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RESEARCH**

APPLICATION NUMBER:

203684Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 10, 2012
From	Alex Gorovets, MD
Subject	Cross-Discipline Team Leader Review
NDA#	203684
Applicant	Bracco
Date of Submission	12/21/2011
PDUFA Goal Date	10/21/2012
Proprietary Name / Established (USAN) names	SonoVue (Sulfur Hexafluoride Lipid Microsphere) Kit for Preparation of Injectable Suspension
Dosage forms / Strength	2 mL during single administration/1.5 to 5.6 x10 ⁸ microspheres per mL
Proposed Indication(s)	For use in patients with suboptimal echocardiograms to opacify the left ventricle and to improve the delineation of the left ventricular endocardial border
Recommended:	<i>Approval (pending resolution of product quality issues)</i>

1. Introduction

This Cross Disciplinary Team Leader review document addresses the New Drug Application (NDA) #203684 for Sulfur Hexafluoride Lipid Microsphere. It is an ultrasound contrast agent indicated for patients with suboptimal echocardiograms to opacify the left ventricle and to improve the left ventricular endocardial border delineation. The review refers to the drug by its proposed but not yet approved proprietary name, SonoVue.

The conclusions of the current review are based on the review of the relevant portions of the application and on examination of the primary review documents from various disciplines. No significant disagreements have been encountered among individual reviewers or among disciplines.

2. Background

Development of SonoVue as an imaging drug took place under the IND 46958 and in 2001 Bracco submitted the NDA #21315 for cardiac indication. The application underwent various revisions but was not approved because of the reports of serious adverse events including death. The IND (b)(4) was eventually withdrawn. In 2007, the sponsor proposed (b)(4) and in 2009 the development of cardiac indication began anew. In the meantime, the understanding of safety of this class of imaging drugs has been evolving primarily based on the experience with two other drugs in the same class already approved in the US: Definity and Optison.

Similar cardio-pulmonary reactions were encountered with these agents and deaths occurred with Definity. All three drugs were discussed at the Cardio-Renal Advisory Committee meetings in 2008 and 2011. The black box warnings originally placed in both approved labels have been since relaxed mostly due to better appreciation of the infrequent nature of these cardio-pulmonary reactions. For a detailed discussion of the safety issues associated with Definity and Optison the reader is referred to the respective applications.

As for SonoVue, the applicant was asked to complete a pulmonary hemodynamic study and present the safety experience accumulated in Europe and elsewhere over the many years of use in these other countries. The same three efficacy trials submitted with the original application have been submitted with this application in support of effectiveness of SonoVue for the proposed indication and have been independently reviewed by the current review staff.

Based on the acoustic properties of microspheres like SonoVue, which are lipid microbubbles containing gas (sulfur hexafluoride, in this case) inside the bubbles, an ultrasound wave gets reflected resulting in an ultrasound image allowing visualization of the structures contrasted by the presence of the nearby microspheres, with the latter acting as a contrast agent. Improved visualization of such structures as a left ventricle in the heart might improve delineation of the cardiac border, help identify intracardiac tumors and clots, evaluate wall motion and measure a cardiac ejection fraction, among other things.

Whereas the original study design in all three efficacy trials involved a comparison to an earlier generation ultrasound contrast agent, non longer in use, and to a placebo, the current review of the data generated by these trials concentrated on the comparison of contrast to baseline, non-contrast images as a main measure of drug's effectiveness. The results of other trials presented in the submission served as supportive evidence of effectiveness. From the safety standpoint, in addition to analyses of the overall safety data base, the pulmonary hemodynamic study served to address some earlier concerns that microbubbles might cause or exacerbate pulmonary hypertension in association with systemic hypotension potentially leading to a cardiovascular collapse.

3. CMC/Device

CMC reviewer has verified the information provided by the applicant and the product microbiology reviewer found no issues with the application. However, the GMP inspections are still ongoing and the product quality evaluation from an inspectional standpoint has not been completed.

SonoVue drug product is a kit for preparation of injectable suspension of sulfur hexafluoride lipid microsphere. The kit has three parts: a vial with 25 mg of lyophilized powder consisting of the microsphere active components, a 5 mL prefilled syringe with 0.9% sodium chloride injection for reconstitution and a transfer device. Following reconstitution the injectable suspension contains 1.5 to 5.6×10^8 microspheres per mL. The product does not contain antimicrobial preservatives.

CDRH reviewers have been consulted for the evaluation of the transfer device and found that the actual device within the drug product has not been previously cleared for use in this country. Additional information is being requested from the applicant.

