

CLINICAL REVIEW

Application Type	Pediatric Supplemental New Drug Application
Application Number	NDA 203684 s005
Priority or Standard	Standard
Submit Date	January 30, 2019
Received Date	January 30, 2019
PDUFA Goal Date	November 30, 2019
Established Name	Sulfur hexafluoride lipid-type A microspheres
Trade Name	Lumason
Applicant	Bracco Diagnostics Inc.
Formulation	Injectable suspension: 25 mg of lipid-type A lyophilized powder with headspace fill of 60.7 mg sulfur hexafluoride in a single-patient use vial for reconstitution. Following reconstitution, Lumason contains 1.5 to 5.6×10^8 microspheres/mL with 45 mcg/mL of sulfur hexafluoride.
Dosing regimen	After reconstitution, administer 0.03 mL per kg as an intravenous injection up to a maximum of 2 mL per injection.
Intended Population	Pediatric patients
Reviewer Name	Stephanie Coquia, MD
Review Completion Date	October 14, 2019

DOCUMENTS REVIEWED

Documents Reviewed under NDA 203684

Final study report for BR1-140 submitted November 27, 2018; 0090/173
sNDA submitted January 30, 2019; 0093/180
Sponsor's response to filing letter information requests submitted April 29, 2019; 0096/189
Pediatric consult dated July 30, 2019
Primary clinical review for liver lesion indication supplement dated February 29, 2016
Division Director's review for the liver lesion supplement dated March 31, 2016
Sponsor's request for a partial waiver of pediatric studies dated May 31, 2013
Office of Surveillance and Epidemiology Pediatric Postmarketing Pharmacovigilance Review dated August 23, 2019

Documents Reviewed under IND 046958

PeRC meeting minutes dated May 9, 2018
Clinical review dated March 28, 2018
Sponsor's response to information requests dated February 21 and 27, 2018
Meeting minutes with the sponsor dated February 13, 2018

Additional Documents

QT-IRT consult for NDA 021064 dated May 16, 2011
Clinical review for NDA 020899 S018/S019 dated September 15, 2016
CardioRenal consult for NDA 020899 dated June 2, 2016
Literature references as cited

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Executive Summary

Bracco Diagnostics submits a supplemental NDA (sNDA) to extend its Lumason echocardiography indication from the currently approved population of adults with suboptimal echocardiograms to pediatric patients with suboptimal echocardiograms. The sNDA is supported by a Pediatric Research Equity Act (PREA) postmarketing requirement (PMR) study that evaluated the safety and efficacy of Lumason for echocardiography in 12 pediatric patients aged 9 to 17 years with previous suboptimal echocardiograms. Together with extrapolation of efficacy from adults and the safety database from the intravenous use of Lumason in children, the sNDA is approvable for all pediatric age groups. Lumason will be the first ultrasound contrast agent approved for echocardiography in the pediatric population.

Risk-Benefit Assessment

The totality of the efficacy data from adult and pediatric studies of Lumason use in echocardiography demonstrate improvement in left ventricular endocardial border delineation (LV EBD) in subjects with suboptimal echocardiograms. This improvement in visualization leads to a decrease in the number of suboptimal echocardiograms post contrast, improving the diagnostic yield and clinical meaningfulness of the exam. Although only 12 patients ages 9 to 17 years were evaluated in the PREA PMR study, the known mechanism of action of Lumason is age independent, allowing for extrapolation of efficacy from the adult data and down to birth. For pediatric patients, especially those who are critically ill, this approval will allow access to a more accurate imaging exam that can be performed at the bedside and without exposure to radiation, iodinated or gadolinium-based contrast agents, anesthesia, or sedation. Lumason is currently approved for all pediatric age groups for liver lesion characterization. Review of the adverse events (AEs) from the PREA PMR study, the literature, and the sponsor's pharmacovigilance database do not raise new safety concerns for extending the adult echocardiography indication to the pediatric population.

Background

On October 10, 2014, Lumason received approval for use in adult patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. The approval included a requirement for a deferred pediatric study under PREA to evaluate pediatric patients in the 9 to 17-year age group as described below:

“Conduct a multicenter clinical evaluation of safety and efficacy in pediatric patients ages 9-17 years of age of Lumason as a contrast agent in pediatric echocardiography. Evaluate the efficacy of Lumason contrasted echocardiography vs. non-contrast echocardiography for left ventricular border delineation in 92 patients (males and

females) 9-17 years old. During the clinical evaluation, pharmacokinetic assessments will be performed on 6 patients, 9-12 years old (3 males and 3 females), and 6 patients, 12-17 years old (3 males and 3 females)."

The requirement to study patients from birth to 9 years of age was waived because the necessary studies were deemed impossible or highly impracticable due to the small number of pediatric patients receiving contrast-enhanced rest echocardiography. The PMR's final report submission deadline was May 31, 2018.

On December 15, 2017, the sponsor submitted a meeting request to discuss the status of this postmarketing study, requesting to terminate the study due to difficulties in enrollment. Out of the 92 required patients to be studied, 12 patients had been enrolled since initiation of the study; none were enrolled for the PK study. After a type B meeting with FDA on February 13, 2018, the sponsor submitted two responses to information requests dated February 21, 2018 and February 27, 2018. These responses included a review of the AEs reported during the study, use data of Lumason for pediatric echocardiography by age provided by (b) (4), and the numbers of potential subjects who ultimately could not be enrolled due to a particular exclusion criterion. These responses were submitted under IND 046958 and evaluated in a clinical review by Dr. Sheldon Kress dated March 28, 2018 and subsequently by this reviewer dated June 8, 2018.

The sponsor's request to terminate the PMR study was presented to the Pediatric Review Committee (PeRC) on May 9, 2018. Following further discussion between the Division of Medical Imaging Products (DMIP) and PeRC, the sponsor was asked to submit a 6-month deferral extension for the PREA PMR. During this extension the sponsor was expected to complete the final study report for BR1-140 (the PMR study) with the available data and submit an efficacy supplement to extend the adult echocardiography indication to pediatric patients. The final study report was submitted on November 27, 2018, and the sNDA was submitted on January 30, 2019.

