoride lipid microsphere for injection through labeling, that is, a boxed warning for serious cardiopulmonary reactions and inclusion of anaphylactoid reactions in the Warnings and Precautions section of label, remains unchanged.

Please contact DRISK if you have any questions.

¹ Amarilys Vega, MD, MPH: DRISK review, dated August 21, 2012.

² Charles Ganley/Susan Johnson: Complete Response letter, dated October 19, 2013.

³ Sulfur Hexafluoride lipid microsphere for injection, proprietary name submission, dated September 13, 2013.

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Management Options Review

Date: 8/21/2012

Reviewer(s): Amarilys Vega, M.D., M.P.H, Medical Officer
Division of Risk Management (DRISK)

Team Leader: Cynthia LaCivita, Pharm.D., Team Leader
DRISK

Division Director: Claudia Manzo, Pharm.D, Director
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Drug Name(s): Sulfur Hexafluoride Microbubbles (SonoVue[®])

Therapeutic Class: Ultrasound contrast media (ATC class: V08DA)

Dosage and Route: 25 mg sterile, non-pyrogenic lyophilized powder in a
(b) (4)-sealed vial

Application Type/Number: NDA 203-684

Submission Number: Sequence No. 0000

Applicant/sponsor: Bracco Diagnostics Inc.

OSE RCM #: 2012-440

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1 INTRODUCTION

This review documents DRISK's evaluation of the proposed Risk Management Plan (RMP) for Sulfur hexafluoride microbubbles (SonoVue™, NDA 203-684) by Bracco Diagnostics Inc. SonoVue is indicated for use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation.

SonoVue is formulated as a 25 mg sterile, non-pyrogenic lyophilized powder in a (b) (4)-sealed vial. The lyophilized powder is made of a combination of pharmaceutical grade polyethylene glycol 4000, phospholipids, and palmitic acid. The gas phase in the vial is Sulfur Hexafluoride (SF₆), an innocuous gas. The microbubble dispersion is prepared before use by injecting (b) (4) 5 mL of sodium chloride injection, USP (0.9% w/v) to the content of the vial.

SonoVue, approved in 36 countries and is marketed in 25 countries, is indicated for use with echocardiography. During worldwide market use (April 01, 2001 through September 30, 2011), an estimated (b) (4) patients have been exposed to SonoVue.

1.1 BACKGROUND

1.2 REGULATORY HISTORY

- **December 23, 1994** – Initial submission to FDA of IND 46958 for initiation of clinical trials in the United States to support the use of SonoVue for echocardiography (NDA 21-135).
- **January 29, 2001** – Bracco submitted an NDA for use of SonoVue in echocardiography in patients with suspected or established cardiovascular diseases to improve visualization of cardiac chambers and endocardial border delineation.

(b) (4)

- **December 20, 2007** – Bracco withdrew NDA 21-315.
- **June 24, 2008** – FDA invited Bracco to present on SonoVue at the Cardiovascular and Renal Drugs Advisory Committee meeting, “Safety Considerations in the Development of Ultrasound Contrast Agents”. The manufacturers of Definity™ and Optison™, other contrast agents used in echocardiography, also presented data on their products during this meeting.
- **November 2, 2009** – Pre-NDA meeting for the following indication: “use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation”. Pre-NDA meeting agreements:
 - FDA agreement
 - Primary database could rely on 3 prior confirmatory studies
 - FDA recommendations to complete prior to NDA submission:
 - Pulmonary hemodynamic study
 - Retrospective observational study among critically ill patients
 - FDA recommended completion as Post-marketing Requirement
 - 1,000 subject prospective “safety study”
- **May 2, 2011** – FDA invited Bracco to present on SonoVue at the Cardiovascular and Renal Drugs and the Safety and Risk Management Advisory Committee joint meeting to discuss the safety of ultrasound contrast agents. The manufacturers of Definity™ and Optison™ also presented data on their products during this meeting. The Committee raised concerns regarding the validity of retrospective studies conducted with Definity and Optison and the limitations of the (b) (4) and propensity score matched analyses. Committee members also made comments about the absence of significant pulmonary hemodynamic effects by ultrasound contrast agents.
- **July 14, 2011** – Bracco seeks FDA guidance in a face-to-face meeting. FDA Meeting agreements: (1) retrospective observational study no longer required prior to submission of NDA, (2) results of pulmonary hemodynamic study (BR1-133) could be submitted with NDA.
- **October 3, 2011** – The International Contrast Ultrasound Society submitted a Citizen Petition requesting FDA to remove the boxed warning on ultrasound contrast agents and to modify the warning language that appears outside the box. As of the date of this review, FDA has not issued a response to this Citizen Petition (TSI # 001300).
- **October 6, 2011** – Bracco presented FDA a preview of the NDA to be submitted for use in echocardiography with indication for left ventricular opacification and endocardial border delineation.

