Ultrasound

LUMASON®

(sulfur hexafluoride lipid-type A microspheres)
for injectable suspension, for intravenous use or intravesical use

From Bracco Diagnostics Inc.—
A GLOBAL LEADER IN ENHANCED ULTRASOUND

LUMASON FORMULARY KIT

Product Monograph
Safety Data Sheet
FDA Approval Letters
Prescribing Information

Please see full Prescribing Information for LUMASON including boxed **WARNING** in this document and at http://www.braccoimaging.com/us-en/products-and-solutions/contrast-enhanced-ultrasound/lumason/prescribing-information.

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LIFE FROM INSIDE

INDICATIONS AND USAGE[1]

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 patients with suboptimal echocardiograms
- in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients
- in ultrasonography of the urinary tract for the evaluation of suspected or known vesicoureteral reflux in pediatric patients

CONTRAINDICATIONS[1]

LUMASON is contraindicated in patients with:

- history of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in LUMASON

IMPORTANT SAFETY INFORMATION[1]

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following the injection of ultrasound contrast agents, including sulfur hexafluoride lipid microspheres *[see Warnings and Precautions (5.1)]*. Most serious reactions occur within 30 minutes of administration *[see Warnings and Precautions (5.1)]*.

- **Assess all patients for the presence of any condition that precludes administration *[see Contraindications (4)]*.**
- **Always have resuscitation equipment and trained personnel readily available *[see Warnings and Precautions (5.1)]*.**

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LUMASON is manufactured for Bracco Diagnostics Inc., Monroe Township, NJ 08831 by Bracco Suisse S.A., Plan-les-Ouates Geneve, Switzerland (LUMASON lyophilized powder vial-25 mg lipid-type A/60.7 sulfur hexafluoride gas); Vetter Pharma-Fertigung GmbH & Co. KG, 88212 Ravensburg, Germany (Sodium Chloride 0.9% Injection, USP); B. Braun Melsungen AG, 34212 Melsungen, Germany (Mini-Spike).

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PRODUCT MONOGRAPH

Our commitment to you…

Bracco Diagnostics Inc. is dedicated to providing imaging agents and solutions that improve diagnostic efficacy, patient safety, and cost effectiveness. LUMASON has been developed to meet the needs of modern ultrasound imaging practices.

The ultrasound contrast agent LUMASON, known internationally as SonoVue®, was approved by the U.S. Food and Drug Administration (FDA) in 2014 for echocardiography, to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border, in adult patients with suboptimal echocardiograms. It is important to note that in December 2016, the contraindication for patients with known or suspected right-to-left, bi-directional, or transient right-to-left cardiac shunts was removed from the LUMASON package insert (PI).

Bracco Diagnostics Inc. is proud to introduce a second and third indication for LUMASON. As of March 2016, LUMASON was approved for use in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients.[1] As of December 2016, LUMASON was approved for use in ultrasonography of the urinary tract for the evaluation of suspected or known vesicoureteral reflux in pediatric patients.[1]

LUMASON consists of microspheres that encapsulate an inert gas [sulfur hexafluoride (SF_6)] in a phospholipid shell. LUMASON is provided in a portable, single-use, 3-part kit that includes all components necessary for reconstitution, and requires no refrigeration for storage or mechanical agitation for reconstitution.[1]