Since its approval for adult echocardiography in 2014, Lumason has received approval for liver lesion characterization in both adult and pediatric patients of all ages and for evaluation of suspected or known vesicoureteral reflux in pediatric patients of all ages. The liver lesion indication was supported primarily by a published clinical study of 44 patients (ages 4 to 18 years) for efficacy and published literature involving use of Lumason in over 900 pediatric patients for safety. The other approved ultrasound contrast agents (Definity and Optison) do not carry any pediatric indications, cardiac or otherwise.

Review Strategy

The current indication for Lumason for echocardiography is shown below with the sponsor's currently proposed revisions appearing in added italic font:

"Lumason is an ultrasound contrast agent indicated for use in echocardiography to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border in adult *and pediatric* patients (b) (4) with suboptimal echocardiograms."

Study BR1-140 was the primary source of evidence of efficacy for the above indication revisions, as augmented by extrapolation of the previously established adult echocardiography efficacy. The following conclusion from the Division Director review for the Lumason liver lesion supplement dated March 31, 2016, provides justification for extrapolation of adult data to pediatric patients: "The following pharmacokinetic and pharmacodynamic considerations support the extrapolations for efficacy: Lumason is restricted to the circulating blood compartment, the mechanism of action is independent of age, and blood volume is proportional to weight in adult and pediatric patients."

For evidence of safety, the following sources were relied upon: study BR1-140 safety results; Lumason AEs reported in the FDA Adverse Event Reporting System (FAERS) and by the sponsor in the pediatric age group; the existing safety database from the 900 pediatric patients reported in the published literature who received intravenous Lumason, which had previously supported approval of the liver lesion indication with the same pediatric dose (0.03 mL/kg) proposed in the current echocardiography supplement; and literature of Lumason use in the pediatric age group for non-cardiac indications published since the liver lesion characterization approval (and thus not reviewed previously).

Review of Efficacy

Study BR1-140

Although 92 subjects were planned for enrollment to achieve 73 evaluable subjects (including 12 for PK evaluation), due to enrollment issues ultimately only 13 subjects were enrolled and 12 subjects dosed at 2 sites in the United States.

Two co-primary endpoints were pre-specified: change in LV EBD score between unenhanced ultrasound (UEUS) and Lumason contrast-enhanced ultrasound (CEUS) and the proportion of subjects with adequate left ventricular opacification (LVO). The rating scales used for the pediatric LV EBD and LVO scores were similar to those used in the adult efficacy studies. For LV EBD score, the left ventricle was divided into 17 segments, with the total score comprising of the sum of the ratings for each segment (maximum LV EBD total score of 34). The rating for each segment was to be chosen by the reader as follows:

- 0 = Inadequate (endocardial border not visible)
- 1 = Sufficient (endocardial border barely visible)
- 2 = Good (endocardial border clearly visible)

Reviewer comment: In the adult studies, the left ventricle was divided into 6 segments, not 17, and only two apical views (2- and 4-chamber) were used for grading, rather than the 2-, 3- and 4-chamber views used in the pediatric study. The 17-segment model is commonly used and is described in the American Society of Echocardiography's Guidance: Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults¹. The increase in the segmentation of the left ventricle is reflective of clinical practice and should not affect the ability to extrapolate the adult data to pediatric patients for efficacy: in both adults and children the change in visualization of the left endocardial border post contrast was adequately assessed.

For LVO, the degree of opacification was graded along the following scale (with grades 2 or 3 considered adequate):

- 0 = None, i.e. no visible contrast within the left ventricular cavity
- 1 = Faint, i.e. weak or trace effect of contrast within the left ventricle
- 2 = non-homogeneous, i.e. some areas of the left ventricle fully opacified but without a time when the whole cavity is filled with contrast to the same high intensity
- 3 = complete, homogeneous and high intensity effect

For the first co-primary endpoint, LV EBD score, success would be achieved if the difference in average LV EBD score between pre- and post-contrast examinations was statistically significant. For the second co-primary endpoint, LVO, success would be achieved if the lower bound of the

¹ Lang R, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L et al. Recommendations for Cardiac Chamber Quantification by the Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; 28:1-39.

95% confidence interval (CI) of the proportion of subjects with adequate LVO scores exceeded 70% in at least 2 out of 3 blinded readers.

Lumason Exposure:

The dose of Lumason administered per subject was 0.03 mL/kg body weight, consistent with the currently proposed dose. However, while the sponsor also currently proposes a 2 mL maximum dose in pediatric patients, total volumes administered in study BR1-140 ranged from 0.84 mL to 3.17 mL. In 4 subjects who had weights greater than 70 kg (subjects [REDACTED] (b) (6) [REDACTED]), administered doses exceeded 2 mL.

Reviewer comment: Although current labeling for adult echocardiography allows for one repeat injection, based on review of the Clinical Study Report (CSR) and eCase Report Form, it appears that subjects received only one injection of Lumason (no contingencies described for re-injection and interpretation of more than one contrast-enhanced study, only one entry for dose, etc.). Thus, while efficacy at the 2 mL maximum recommended dose cannot be specifically assessed in these particular 4 subjects, it is generally extrapolatable from adults, where the approved dose per injection is also 2 mL.

Results:

Table G of the CSR (reproduced below as Table 1) summarizes the co-primary analysis of LV EBD scores given by each reader. Mean values and 95% CIs are given for the LV EBD scores for UEUS and CEUS as well as for the intra-patient difference between CEUS and UEUS.