- **October 24, 2011** – FDA approved labeling changes for Definity representing the best consensus agreement between the totality of the safety data, FDA review, and Advisory Committee recommendations. The labeling changes still included a boxed warning.
- **December 21, 2011** – Bracco submitted NDA 203-684 for SonoVue, seeking an indication for use in echocardiography in patients with suboptimal echocardiograms to obtain left ventricular opacification and improve endocardial border delineation.

1.3 OTHER PRODUCTS USED IN ECHOCARDIOGRAPHY

Definity™ (Perflutren Lipid Microsphere)¹ and Optison™ (Perflutren Protein-Type A Microspheres)² are other FDA-approved products indicated for echocardiography. Both products have a boxed warning.

DEFINITY:

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perflutren-containing microsphere administration [see WARNINGS AND PRECAUTIONS (5.1)]. Most serious reactions occur within 30 minutes of administration.

- Assess all patients for the presence of any condition that precludes DEFINITY® administration [see [CONTRAINDICATIONS \(4\)](#)].
- Always have resuscitation equipment and trained personnel readily available.

OPTISON:

WARNING: Serious Cardiopulmonary Reactions

Serious cardiopulmonary reactions, including fatalities, have occurred during or following perflutren-containing microsphere administration.

- Assess all patients for the presence of any condition that precludes OPTISON administration (see [CONTRAINDICATIONS](#)).
- In patients with pulmonary hypertension or unstable cardiopulmonary conditions, monitor vital sign measurements, electrocardiography, and cutaneous oxygen saturation during and for at least 30 minutes after OPTISON administration (see [WARNINGS](#)).
- Always have resuscitation equipment and trained personnel readily available.

¹ DEFINITY – Activated DEFINITY® (Perflutren Lipid Microsphere) Injectable Suspension is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. Source: Product label.

² OPTISON - Optison™ (Perflutren Protein-Type A Microspheres) is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricle and to improve the delineation of the left ventricular endocardial borders. Source: Product label.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- SonoVue (sulfur hexafluoride microbubbles for injection), Introduction, Clinical Overview, Risk Management Plan, Summary of Clinical Safety, proposed label, Bracco Diagnostics Inc., December 21, 2011.
- TSI # 001300 - Octafluoropropane microbubble contrast agent (Definity, Optison); CP Remove Box Warning Ultrasound Contrast Agents; Sequence No.0001 (Citizen Petition) and 0002 (Division of Medical Imaging Products draft memo).
- Scheldon Kress, MD: SonoVue (sulfur hexafluoride microbubbles for injection), Mid-cycle clinical presentation, June 28, 2012.

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM OR POSTMARKETING EXPOSURE

The objectives of the clinical development program were: (1) determine the optimal dose of SonoVue for endocardial border delineation through provision of adequate and prolonged opacification of the left ventricular cavity; (2) compare the diagnostic performance of SonoVue to a control agent (Albunex³ and/or saline) in the delineation of the ventricular border; and (3) to evaluate the effectiveness of SonoVue in improving the delineation of the endocardial border in patients with suspected cardiac disease and suboptimal unenhanced echocardiography.