LUMASON®
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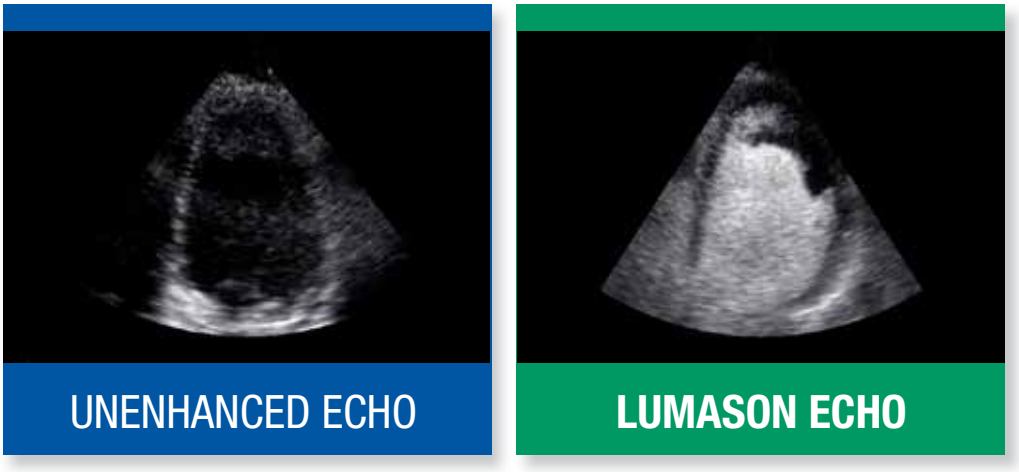

Echocardiographic images are courtesy of Stephen Glen, Forth Valley Royal Hospital, Larbert, United Kingdom.
Individual results may vary.

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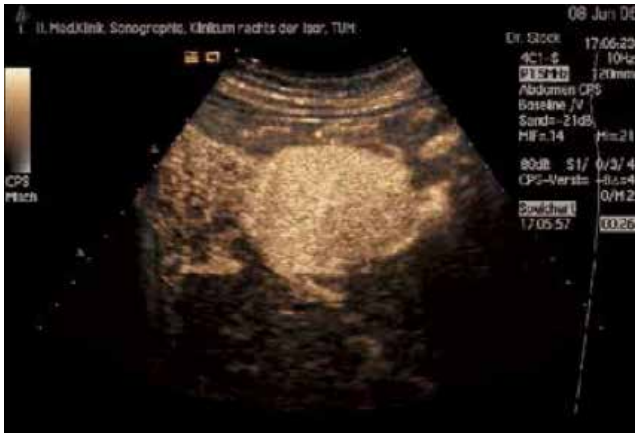

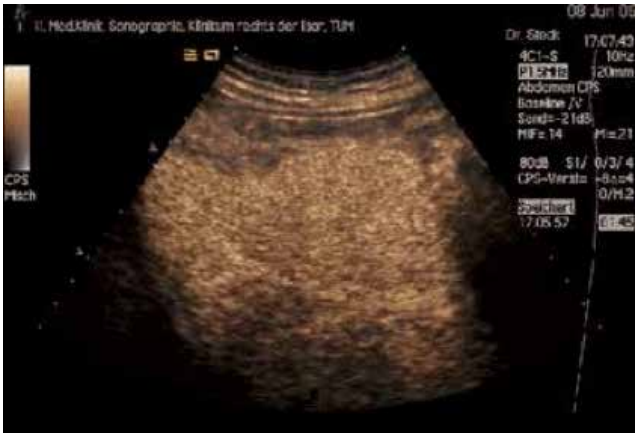

Liver ultrasound images are courtesy of Dr. Stock, Clinic Rechts der Isar of the Technical University of Munich. Individual results may vary.