Table 1: Summary of Total LV EBD Score

Off-site Readers	UEUS	CEUS	Difference (CEUS - UEUS)
Reader 1			
N	12	11	11
Mean (SD)	6.4 (5.57)	33.5 (1.29)	27.5 (5.73)
Median	5.5	34.0	29.0
Range (min, max)	(0, 20)	(30, 34)	(14, 34)
95% CI	(2.9, 10.0)	(32.6, 34.3)	(23.7, 31.4)
p-value (95% CI) ^a			<0.0001
Reader 2			
N	11	9	9
Mean (SD)	10.6 (5.66)	33.3 (2.00)	23.0 (5.77)
Median	8.0	34.0	26.0
Range (min, max)	(3, 21)	(28, 34)	(11, 29)
95% CI	(6.8, 14.4)	(31.8, 34.9)	(18.6, 27.4)
p-value (95% CI) ^a			<0.0001
Reader 3			
N	12	11	11
Mean (SD)	7.3 (5.17)	33.0 (1.79)	26.0 (6.48)
Median	8.0	34.0	25.0
Range (min, max)	(0, 14)	(29, 34)	(17, 34)
95% CI	(4.0, 10.5)	(31.8, 34.2)	(21.6, 30.4)
p-value (95% CI) ^a			<0.0001
<small>UEUS, unenhanced ultrasound; CEUS, contrast-enhanced ultrasound; SD, standard deviation; CI, confidence interval. NOTE: Total EBD score for a subject is calculated as the total of the EBD scores from the 17 segments. ^a p-value from paired t-test of the difference between CEUS and UEUS (CEUS - UEUS). Data source: <i>End-of-Text Table 14.6.1</i></small>			

For each reader, the 95% CIs for LV EBD score for UEUS and CEUS do not overlap and the lower bound of the 95% CI of the mean intra-patient difference in LV EBD score between CEUS and UEUS is above 0.

Reviewer comments:

The last column of the above table (other than the p-value row) appears to have been generated by subtracting the UEUS LV EBD score from the CEUS LV EBD score for each subject and calculating the mean of these differences across all subjects. While not a pre-specified analysis, the results add supportive subject-level information as an improvement in LV EBD score was seen post contrast in each subject as evidenced by minimum range values above 0 in all 3 readers.

Note that for evaluation of UEUS and CEUS LV EBD, not all subjects were always analyzed by each reader, resulting in N of less than 12. If for a given reader, a subject had a missing segment value, that entire exam was not included in the analysis for that reader. Using imputation under a worst-case scenario (missing segment rated as 0), this reviewer has recalculated the mean, median, and ranges for UEUS and CEUS LV EBD scores. Even with this new analysis, there is clear improvement in LV EBD score post-contrast.

Table 2: Clinical Reviewer Analysis of LV EBD scores with Imputation of Missing Data Under Worst Case Scenario

Reader 1	UEUS	CEUS
N	12	12
Mean	6.4	32.8
Median	5.5	34
Range (min, max)	(0, 20)	(26, 34)
Reader 2		
N	12	12
Mean	10.25	31.5
Median	8	34
Range (min, max)	(3, 21)	(26, 34)
Reader 3		
N	12	12
Mean	7.25	32.4
Median	8	34
Range (min, max)	(0, 14)	(26, 34)

For the co-primary analysis of LVO, all readers rated all exams as demonstrating complete LVO following contrast administration (Table H from CSR, reproduced as Table 3 below):

Table 3: Summary of LVO at CEUS

Characteristics	Reader 1	Reader 2	Reader 3
Total ^a	12	12	12
None n(%) (95% CI) ^b	0 (0, 26.5)	0 (0, 26.5)	0 (0, 26.5)
Faint n(%) (95% CI) ^b	0 (0, 26.5)	0 (0, 26.5)	0 (0, 26.5)
Non-Homogenous n(%) (95% CI) ^b	0 (0, 26.5)	0 (0, 26.5)	0 (0, 26.5)
Complete n(%) (95% CI) ^b	12 (100) (73.5, 100)	12 (100) (73.5, 100)	12 (100) (73.5, 100)
Adequate n(%) (95% CI) ^b	12 (100) (73.5, 100)	12 (100) (73.5, 100)	12 (100) (73.5, 100)
LVO, left ventricular opacification; ITD, intent-to-diagnose; CI, confidence interval. NOTE: The degree of LVO will be graded according to a 4-point rating scale. A rating of +2 (non-homogenous) or +3 (complete) will be considered as adequate LVO. ^a Denominator for percentages. ^b The 2-sided 95% confidence interval will be calculated, based on the exact binomial distribution using Clopper-Pearson method. Data source: <i>End-of-Text Table 14.7.1</i>			

In the sponsor's secondary analysis of UEUS and CEUS scores, an exam was considered suboptimal if there was inadequate visualization of the endocardial border (rating of 0) in two adjacent segments. As part of the inclusion criteria, all subjects were required to have a prior suboptimal examination. Table J from the CSR (reproduced as Table 4 below) demonstrates the conversion of suboptimal exams to adequate exams with the use of contrast.

Table 4: Cross Tabulation of Inadequate LV EBD in at Least Two Adjacent Segments

UEUS	CEUS			Total n (%)
	Suboptimal n (%)	Adequate n (%)	Not Available n (%)	
Reader 1				
Suboptimal	1 (8.3)	10 (83.3)	1 (8.3)	12 (100) ^a
Adequate	0	0	0	0
Not Available	0	0	0	0
Total	1 (8.3)	10 (83.3)	1 (8.3)	12 ^a
Reader 2				
Suboptimal	0	9 (81.8)	2 (18.2)	11 (91.7) ^a
Adequate	0	0	0	0
Not Available	0	0	1 (100)	1
Total	0	9 (75.0)	3 (25.0)	12 ^a
Reader 3				
Suboptimal	0	11 (91.7)	1 (8.3)	12 (100) ^a
Adequate	0	0	0	0
Not Available	0	0	0	0
Total	0	11 (91.7)	1 (8.3)	12 ^a
LV EBD, left ventricular endocardial border delineation; UEUS, unenhanced ultrasound; CEUS, contrast-enhanced ultrasound; ITD, intent-to-diagnose. NOTE: For an apical view (if an apical view is available): If >=2 adjacent segments with inadequate LV EBD in an apical view, that view is suboptimal; Otherwise, the view is adequate. For overall subjects: the subject is suboptimal if any of the 3 apical views is suboptimal; the subject is adequate if all 3 apical views are adequate; and the subject is not available if any of the views is not available. ^a Denominator for percentages on the same row. Table data derived from <i>End-of-Text Table 14.6.4</i> .				