The drug substance consists of sulfur hexafluoride (SF₆) gas in the core surrounded by an outer shell monolayer with two kinds of phospholipids. The microspheres are composed of the drug substance with palmitic acid as a stabilizer and polyethylene glycol as a (b) (4). The mean diameter of a sulfur hexafluoride lipid microsphere is 1.5 to 2.5 microns, with 99% of microspheres being under 10 microns in diameter and with none being larger than 20 microns. In comparison, the mean diameter of Optison and Definity microspheres is 3 to 4.5 and (b) (4) microns, respectively. Of note, the early non-clinical and clinical studies were carried out without palmitic acid in the formulation. Based on the reviewed data, the addition of palmitic acid did not affect the size distribution or acoustic properties of the microspheres. All pivotal and other efficacy trials were conducted with the formulation containing palmitic acid.

4. Nonclinical Pharmacology/Toxicology

The non-clinical review of the current submission relied mostly on the review of data in the original application. Routine animal toxicology and safety studies, reproductive toxicology and genotoxicity studies did not produce any safety signals. Carcinogenicity studies were not performed. As discussed in the Advisory Committee meetings, studies of SonoVue in the pig heart/lung model, while initially reinforcing the concern about microspheres' effect on pulmonary circulation, in the end were not thought to be representative of the effects observed in humans.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology data have been presented in this application and the submitted data have been previously reviewed in the original application.

The recommended dose of SonoVue for left ventricular opacification and endocardial border delineation is 2 mL administered as an intravenous bolus injection during echocardiography. The suspension has to be shaken vigorously just prior to the administration. A bolus injection of the recommended dose of SonoVue provides useful signal intensity for echocardiography for 2 minutes. It is acceptable to administer a second injection of 2 mL if deemed necessary during a single echocardiographic examination. Imaging should be conducted at a mechanical index (MI) ≤ 0.8 . SF₆ concentration peaks at 1 to 2 minutes after the administration, with the half life of a clinically relevant dose measuring about 10 minutes. Phospholipid components of microspheres are metabolized and SF₆ gas is eliminated through the lungs.

6. Clinical/Statistical- Efficacy

The study populations in the three confirmatory studies were comprised of male and female patients, ≥ 18 years of age, with suspected cardiac disease and suboptimal border delineation on non-contrast echocardiography at rest. Border delineation was determined to be suboptimal based on the predefined scoring criteria.

Altogether, 191 patients received SonoVue in these three studies: 76 patients in Study 19A (Study A), 62 in Study 19B (Study B) and 53 in Study 13 (Study C). The patient population was consistent with a population of intended use. Overall, there were 127 men and 64 women. The mean age was 58.5 years (range 22 to 96 years). The racial and ethnic representations were 79% Caucasian, 16% Black, 4% Hispanic, 0.5% Asian, and 0.5% other racial or ethnic groups. The mean weight was 204 lbs (range 92 to 405 lbs). Approximately 20% of the patients had a chronic pulmonary disorder and 30% had a history of heart failure. Of the 106 patients for which a New York Heart Association (NYHA) classification of heart failure was assigned, 49% were Class I, 33% were Class II, and 18% were Class III.

In Studies A and B, each patient received four intravenous bolus injections of SonoVue (0.5, 1, 2, and 4 mL), in randomized order. In Study C, each patient received two doses of SonoVue (1 mL and 2 mL) in randomized order. All three studies assessed endocardial border delineation and left ventricular opacification. For each patient in each study, echocardiography with SonoVue was compared to non-contrast (baseline) echocardiography. A recording of 2D echocardiography was obtained from 30 seconds prior to each injection to at least 15 minutes after dosing or until the disappearance of the contrast effect, whichever was longer. Contrast and non-contrast echocardiographic images for each patient were evaluated by two independent reviewers, who were blinded to clinical information and SonoVue dose. Left ventricular endocardial border delineation was evaluated by segment using six endocardial segments with two apical views (2- and 4-chamber views).

In all three studies, administration of SonoVue improved left ventricular endocardial border delineation. The majority of the patients who received a 2.0 mL dose of SonoVue had improvement in endocardial border delineation manifested by visualization of at least two additional endocardial border segments. Combining the reads of two- and four-chamber views for each reader, one of the readers in Study A found that 79% of patients, and the other reader – 82% of patients, had inadequate border delineation in at least one pair of adjacent segments. Following SonoVue administration there was a reduction in percentage of such patients to 33% and 37%, respectively. In Study B, for one reader, the percentage of patients with inadequate border delineation was reduced from 50% to 19%, for the other reader, from 87% to 10%. In study C, one reader's "inadequate" percentage went from 85% to 38%; the other reader read non-contrast images well enough, so it went only from 23% at baseline to 19% with contrast. The primary clinical and statistical reviews contain results of other analyses, patient and segment based, using segmental scores as well as patient percentages, which verify the demonstration of the drug's effectiveness in improving the delineation of the left ventricular endocardial border.