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LUMASON PROFILE AT A GLANCE

- LUMASON is a second-generation ultrasound contrast agent that has been developed to provide an optimal backscattered signal over a broad frequency range, with good pressure stability and persistence in the blood stream.[2]
- LUMASON is characterized by a microsphere structure consisting of a low solubility gas (sulfur hexafluoride, SF_6) surrounded by a monolayer phospholipid outer shell.[1]
- LUMASON is indicated: (1) in echocardiography 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, (2) in ultrasonography of the liver for use in adult and pediatric patients to characterize focal liver lesions, and (3) in ultrasonography of the urinary tract for the evaluation of suspected or known vesicoureteral reflux in pediatric patients.[1]
- LUMASON is contraindicated in patients with history of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in LUMASON.[1]
- LUMASON is provided in a portable 3-part kit, allowing for easy reconstitution, and requires no refrigeration or agitation device. Each kit contains a LUMASON vial containing 25 mg lipid-type A lyophilized powder with headspace filled with 60.7 mg of SF_6; a prefilled syringe containing 5 mL Sodium Chloride 0.9% Injection, USP (diluent); and a Mini-Spike.[1]
- Mechanism of action (MOA): Within the blood, the acoustic impedance of LUMASON microspheres is lower than that of the surrounding nonaqueous tissue. When an ultrasound beam is reflected from the interface between the microspheres and the surrounding tissue, that reflected ultrasound signal provides a visual image that depicts contrast between the blood and the surrounding tissues.[1] For ultrasonography of the urinary tract in pediatric patients, the intravesically administered LUMASON microspheres increase signal intensity of fluids within the urethra, bladder, ureters, and renal pelvis.[1]
- Pharmacokinetics: When administered to healthy volunteers at approximately 1 and 10 times the recommended doses, concentrations of the SF_6 gas component of LUMASON in blood peaked within 1 to 2 minutes for both doses. The terminal half-life of SF_6 in blood was approximately 10 minutes for the higher dose; the terminal half-life could not be estimated for the recommended dose.[1]
  - In a study of patients with pulmonary impairment, blood concentrations of SF_6 peaked at 1 to 4 minutes following LUMASON administration. The cumulative recovery of SF_6 in expired air was 102% ± 18% (mean ± standard deviation), and the terminal half-life of SF_6 in blood was similar to that measured in healthy subjects.
- Elimination and metabolism: The SF_6 gas component of LUMASON is eliminated via the lungs. SF_6 undergoes first-pass elimination within the pulmonary circulation, with approximately 40% to 50% of the SF_6 eliminated in the expired air during the first minute after LUMASON injection. Because SF_6 undergoes little or no biotransformation, 88% of an administered dose is recovered unchanged in expired air.[1] The phospholipid component of the microsphere shell is metabolized, re-entering the endogenous phospholipid metabolic pathway.[3]

LUMASON PRODUCT CHARACTERISTICS

LUMASON DESCRIPTION

Each vial is formulated as a 25 mg sterile, pyrogen-free lyophilized powder containing 24.56 mg polyethylene glycol 4000, 0.19 mg distearoylphosphatidyl-choline (DSPC), 0.19 mg dipalmitoylphosphatidylglycerol sodium (DPPG-Na), and 0.04 mg palmitic acid. The headspace of each vial contains 6.07 mg/mL (±2%) sulfur hexafluoride (SF_6), or 60.7 mg per vial. Each prefilled syringe with 5 mL of diluent 0.9% Sodium Chloride Injection is sterile, nonpyrogenic, and preservative free containing 9 mg sodium chloride per mL. Upon reconstitution with 5 mL diluent, LUMASON is a milky white, homogeneous suspension containing sulfur hexafluoride lipid-type A microspheres. The suspension is isotonic and has a pH of 4.5 to 7.5; it is only for intravenous and/or intravesical administration.[1]

The sulfur hexafluoride lipid microspheres are composed of SF_6 gas in the core surrounded by a monolayer phospholipid outer shell consisting of DSPC and DPPG-Na with palmitic acid as a stabilizer. Each milliliter of reconstituted LUMASON suspension contains 1.5 to 5.6 $\times 10^8$ microspheres, 68 mcg SF_6 (12 mcL), 0.038 mg DSPC, 0.038 mg DPPG-Na, 4.91 mg polyethylene glycol 4000, and 0.008 mg palmitic acid. The sulfur hexafluoride associated with the microspheres suspension is 45 mcg/mL. 15 to 23 percent of the total lipids in the suspension are associated with the microspheres. The sulfur hexafluoride lipid microsphere characteristics are listed in **Table 1**.[1]