For all readers, all completed exams were considered suboptimal with UEUS. For reader 1, only one completed exam was considered suboptimal post-contrast, although one other exam had incomplete data and was excluded from the analysis. For readers 2 and 3, no complete exams were considered suboptimal post contrast. For reader 2, 3 subjects had incomplete data either pre- or post-contrast and were excluded from the analysis. For reader 3, one subject had incomplete data and was excluded from the analysis. In addition, on a segment-level, "all inadequate segments at UEUS had an improved score of either sufficient or good at CEUS except 2 segments for Reader 1."

Literature

The sponsor performed a literature search to identify relevant publications "describing efficacy for contrast enhancement during transthoracic echocardiography examinations at rest or stress." All studies were reviewed by a cardiologist for relevance. Four references were

identified; however, none used Lumason. Therefore, these references were not reviewed for evidence of safety or efficacy.

Review of Safety

Study BR1-140

Demographics:

The mean age of the subjects was 13.8 years, range 9-17 years. There were 7 female and 5 male subjects. There were 10 white and 2 black subjects.

Medical History:

Many of the subjects evaluated in the study had significant medical history. For example, 6 subjects had undergone heart transplantation. Cardiac disorders including cardiac failure, congestive cardiomyopathy, cardiogenic shock, myocarditis, ventricular tachycardia, and Wolff-Parkinson-White syndrome were reported. A total of 10 subjects were on at least one medication. Medications included those in the anti-infective, antineoplastic/immunomodulating, cardiovascular, and respiratory categories.

Lumason exposure:

As described previously, all subjects received the weight-based dose of Lumason of 0.03 mL/kg body weight with 4 subjects receiving doses greater than 2 mL (greater than the recommended adult single dose or proposed pediatric maximum single dose). None were given a second dose.

Adverse events:

MedDRA 18.1 was used to code for AEs. A total of 5 subjects experienced 7 AEs that were reported as either mild or moderate in severity. The AEs were as follows: vomiting, injection site bruising, pyrexia, headache, abnormal behavior, hemoptysis, and rash. Per the CSR, all subjects recovered from the AEs, with 4 receiving treatment. None of the AEs reported were felt by the sponsor to be related to Lumason. There were no serious AEs, deaths, or dropouts. Under IND 046958, in an information request response dated February 21, 2018, the sponsor provided narratives of the 7 AEs reported under BR1-140. This information was reviewed by Dr.

Scheldon Kress, the previous primary reviewer for Lumason, who concurred with the sponsor in his March 28, 2018 review, stating: "All the observed AEs were non-serious, mild or moderate in intensity, did not occur in close proximity to the ultrasound administration and were considered unrelated to exposure to Lumason. Thus, based on Lumason administration to a limited number of patients aged 9-17, Lumason administered intravenously did not present unique safety concerns in children."

Reviewer comment: This reviewer evaluated the same information submitted under IND 046958 and concurs with Dr. Kress's assessment of the study AEs. The AEs of vomiting, pyrexia, headache, abnormal behavior, hemoptysis, and rash occurred hours to days after Lumason administration and could be attributed to the subject's underlying conditions and/or transfusions.

Other Assessments (Laboratory, ECG, physical exam, vital signs):

For changes in physical exam, the report of rash occurred 7 hours and 45 minutes after Lumason administration, at the end of a red blood cell transfusion.

For vital signs, no subjects experienced a change in systolic blood pressure outside of the defined acceptable range (90 to 160 mm Hg) due to a ≥ 20 mm Hg change from baseline. One subject (b) (6) had a systolic blood pressure increase of 22 mm Hg from 131 mm Hg to 152 mm Hg at 24 hours.

The normal range of heart rate (HR) was defined as 60 to 100 beats per minute. Except for one subject (b) (6), all subjects who had HRs above the normal range post-dose had elevated HRs pre-dose. Subject (b) (6) had an increase in HR > 10 beats per minute at 30 minutes and 24 hours post dosing, but the HR was normal at 5 minutes post Lumason administration and systolic blood pressure remained within normal range. One subject (b) (6) had a decrease in HR > 10 beats per minute at all times post-dosing, but systolic blood pressure remained within normal range.

For respiratory rate (RR), two subjects had RR > 30 respirations/minute post-dosing. Subject (b) (6)'s RR increased from 28 respirations/minute pre-dose to 36 respirations/minute at 24 hours (at 5 minutes the respiratory rate was 26 respirations/minute). For another subject, (b) (6), the RR pre-dose was 42 respirations/minute, while post-dose it ranged from 34-38 respirations/minute.

Reviewer comment: As the half-life of the sulfur hexafluoride (SF₆) gas in blood is approximately 10 minutes and peak gas concentration in the blood occurs at 1 to 2 minutes (per Lumason label), vital sign abnormalities seen only at the 30-minute and/or 24-hour time point are of less concern for being drug-related than those seen at the 5-minute timepoint.

Pulse oximetry was not measured for any of the subjects. It was pre-specified in the protocol that only subjects with pulmonary hypertension or unstable cardiopulmonary conditions were to have pulse oximetry continuously monitored; none of the subjects had these conditions.