Left ventricular opacification was evaluated in all three studies. Overall, complete left ventricular opacification was observed in 52% to 80% of the patients following administration of a 2.0-mL dose of SonoVue. Details of analyses are presented in the primary reviews.

An adequate left ventricular opacification is needed for measurement of an ejection fraction and for assessing ventricular wall motion, both commonly used as cardiac diagnostic characteristics. The applicant had attempted to address these measurements in Study C however the submitted assessments did not sufficiently evaluate the effect of SonoVue on either measure.

Among the submitted supportive studies the applicant also presented data for stress echocardiography. The results were inconclusive and the studies were not done in patients with suboptimal echocardiograms.

7. Safety

The clinical trial safety data base submitted with the application consisted of 5275 adult subjects (128 healthy volunteers and 5147 patients). The overall demographics were similar to the ones found in the three confirmatory efficacy trials. The most commonly reported adverse reactions in subjects who received the drug were headache (1.1%) and nausea (0.5%). In addition, local injection site reaction occurred in 0.9% of all subjects. Most adverse reactions were mild to moderate in intensity and resolved spontaneously. There were infrequent hypersensitivity reactions as well as the events that could be attributed to an underlying cardiac disease. There were only three serious adverse reactions and no deaths.

The serious hypersensitivity and cardio-pulmonary reactions including fatalities reported as postmarketing events have been extensively reviewed for both marketed in US ultrasound contrast agents and for SonoVue and this safety issue has been twice the subject of Advisory Committee meetings. There were nine such fatality reports for SonoVue since it has been marketed outside US. These cases are discussed in great detail in the primary review. There have been no new reports over the past several years.

The current review cycle included a consultation with the QT team. No QT prolongation signals have been found.

The application contains several reports of studies conducted in special populations (CHF, COPD etc.) including the one addressing the effect on pulmonary arterial pressure. The effect of SonoVue on pulmonary hemodynamics was studied in a prospective, open-label study of 36 patients scheduled for right heart catheterization, including 18 with mean pulmonary arterial pressure (MPAP) >25 mmHg and 18 with MPAP ≤ 25 mmHg. No clinically important pulmonary hemodynamic changes were observed. The other studies in special populations are presented in the primary review.

8. Advisory Committee Meeting

No Advisory Committee meeting has been held in connection with this application.

9. Pediatrics

(b) (4)
The matter has not been presented yet to the Pediatric Review Committee (PeRC) although the pediatric labeling consultant (b) (4) recommended to consider issuing a Written Request under the Best Pharmaceuticals for Children Act (BPCA) to study pharmacokinetics and safety of SonoVue in children for possible use in uncommon pediatric conditions or in certain post-operative situations.

Of note, Definity has been studied in children but not in those with suboptimal echocardiograms, and no pediatric information is provided in the labeling. (b) (4)

(b) (4)

For SonoVue, which has not been marketed in this country yet, this reviewer recommends (b) (4) considering a deferral under PREA, if requested and justified by the applicant. (b) (4)

The applicant would have to come up with the pediatric development plan, and the issues surrounding the practicality of carrying it out would have to be reconsidered depending on the proposed plan. (b) (4)

10. Other Relevant Regulatory Issues

There are no other regulatory issues.

11. Labeling

Labeling has not been finalized yet although it is anticipated that it will carry the same black box warning and the overall risk related information as conveyed in the labels of the two currently approved ultrasound contrast agents.

It is noted that an extensive labeling review has been carried out by the Division of Medication Prevention and Analysis which resulted in multiple recommendations to revise Dosage and Administrations section to make it clearer and to revise vial and carton labels among other things. The recommendation has also been made to prominently place a sheet with the "Information for Use" inside the kit. The applicant has not responded yet to these proposals.

The review by the Division of Medication Error Prevention and Analysis has also rejected the proprietary name of SonoVue (b) (4). The applicant has filed a response with a request for re-consideration. The review is ongoing.

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The CDTL recommends approving Sulfur Hexafluoride Lipid Microsphere Kit for Preparation of Injectable Suspension for use in patients with suboptimal echocardiograms to opacify the left ventricle and to improve the delineation of the left ventricular endocardial border. The proposed proprietary name of SonoVue is still under review. If some of the product quality issues originating in facilities inspections and the drug product device clearance issues remain unresolved the recommendation for approval would have to be changed to a Complete Response.