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Table 1. Microsphere Characteristics[1]

Mean diameter range	1.5–2.5 µm
Percent of microspheres ≤10 µm	≥99%
Upper size limit	100.0% ≤20 µm

MECHANISM OF ACTION

LUMASON microspheres are transported in the body by the blood stream. They move freely within the capillaries because they are smaller than red blood cells; however, they are large enough that they do not leave the vascular system. They are capable of circulating throughout the body and are much more effective at scattering sound than red blood cells, thus providing a greatly enhanced blood pool signal.[4,5]

Within the blood, the acoustic impedance of LUMASON microspheres is lower than that of the surrounding non-aqueous tissue. Therefore, an ultrasound beam is reflected from the interface between the microspheres and the surrounding tissue. The reflected ultrasound signal provides a visual image that depicts contrast between the blood and the surrounding tissues.[1] For ultrasonography of the urinary tract in pediatric patients, the intravesically administered LUMASON microspheres increase signal intensity of fluids within the urethra, bladder, ureters, and renal pelvis.[1]

PHARMACODYNAMIC PROPERTIES

LUMASON provides useful echocardiographic signal intensity for 2 minutes after the injection. LUMASON microspheres are destroyed and contrast enhancement decreases as the mechanical index increases (values of 0.8 or less are recommended). For ultrasonography of the liver, LUMASON provides dynamic patterns of differential signal intensity enhancement between focal liver lesions and liver parenchyma during the arterial, portal venous, and late phase of signal intensity enhancement of the microvasculature.[1] In ultrasonography of the urinary tract, LUMASON facilitates the detection of reflux of fluid from the bladder into the ureters.[1]

PHARMACOKINETIC PROPERTIES

The pharmacokinetics of the SF_6 gas component of LUMASON was evaluated in 12 healthy adult subjects (7 men and 5 women). After intravenous bolus injections of 0.03 mL/kg and 0.3 mL/kg of LUMASON, corresponding to approximately 1 and 10 times the recommended doses, concentrations of SF_6 in blood peaked within 1 to 2 minutes for both doses. The terminal half-life of SF_6 in blood was approximately 10 minutes for the 0.3 mL/kg dose. (At the 0.03 mL/kg dose, terminal half-life could not be estimated). The area-under-the-curve of SF_6 was dose-proportional over the dose range studied.[1]

Distribution

In a study of healthy subjects, the mean values for the apparent steady-state volume of distribution of SF_6 were 341 mcL and 710 mcL for LUMASON doses of 0.03 mL/kg and 0.3 mL/kg, respectively. Preferential distribution to the lung is likely responsible for these values.[1]

Elimination

Elimination of the active ingredient of LUMASON (SF_6) is via exhalation from the lungs. In a clinical study that examined SF_6 elimination 20 minutes after LUMASON injection, the mean (±SD) cumulative recovery of SF_6 in expired air was 82% ± 20% at the 0.03 mL/kg dose and 88% ± 26% at the 0.3 mL/kg dose. SF_6 undergoes first-pass elimination within the pulmonary circulation; approximately 40% to 50% of the SF_6 content was eliminated in the expired air during the first minute after LUMASON injection.[1]

Metabolism

SF_6 undergoes little or no biotransformation; 88% of an administered dose is recovered unchanged in expired air.[1] While SF_6 is exhaled through the lungs, the phospholipid component of the microsphere shell is metabolized, re-entering the endogenous phospholipid metabolic pathway.[3]

PHARMACOKINETICS IN SPECIAL POPULATIONS

Pulmonary Impairment

In a study of patients with pulmonary impairment, blood concentrations of SF_6 peaked at 1 to 4 minutes following LUMASON administration. The cumulative recovery of SF_6 in expired air was 102% ± 18% (mean ± SD), and the terminal half-life of SF_6 in blood was similar to that measured in healthy subjects.[1]