A thorough QT study was not performed. However, ECGs were obtained at 30 minutes and 24 hours post-Lumason administration. Per the CSR, no subjects experienced an increase in QTcB or QTcF intervals > 60 msec. Note that the time-points at which the post-administration ECGs were obtained were much later than the expected T_{max} of 1 to 2 minutes (per the Lumason label, concentrations of SF₆ in the blood peak at 1 to 2 minutes). A similar issue with timing occurred with the ECG data from studies (in adults) for Definity: per the QT-Interdisciplinary Review Team consult dated May 16, 2011, ECG data not obtained at T_{max} was considered non-informative. However, the warning for QT prolongation that once appeared on the Definity label was removed in January 2017. Moreover, the Lumason label does not currently have a warning for QT prolongation.

The central laboratory range for normal white blood cell (WBC) counts was defined as 4.35 to 13.15 x 10³/μL. Two subjects ((b) (6)) experienced “markedly abnormal WBC 24 hours post dose” per the sponsor. However, subject (b) (6) had an elevated WBC count at baseline (14.26 x 10³/μL at baseline and 17.85 x 10³/μL post dose) and was also on steroids and immunosuppressants for heart transplant. Subject (b) (6) had a minimally elevated WBC count of 13.68 x 10³/μL post dose, increased from 11.60 x 10³/μL at baseline. Subject (b) (6) was also status post heart transplant. In those subjects who had a pre-dose WBC count below the lower limit of normal, none had a lower WBC count post dose.

Reviewer comment: An internet search of normal WBC counts in children revealed use of various ranges to define normal; however, a laboratory reference chart from the Children's Hospital of Minnesota did show the normal range being used at that institution for children aged 9 to 12 years was 4.5 to 13.5 x 10³/μL.²

² <https://www.childrensmn.org/references/lab/hematology/cbc-reference-value-table.pdf>. Accessed August 2, 2019.

The sponsor defined an increase in WBC count of $1.98 \times 10^3/\mu\text{L}$ as a substantial change, which Subjects (b) (6) met. One additional subject had a substantial increase in WBC count, but the WBC count remained in the normal range. The sponsor defined a decrease in WBC count of $1.81 \times 10^3/\mu\text{L}$ as a substantial change. One subject met this substantial decrease criterion, but both the pre-dose and post-dose WBC remained within the normal range.

Two subjects (subjects (b) (6)) experienced "markedly abnormal" lactate dehydrogenase (LDH) values 24 hours post-dose. The normal range was defined as 120 to 290 U/L. Subject (b) (6) had LDH values increasing from 333 U/L to 422 U/L while subject (b) (6) had LDH values increasing from 236 U/L to 324 U/L, increases considered to be substantial (defined as ± 25 U/L). Two other subjects had elevated LDH values post-dose. Subject (b) (6) had a post-dose value of 316 U/L; the pre-dose LDH sample had hemolyzed, therefore no baseline value was available to compare. Subject (b) (6) had pre-dose LDH value of 280 U/L and post-dose LDH value of 304 U/L, a change that was not considered by the sponsor to be substantial. LDH can be elevated in several conditions including cancer, infection, and heart and liver conditions. Subjects (b) (6) all had histories of heart transplantation, and subject (b) (6) had an additional history of cirrhosis.

Literature

Lumason is approved in pediatric patients for liver lesion characterization. As part of the *Liver sNDA Safety Update*, the sponsor provided "6 references about the safety of intravenously administered SonoVue in a population < 18 years of age," with cut-off date of September 2014. Note that SonoVue is the name used for Lumason outside of the United States. These 6 references resulted in a safety database of more than 900 pediatric patients who received Lumason intravenously; this database was used for the liver lesion characterization sNDA as evidence of safety. For the current sNDA, the sponsor has performed a search with cut-off date of September 2018. Search terms included: SonoVue or Lumason, intravenous, and pediatric. Most of the literature references retrieved in the search were previously submitted for the liver lesion indication. Per the sponsor, "four original peer-reviewed publications met all selection criteria, reporting safety data from studies of the use of Lumason in at least one pediatric patient." None of these studies were for cardiac indications. These studies are briefly summarized below.

*Yusuf et al, "Retrospective Analysis of Safety and Cost Implications of Pediatric Contrast-Enhanced Ultrasound at a Single Center."*³

This was a retrospective review of all CEUS examinations performed in children (18 years of age and under) between January 2008 and December 2015 at King's College London. A total of 305 children underwent CEUS, with ages ranging between 1 month to 18 years of age. 48% of cases were for the evaluation of liver lesions; 37% of cases were for the evaluation of trauma. Doses varied by patient age (rather than weight) and reason for exam/organ to be imaged, with a maximum dose of 4.8 mL for bowel and testicular indications. No immediate adverse reactions were reported. Two patients experienced transient hypertension (141/80 mm Hg, occurring 1 hour after the procedure, and resolved within 3 hours) and transient tachycardia (140 bpm, occurring 3 hours after the procedure, and resolved at 90 minutes) on follow-up assessment of the medical record (24 hours after injection), but both were asymptomatic.

*Torres A et al, "Contrast-enhanced ultrasound using sulfur hexafluoride is safe in the pediatric setting"*⁴

This was a retrospective review of all abdominal CEUS exams performed between January 2004 to December 2014 at Karolinska University Hospital in Sweden. A total of 183 patients underwent a total of 287 exams. The mean age was 11 years (range 0.1 to 18 years). The institution administered Lumason at a dose of 0.1 mL/kg (more than 3 times the labeled dose of 0.03 mL/kg). Total doses ranged from 0.1 mL to 8.1 mL. No immediate or delayed AEs related to the drug were noted in the medical record.

*Pschierer K et al, "Evaluation of the diagnostic accuracy of CEUS in children with benign and malignant liver lesions and portal vein anomalies"*⁵

This was a retrospective review of the diagnostic imaging findings of abdominal CEUS, MRI, and CT in 56 children who had either a liver lesion (benign or malignant) or an anomaly of the portal vein. The imaging examinations were performed at University Hospital Regensburg in Germany

³ Yusuf GT, Sellars ME, Deganello A, Cosgrove DO, Sidhu PS. Retrospective Analysis of the Safety and Cost Implications of Pediatric Contrast-Enhanced Ultrasound at a Single Center. *AJR* 2017; 208: 1-7.