- Risk Benefit Assessment

Echocardiography is one of the most common, useful and beneficial methods of cardiac evaluation. Its usefulness is contingent on the ability of echocardiography to visualize cardiac chambers and specifically the left ventricle. The efficacy of this imaging drug lies in its ability to help visualize the ventricle by opacifying it and delineating its internal border. The studies submitted in this application clearly demonstrate such an efficacy and therefore provide a substantial evidence of effectiveness of SonoVue for the proposed indication. One could infer further that by better visualizing the left ventricle, using SonoVue, in patients with suboptimal non-contrast echocardiogram one could be better able to assess the wall motion, especially useful for assessing ischemia, and the ejection fraction, a common parameter of cardiac function, dysfunction and failure. Unfortunately the data submitted with this application are not sufficient for directly demonstrating the drug's effectiveness in evaluating wall motion and ejection fraction and the assessment of such a benefit remains inferential.

The risk associated with the use of SonoVue is manifested by cardio-pulmonary reactions which could be fatal but which are quite uncommon. Therefore close monitoring during and immediately after the use of the drug is required. The risk profile otherwise is quite benign. Of note, there are two other drugs from the same class approved in this country and, while approval of SonoVue for the proposed indication would not be addressing an unmet medical need, finding a significantly different risk/benefit ratio would not be expected either.

Overall, the assessment of risk and benefit of SonoVue for the currently proposed indication favors the approval.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

The clinical team agrees with the Division of Risk Management recommendations that postmarketing risk for this drug can be managed by labeling, including the black box warning, and an ongoing pharmacovigilance.

- Recommendation for other Postmarketing Requirements and Commitments

No postmarketing requirements or commitments are contemplated other than a possible pediatric study as mentioned above in section 9.

- Recommended Comments to Applicant

The applicant will be notified of the approval of the NDA 203684. The proposed action, and thus the comments to the applicant, might have to be changed to a Complete Response if product quality issues are not resolved by the action date.

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/s/

ALEXANDER GOROVETS
09/14/2012

Division of Medical Imaging Products

Cross-Discipline Team Leader (CDTL) Review Memorandum

NDA: 203684 Class 2 Resubmission
Supporting Doc No: 15 (Serial No. 0017)
Date Submitted: 5/31/2013
Product: Sulfur Hexafluoride Microbubbles (Lumason)
Sponsor: Bracco Diagnostics
CDTL: Brenda Ye, M.D.

Regulatory History

Sulfur Hexafluoride Microbubbles is an ultrasound contrast agent being developed by Bracco for use in patients with suboptimal echocardiography. The NDA was originally submitted 12/21/2011. FDA issued a Complete Response Letter on 10/19/2012 for deficiencies in manufacturing facility inspection, related apparatus, proposed proprietary name, and required pediatric assessment.

Summary of Updates during the Current Review Cycle

1) Manufacturing Facility Inspection

During an inspection of the Bracco Suisse manufacturing facility for this application, FDA field investigator conveyed deficiencies including the lack of temperature controls to the representative of the facility. The batch records provided in the most recent response didn't identify temperature ranges in the manufacturing process. The Bracco Suisse manufacturing facility remains in a "withhold" status from the district office, and the facility needs to be re-inspected. Additionally, the applicant needs to amend the chemistry, manufacturing and controls (CMC) sections in Module 2 and Module 3 of the application to contain applicable information if resolution of the inspectional deficiencies requires any new manufacturing and control.

2) Related Apparatus

Bracco conducted a study which compared the microbubble suspension characteristics following reconstitution using two transfer devices: the (b) (4) Mini- Spike (b) (4) and FDA cleared Mini-Spike (b) (4). The study showed that the microbubble concentration and size distribution are nearly identical regardless of the transfer device used. CDRH is satisfied with the conclusion of the study.

3) Proprietary Name

Bracco proposed a new proprietary name "Lumason" for the product. The DMIP review team found the proposed proprietary name acceptable. In addition, the Division of Medication Error Prevention and Analysis (DMEPA) has determined that the proposed proprietary name is acceptable, based upon the information submitted by the Applicant, OPDP's promotional evaluation, DMIP's initial comments, and DMEPA's safety evaluation.

4) Required Pediatric Assessment

Bracco submitted a pediatric development plan (PDP) which includes a proposed study in children 9 to 17 years of age, and a request for partial waiver for children younger than 9 years of age. The partial waiver request was granted. The DMIP review team and PMHS concluded that the number of obese children younger than 9 years old with poor non-contrast enhanced EBD is small, and there are insufficient data to conclude that obese children younger than 9 years old with poor non-contrast enhanced EBD would benefit from the product. PMHS further commented that a waiver of PREA-required studies for the proposed cardiac indication would not preclude additional studies for other indications.

Recommendation of Regulatory Action

The CDTL recommends Complete Response based on unresolved deficiencies identified in the product's manufacturing facility.

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/s/

BRENDA Q YE
11/14/2013