SonoVue's clinical development program included 866 subjects (718 subjects received SonoVue, 53 subjects received SonoVue and control (crossover study BR1-013). Listed below are the studies conducted in support of this NDA:

- 5 clinical pharmacology exploratory studies (BR1-001, BR1-001b, BR1-002, BR1-007, BR1-005)
- 2 prospective Phase II/III studies (437 patients)
 - BR1-011: 4 Doses at rest; 218 patients
 - BR1-012: 2 Doses (rest & stress); 219 patients
- 3 confirmatory studies (191/317 patients)
 - BR1-019A, BR1-019B, and BR1-013 rest

Primary objectives of studies 019A and 019B were to: (1) determine the optimal efficacious dose for SonoVue (based on Endocardial Border Delineation (LV EBD) and Left Ventricular Opacification (LVO) and duration of useful contrast enhancement); (2) compare the efficacy profile of the SonoVue dose regimen to control agent (based on LV EBD, LVO, and duration of useful contrast enhancement); and to assess the safety

³ Albunex: ultrasound contrast agent consisting of air-filled albumin microspheres suspended in a solution of 5% (w/v) human albumin. This was the only FDA approved agent at the time of the trials.

profile. The primary objective of study 013 was to compare two SonoVue doses to control on LV EBD.

The primary efficacy endpoints of SonoVue studies was to assess changes from baseline in total LV EBD score and the evaluation and quantification of improvement in chamber visualization compared with control. Secondary endpoints for all three studies were the duration of total contrast effect, duration of contrast shadowing, and diagnostic confidence. For study 013, additional endpoints include a comparison of Left Ventricular Ejection Fraction (LVEF) performed by SonoVue (echocardiography) and by radionuclide ventriculography.

3.2 EFFICACY FINDINGS

Clinical Trials

Following are key findings from confirmatory trials 019A, 019B, and 013.

- Significant increase of EBD scores when compared to baseline unenhanced echocardiography and to controls (saline or Albunex).
- Higher percentage of patients who converted from suboptimal to adequate image quality.
- Marked reduction in the proportion of patients with inadequate EBD in ≥ 1 segment, ≥ 2 segments, ≥ 2 adjacent segments, and in at least one or two critical segments could be observed with SonoVue.
- Higher percentage of patients with LVO scores of +2 or +3 when compared to patients in the control groups.
- Greater mean duration of useful contrast when compared to the highest dose of the comparator. Duration of useful contrast was dose-dependent and ranged from 1 minute to 4 minutes.

3.3 SAFETY FINDINGS

Clinical Trials

The safety database included 70 completed studies, 5,275 subjects (128 healthy volunteers and 5,147 patients). Five hundred seventy-two (10.8%) subjects experienced adverse events; 5.7% were study-related, but the majority were mild and resolved without sequelae. Serious adverse events were reported in 21 patients; 18 events were considered not related to SonoVue and two were of unknown relationship to SonoVue. Ten patients died, but none of these deaths was related to SonoVue. The most frequently reported adverse events ($\geq 0.5\%$ of patients) were headaches (2.1%), nausea (0.9%), chest pain (0.6%), chest discomfort (0.6%), and injection site pain (0.5%). All other events occurred at a frequency of $<0.5\%$.

Other important safety findings include the following:

- There were no significant differences observed in mean changes from baseline to “post dose” time points following SonoVue administration compared to placebo in

patients with congestive heart failure and pulmonary hypertension (defined as mean pulmonary arterial pressure at baseline ≥ 25 mmHg).

- SonoVue had no negative effect on pulmonary function in patients with chronic obstructive pulmonary disease and diffuse interstitial pulmonary fibrosis.
- In the continuous ECG studies,
 - there were no statistically significant differences in the maximum increases from baseline in corrected QT interval following administrations of SonoVue and placebo,
 - there was no evidence of a dose-response relationship or relationship to different mechanical indexes of ultrasound applied during echocardiography.
- SonoVue was safe in patients with documented severe coronary artery disease and in patients undergoing stress echocardiography.