⁴ Torres A, Koskinen SK, Gjertsen H, Fischler B. "Contrast-enhanced ultrasound using sulfur hexafluoride is safe in the pediatric setting." *Acta Radiologica* 2017; 58(11):1395-1399.

⁵ Pschierer K, Grothues D, Rennert J, Platz Batista da Silva N, Schreyer AG, Melter M et al. "Evaluation of the diagnostic accuracy of CEUS in children with benign and malignant liver lesions and portal vein anomalies." *Clinical Hemorheology and Microcirculation* 2015; 61:333-345.

between April 2009 and June 2015. The mean age of the patients was 9.1 years (range 0.1 to 17 years). The mean dose administered was 0.07 mL/kg (more than 2 times the labeled dose of 0.03 mL/kg). No complications or side effects were reported.

Teusch VI et al, "Color-coded perfusion analysis of CEUS for pre-interventional diagnosis of microvascularisation in cases of vascular malformations"⁶

This was a prospective pilot study that analyzed the contrast-enhanced perfusion of vascular malformations. A total of 28 patients with vascular malformations were evaluated, with mean age 24.9 years (range 3.8 to 53.4 years). The number and ages of the pediatric patients were not specified other than the minimum age provided in the range. The Lumason doses administered to children were according to body weight; the exact weight-based dosing was not specified. Maximum dose was 2.4 mL. No minor or major complications were reported.

Conclusion: The four papers include at least 546 pediatric patients (545 patients from the first three studies and at least one 3.8-year-old patient from the last study) exposed to intravenous Lumason. The exposures include those for on-label and off-label non-cardiac use as well as those for patients less than 9 years of age. No immediate complications related to Lumason were reported. Most of the children received total doses greater than the labelled dose of 0.03 mL/kg body weight. As per the Lumason label, "safety of intravenous use of Lumason was based on evaluation of published literature involving use of Lumason in over 900 pediatric patients." With the four additional papers submitted for review, the pediatric safety database from the literature for intravenous use of Lumason now includes at least 1446 patients.

Reviewer comment: Although these studies were for non-cardiac indications, the safety experience is applicable to the proposed cardiac indication because Lumason is a completely intravascular intravenous imaging agent; the major difference is where the transducer is placed on the patient for imaging.

Postmarketing AE reporting

In the filing letter dated April 11, 2019, FDA requested that the sponsor "provide a line listing of all pediatric adverse events received by Bracco" for Lumason/SonoVue. Case narratives for the

⁶ Teusch VI, Wohlgemuth WA, Piehler AP, Jung EM. "Color-coded perfusion analysis of CEUS for pre-interventional diagnosis of microvascularisation in cases of vascular malformations." *Clinical Hemorheology and Microcirculation* 2014; 58:183-193.

serious reports were also requested. The sponsor responded with the requested information on April 29, 2019.

The company's Lumason/SonoVue postmarketing safety database was searched for pediatric AEs received between March 26, 2001, and March 31, 2019. Neither the original sNDA submission nor the response provided an estimate of how many pediatric patients have been exposed overall. Per the Clinical Summary, "cumulatively during market use from 26 March 2001, the date of the first marketing authorization, through 30 September 2018, an estimated 6,334,225 patients (adult and pediatric population) have been exposed to SonoVue/Lumason during the market use of this product."

A total of 50 AEs were retrieved: 13 serious and 37 non-serious. Excluding urethral routes of administration, there were 12 serious and 22 non-serious AEs. Most were foreign except for 3 non-serious AEs in the United States.

Age

Of the 12 intravenous serious AEs, 4 (33%) occurred in children under 9. The youngest was a 30-day old male. Of the 22 non-serious AEs, 6 (27%) occurred in children under 9, but 6 other AEs (27%) that occurred in children did not have ages specified.

Description of Serious Adverse Events

None of the serious events occurred in exams with cardiac indications; however, this should be taken into context with the previous use data provided by the sponsor which showed no use of Lumason in pediatric echocardiography (response to information request under IND 046958 dated February 27, 2018). At least three of the serious AEs occurred in subjects who had received Lumason without incident previously. Most of the serious AEs had symptoms consistent with anaphylactic or anaphylactoid reactions, such as erythema, generalized redness, hypotension, shortness of breath, feeling of throat tightness, etc., occurring within minutes of the injection and treated with steroids, anti-histamines, fluids, and epinephrine. Two of these suspected anaphylactic or anaphylactoid reactions occurred in children under 9 where one experienced cardiac arrest and the other hypoxia requiring intubation. The other 3 serious AEs that were not exactly consistent with anaphylactic or anaphylactoid reactions are described below.

One AE of necrotizing enterocolitis was reported in a 30-day-old male who was born prematurely at 32 weeks with co-morbidities including cardiac failure, hydrops, and persistent

pulmonary hypertension of the newborn. A liver ultrasound was performed due to suspicion of vascular malformation. The evening following the CEUS, within 24 hours after examination, the patient developed hemodynamic instability and necrotizing enterocolitis.

Reviewer comment: The patient's co-morbidities and prematurity provide alternative explanations for hemodynamic instability and necrotizing enterocolitis. The reporter provided two alternative explanations for ischemia in the region supplied by middle mesenteric artery: thromboembolism from the patient's existing vascular malformation or air embolism due to contrast injection. The narrative did not provide a history of significant right-to-left shunt. While the labeling does include a warning regarding systemic embolization in those with cardiac shunts, the causes of embolism suggested by the reporter are more plausible than embolism directly related to the ultrasound microbubbles as air emboli or thromboemboli are much larger than microbubbles. None of the other AEs submitted involve complications related to systemic embolization. With respect to the patient's pulmonary hypertension playing a contributory cause to the hemodynamic instability when combined with Lumason, note that Lumason is not contraindicated in adults with pulmonary hypertension. As per the label, a prospective open-label study was performed in 36 patients undergoing right heart catheterization. In those with elevated mean pulmonary arterial pressure, no clinically important pulmonary hemodynamic changes were observed. The other ultrasound contrast agents' PMR studies demonstrated similar findings. Lastly, based on the narrative provided, onset of events appears to have taken place hours after Lumason injection.