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CONTRAST-ENHANCED ECHOCARDIOGRAPHY

INDICATION

LUMASON is an ultrasound contrast agent indicated 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.[1]

CLINICAL STUDIES IN ECHOCARDIOGRAPHY

A total of 191 patients with suspected cardiac disease and suboptimal non-contrast echocardiography received LUMASON in three multi-center controlled clinical trials (76 patients in Study A, 62 patients in Study B, and 53 patients in Study C). Among these patients, there were 127 men and 64 women. The mean age was 59 years (range 22 to 96 years). The racial and ethnic representations were 79% Caucasian, 16% Black, 4% Hispanic, <1% Asian, and <1% other racial or ethnic groups. The mean weight was 204 lb (range 92 to 405 lb). Approximately 20% of the patients had a chronic pulmonary disorder and 30% had a history of heart failure. Of the 106 patients for whom 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. Patients with NYHA Class IV heart failure were not included in these studies.[1]

In Studies A and B, each patient received four intravenous bolus injections of LUMASON (0.5, 1, 2, and 4 mL), in randomized order. In Study C, each patient received two doses of LUMASON (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 LUMASON was compared with 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 the LUMASON dose. Evaluation of left ventricular endocardial border consisted of segment based assessment involving six endocardial segments and using two apical views (2- and 4-chamber views).[1]

Endocardial Border Delineation and Duration of Useful Contrast Effect

In all three studies, administration of LUMASON improved left ventricular endocardial border delineation. The majority of patients who received a 2.0 mL dose of LUMASON had improvement in endocardial border delineation manifested as visualization of at least two additional endocardial border segments. **Table 2** demonstrates the improvement in endocardial border delineation following LUMASON administration as a reduction in percentage of patients with inadequate border delineation in at least one pair of adjacent segments (combined 2-chamber and 4-chamber view). The results are shown by reader.[1]

Table 2. Reduction in Percentage of Patients with Inadequate Border Delineation[1]

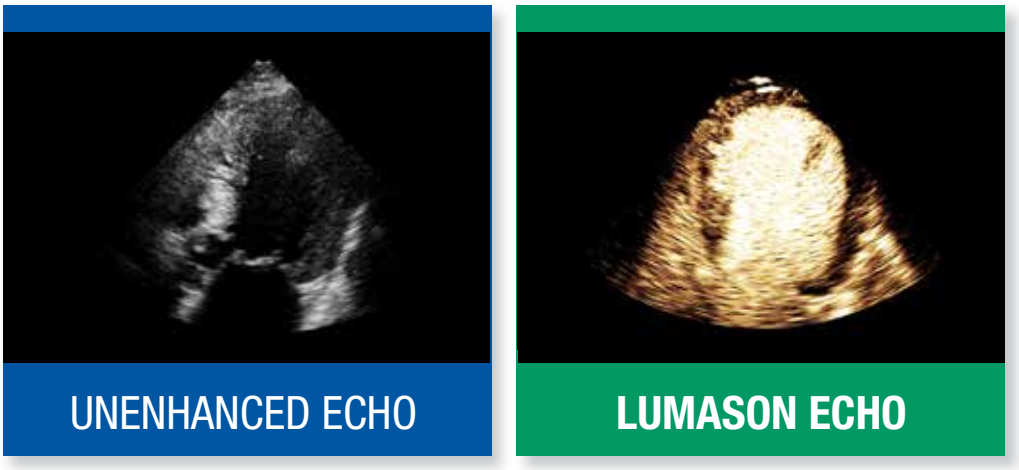
	Study A N = 76		Study B N = 62		Study C N = 53	
Reader	Non-contrast	LUMASON	Non-contrast	LUMASON	Non-contrast	LUMASON
A	60 (79%)	22 (33%)	31 (50%)	12 (19%)	12 (23%)	10 (19%)
B	62 (82%)	29 (37%)	54 (87%)	6 (10%)	45 (85%)	20 (38%)

Following the first appearance of contrast within the left ventricle, the mean duration of useful contrast effect ranged from 1.7 to 3.1 minutes.[1]

Left Ventricular Opacification

In all three studies, complete left ventricular opacification was observed in 52% to 80% of the patients following administration of a 2.0-mL dose of LUMASON. The studies did not sufficiently assess the effect of LUMASON upon measures of left ventricular ejection fraction and wall motion.[1] Examples of left ventricular opacification are provided in **Figure 1**.