Postmarketing Adverse Events

The reporting rate of serious adverse reactions with SonoVue is low and remained stable through time (ranging from 0.0110% to 0.0196%). From 2001 to September 30, 2011 the sponsor reports (b) (4) exposures to SonoVue with 450 adverse reactions of which 246 were considered serious. Serious cardiac-related events were reported at a rate of (b) (4)% of exposed cases (some cases associated to anaphylactoid reactions). The reporting rate of allergic-like reactions (anaphylactoid reaction/shock, anaphylactic reaction/shock, and hypersensitivity) is (b) (4)% (1 in 10,000).

The adverse events most frequently reported were headache (2%), nausea (1%), chest pain (1%), chest discomfort (1%), and injection site pain (0.5%). The safety database included nine deaths since the launch of the product in 2001. For seven of the nine deaths, an association with the use of SonoVue could not be ruled out; the remaining two cases were not related to SonoVue.

Literature search

The results of a literature review conducted by the sponsor demonstrated to be consistent with the results from the clinical trials in the SonoVue program.

4 SPONSOR'S PROPOSED RISK MANAGEMENT APPROACH

The sponsor proposed to manage the risk of cardiopulmonary reactions and hypersensitivity through labeling, including a boxed warning, and routine pharmacovigilance.

Proposed labeling:

- **Boxed Warning:** the proposed boxed warning refers to the risk of serious cardiopulmonary reactions after the administration of SonoVue.

- **Contraindications:** states that SonoVue is contraindicated in patients with known hypersensitivity to sulphur hexafluoride or to any of the components of SonoVue.
- **Warning and Precautions:** states that rare cases of serious cardiopulmonary reactions, including fatalities, have occurred following the injection of sulfur hexafluoride containing microbubbles. In addition, this section mentions there is an increased risk for these reactions in patients with unstable cardiopulmonary conditions and together with the recommendation to always have cardiopulmonary resuscitation personnel and equipment readily available prior to administration of SonoVue.

Proposed pharmacovigilance activities include:

- Systematic collection of adverse events from multiple sources (including cases that originate from published literature).
- Expedient and periodic medical assessments of single and aggregate reports.
- Identification of potential safety signals.
- Evaluation of the risk-benefit balance of the product through its life cycle.

5 DISCUSSION

The clinical development program for SonoVue demonstrated its efficacy for use in echocardiography. The reporting rate of cardiopulmonary reactions associated with SonoVue is low (0.0033% of exposed patients). In some cases, these cardiopulmonary reactions are associated with anaphylactoid reactions. The reporting rate of allergic-like reactions during the market use of SonoVue is 0.01% and its overall safety profile has been stable during the last 10 years. Definity and Optison, other contrast agents approved in the US for echocardiography, also have a risk for cardiopulmonary reactions, which is managed through labeling and routine pharmacovigilance. The label for Definity and Optison reflect the recommendations provided in May 2011 by members of the Cardiovascular and Renal Drugs Advisory Committee and the Safety and Risk Management Advisory Committee. The proposed label for SonoVue is similar to that of Definity and Optison. SonoVue's safety profile has remained consistent since product

launch in other jurisdictions in 2001. There are no REMS implemented for other contrast agents and the sponsor did not propose a REMS for SonoVue.

6 CONCLUSION AND RECOMMENDATIONS

In conclusion, the reporting rate of serious cardiopulmonary reactions associated to the use of SonoVue is relatively small and consistent with that of other approved contrast agents used in echocardiography. For the above reasons, DRISK does not recommend a REMS to manage the risk of serious cardiopulmonary reactions for this product and concurs with the sponsor's recommendation to manage the risks associated to SonoVue through labeling, including a boxed warning for the serious risk of cardiopulmonary reactions, and routine pharmacovigilance.

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