One 15-year old female patient experienced arterial hypotension, abdominal pain, and diarrhea following administration of Lumason for a CEUS for liver lesion characterization. The report states that these AEs began on the same day as Lumason injection but does not otherwise specify the exact onset relative to the injection. The patient was treated with steroids and fluids and recovered the same day. Co-morbidities included acute lymphocytic leukemia as well as lung and liver abscesses. The patient had received Lumason the previous month without incident.

Reviewer comment: Although the patient responded to steroids and fluids suggesting that the symptoms described above were the result of a hypersensitivity reaction, the patient's co-morbidities could provide alternative explanations for the reported symptoms; the exact time course relative to the Lumason injection is also uncertain.

One 14-year old male patient experienced abdominal pain, hypoxia, and cyanosis 10 minutes after receiving Lumason for CEUS of the liver for assessment of metastatic lesions. The

symptoms were relieved with dexamethasone and epinephrine injection. The sponsor deemed the causality to Lumason as plausible.

Reviewer comment: Hypoxia and dyspnea are described in the label under serious cardiopulmonary reactions that may occur following administration of ultrasound contrast.

In addition to this reviewer's evaluation of the AEs in the sponsor's post-marketing database, the Division of Pharmacovigilance in the Office of Surveillance and Epidemiology performed a Pediatric Postmarketing Pharmacovigilance Review in accordance with PREA. Reports of serious AEs involving the use of Lumason in pediatric patients between October 10, 2014 and July 18, 2019 were retrieved from the FDA Adverse Events Reporting System (FAERS) database. The review identified no new safety signals or an increased severity or frequency of serious AEs.

Usage in Age Group ≤ 9 Years

At the time of submission of the Request for Waiver of Pediatric Studies in the age group below 9 years of age, Bracco reported "absence of clinical experience of contrast use in rest echocardiography in that age group, implying absent or extremely limited clinical need of the intended indication in patients aged between 1 and 8 years."⁷ This justification was based on (1) Bracco's survey of 10 pediatric cardiologists from 10 well-established pediatric cardiology departments, which reported that contrast-enhanced echocardiography was rarely performed (1 center reported use) and when performed it was in the setting of stress echocardiography in patients with Kawasaki's disease, a rare disease, and (2) literature search finding only a single study of use in children with severely limited transthoracic echocardiographic views, which evaluated 20 children between 9 to 18 years of age⁸.

(b) (4)

⁷ Bracco Diagnostics Inc. Request for Waiver of Pediatric Studies, 5/13/2013, NDA 203684

⁸ McMahon CJ, Ayres NA, Bezold LI, Lewin MB, Alonzo M, Altman CA, Kovalchin JP, Eidem BW, Pignatelli RH. Safety and efficacy of intravenous contrast imaging in pediatric echocardiography. *Pediatr Cardiol.* 2005;26:413-17.

Reviewer comment: Lumason is currently approved in all pediatric age groups for liver lesion characterization without special concern for pulmonary maturity. Per the PK study described in the label, in patients with pulmonary impairment, the terminal half-life of SF₆ was similar to that measured in healthy subjects. Additionally, the 4 literature studies submitted for safety included children less than 9 years of age and included off-label use of Lumason.

The (b) (4) usage data⁹ reported 2726 contrast-enhanced echocardiograms performed in the 0 to 12 age group during the time the sponsor was recruiting patients for this PMR study (year 2015 to 2017); however, there is no breakdown by age, reason for echocardiographic examination (rest or stress imaging), or reason for contrast-enhanced examination (presence of suboptimal unenhanced imaging). Regardless, the numbers suggest that children ≤ 9 years of age may benefit from contrast-enhanced echocardiography.

The sponsor's Table A (reproduced as Table 5 below) presents this use data. Note that the numbers provided are for use of all approved ultrasound contrast agents: Definity, Optison, and Lumason. However, Bracco provided a similar table restricted to Lumason use only, and no use was seen in children 17 years of age and younger for pediatric echocardiography.

Table 5: Contrast Enhanced Cardiac Echo Exams by Year and Age (All Approved Agents)

Age Group (years)	Number of Contrast Enhanced Echocardiography Procedures (1)							
	2015	% Total CE Procedures	2016	% Total CE Procedures	2017 (first half)	% Total CE Procedures	Cumulative 2015-1H2017	% Total Cumulative CE Procedures
0-12	277	0.02%	0	0.00%	2,449	0.28%	2,726	0.07%
13-17	0	0.00%	1,457	0.09%	0	0.00%	1,457	0.04%
18-29	41,696	2.88%	12,612	0.78%	12,300	1.38%	66,304	1.68%
30-49	341,149	23.73%	239,681	14.90%	78,969	8.87%	659,799	16.76%
50-64	375,959	26.15%	586,990	26.50%	239,361	26.90%	1,202,310	30.55%
65-74	398,898	27.75%	418,461	26.02%	299,193	33.62%	1,116,552	28.37%
≥75	279,933	0.02%	349,083	21.71%	257,590	28.950%	886,606	22.53%
Total	1,437,608	100.00%	1,608,284	100.00%	889,862	100.00%	3,935,754	100.00%
All <18	277	0.03%	1,457	0.09%	2,449	0.28%	4,183	0.11%
All ≥18	1,157,678	99.97%	1,606,827	99.91%	887,413	99.72%	3,931,571	99.89%

(1) Includes all recorded CE Echocardiography procedures for Lumason, Definity and Optison during specified time interval. CE Echocardiography = 2D Transthoracic echo; 2D Stress/Rest echo; Transesophageal echo

⁹ Source: Bracco Diagnostics Inc. submission dated February 27, 2018 reporting data obtained from (b) (4)

In addition, although the non-Lumason published studies submitted by the sponsor were not evaluated for efficacy or safety, at least one study did include children under 9 for either rest or stress contrast-enhanced echocardiography, indicating potential use in children below 9. In this publication by Kutty, et al. (2016), an age range for 5 to 21 years was described for the 113 patients studied.¹⁰

Pediatrics Consult:

The pediatric consult team provided recommendations for the relevant sections in the label. In addition, they provided input on the applicability of the pediatric safety data used for the liver indication to the proposed pediatric echocardiography population: “DPMH also agrees that the pediatric safety information for the liver indication is directly relevant to pediatric patients being studied for the echocardiography indication.” They did not raise any specific safety concerns in the pediatric echocardiography population that are not present in the population undergoing evaluation for the liver lesion characterization indication and agreed with extension of the pediatric echocardiography indication down to birth.

Emboic Potential in Children with (Large) Shunts:

Study BR1-140 excluded patients with known right-to-left, bidirectional or transient cardiac shunts. Patients were to be evaluated for possible shunts with an agitated saline study performed before the administration of Lumason. Previously Lumason (like all ultrasound contrast agents) was contraindicated in patients with shunts; that contraindication has since been removed with the following warning in place in section 5.3: “When administering Lumason to patients with cardiac shunt, microspheres can bypass filtering by the lung and enter the arterial circulation.” The removal of the contraindication was requested by the sponsor of Optison^{11,12} and was supported by the lack of embolic phenomena in post-marketing reporting as well as a study by Kalra¹³ which included 418 adult patients with right-to-left shunts who

¹⁰ Kutty S, Xiao Y, Olson J, Xie F, Danford DA, Erickson CC et al. Safety and Efficacy of Cardiac Ultrasound Contrast in Children and Adolescents for Resting and Stress Echocardiography. *J Am Soc Echocardiogr* 2016; 29:655-62.

¹¹ Clinical Review, September 15, 2016, NDA 20899 by Scheldon Kress.

¹² Consult Memorandum from the Division of CardioRenal Products, June 2, 2016, NDA 20899 by Shari Targum.

¹³ Kalra A, Shroff GR, Erlie D, Gilertson DT, Herzog CA. Perfluten-Based Echocardiographic Contrast in Patients with Right-To-Left Intracardiac Shunts. *JACC: Cardiovascular Imaging* 2014; 7(2):204-9.

underwent contrast echocardiography without AEs. The Kalra study did exclude patients with cyanotic congenital heart disease, however.

For the June 24, 2008, CardioRenal Drugs Advisory Committee, Bracco provided a briefing package which included pre-clinical studies of intra-arterial injections of Lumason¹⁴. In the first experiment, "SonoVue was administered directly into the right carotid artery of anesthetized rats at a dose of 1 mL/kg (approximately 30 times the expected human dose)...No cerebral infarct was detected in the brain after intracarotid injections of SonoVue." The study did include a positive control group where detection of cerebral injury occurred. In the second experiment, following intra-arterial administration of SonoVue into rats (spinothoracic microcirculation), "the microvascular behavior of SonoVue microbubbles and the extent of microbubbles retention were evaluated by intravital microscopy immediately after intra-arterial injection at dose levels corresponding to large multiples of the imaging dose...In few microvessels some rare bubbles were transiently retained. There was no evidence of red blood cell modification, or of leukocyte and platelet adhesion at the site of retainment, nor of thrombosis. Retained microbubbles were primarily observed in capillaries (< 6 μm). Retained microbubbles were very flexible and could modify their shape. Elongation of microbubbles was seen in microvessels. Retained microbubbles moved along the microvessels intermittently while decreasing size due to gas dissolution. No retained microbubbles were observed 20 minutes after intra-arterial injection."

For reference, the diameter of the neonatal capillaries can be as small as 3 to 5 μm ¹⁵, and the average red blood cell diameter in neonates is 8.5 μm ^{15,16}. Per the Lumason label, the mean diameter of the microspheres is 1.5 to 2.5 μm , with $\geq 99\%$ of microbubbles $\leq 10 \mu\text{m}$, and 100% of microbubbles $\leq 20 \mu\text{m}$. The size of Lumason microbubbles relative to the neonatal capillaries and red blood cells together with Bracco's pre-clinical studies of microbubble deformability and intra-carotid injection makes an embolic event related to shunting seem unlikely. The existing warning regarding cardiac shunts appears to adequately address any residual concern, even in patients aged down to birth.

¹⁴ <https://wayback.archive-it.org/7993/20170405035223/https://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4369b1-06.pdf>

¹⁵ Rosenkrantz TS and Oh W. (2013). Polycythemia and hyperviscosity in the newborn. In de Alarcon P, Werner E, and Christensen RD (Eds.), *Neonatal Hematology: Pathogenesis, Diagnosis, and Management of Hematologic Problems* (2nd ed, p 130). Cambridge, UK: Cambridge University Press.

¹⁶ Linderkamp O, Wu PY, Meiselman JH. Geometry of neonatal and adult red blood cells. *Pediatr Res* 1983; 17(4):250-3.

Conclusion

This efficacy supplement to extend the echocardiography indication from adults to pediatrics is approvable based on extrapolation from adult data as supported by new pediatric evidence provided by study BR1-140. While we do not directly have use data from the 0 to 9 year age group (only 0 to 12 year age group as above), there are no specific safety concerns for the use of Lumason in children under 9 years of age for echocardiography. Given the published literature of the safety of intravenous use of Lumason in pediatric patients, including those under 9 years of age, and the fact that the drug is already approved for all pediatric age groups for the liver lesion indication, the pediatric echocardiography indication should be extended to pediatric patients of all ages.

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