Figure 1. Echocardiography without and with LUMASON.



Echocardiographic images are courtesy of Nicola Gaibazzi, Cardiology Department, Parma University Hospital, Parma, Italy.
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PULMONARY HEMODYNAMIC EFFECTS

The effect of LUMASON 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. This study did not assess the effect of LUMASON on visualization of cardiac or pulmonary structures.[1]

CONTRAST-ENHANCED ULTRASOUND OF THE LIVER

The incidence of hepatocellular carcinoma (HCC) in the United States has tripled between 1975 and 2005, and it is now the third leading cause of cancer mortality worldwide.[6] The American Cancer Society estimates that in 2016, about 39,230 new cases of liver and intrahepatic bile duct cancer (28,410 in men and 10,820 in women) will be diagnosed in the United States, and about 27,170 people (18,280 men and 8890 women) will die of these cancers.[7] Liver may also be the site of metastasis from virtually any primary cancer and represents the second most commonly involved organ in metastatic disease.[8] Based on autopsy studies in Japan and the USA, up to 40% of patients with an extrahepatic primary tumor have hepatic metastases.[9] In addition to considerations of patient-related risk factors, physical examination, and liver function tests, imaging plays a major role in noninvasive diagnosis of liver disease, including liver cancer, metastases, and recurrences, and for characterization of focal liver lesions.[10,11] Since benign focal liver lesions are common in both the general population (prevalence of 5%-10%) and patients with known malignancy, an accurate and reliable assessment of the nature of the hepatic lesion is critical in order to differentiate neoplastic lesions from benign abnormalities which might not require treatment.[12] As a matter of fact, characterization of focal liver lesions is a frequently encountered challenge in clinical practice both in patients with neoplastic disease and in those with non-neoplastic disease.[13]

Ultrasound is often used as the first-line imaging modality because it is noninvasive, cost-effective, and safe. Ultrasound may be followed by magnetic resonance (MRI) and/or computed tomography (CT) imaging, with or without contrast.[13] Contrast-enhanced ultrasound (CEUS) has been shown to be more accurate than unenhanced ultrasound for diagnosis of focal liver lesions.[14–17] In addition, CEUS has several advantages over contrast-enhanced MRI and CT imaging, including the ability to evaluate contrast enhancement of lesions in real time and the lack of exposure to ionizing radiation and iodine, therefore representing an imaging alternative for patients with renal function impairment.[14,15,18]

Unlike MRI or CT contrast agents, ultrasound contrast agent microspheres have a purely intravascular distribution and do not distribute throughout the interstitial fluid. This intravascular property contributes to the distinct, characteristic contrast wash-in and wash-out patterns that aid in the characterization of focal liver lesions (**Figures 2 and 3**).[19–22] A large multicenter study of the German Society for Ultrasound in Medicine (DEGUM) involving 1,349 patients investigated the reliability of focal liver lesion characterization on CEUS in comparison to a reference standard (histology or CT and/or MRI). After LUMASON (known globally as SonoVue®) administration, 723 of 755 malignant lesions (sensitivity 95.8%) and 476 of 573 benign lesions (specificity 83.1%) were classified correctly.[23] The sensitivity and specificity of CEUS with LUMASON were comparable to those of CT and MR imaging.[24,25] The high accuracy of LUMASON for the characterization of focal liver lesions has been confirmed by several other large multicenter studies.[17,26–29]

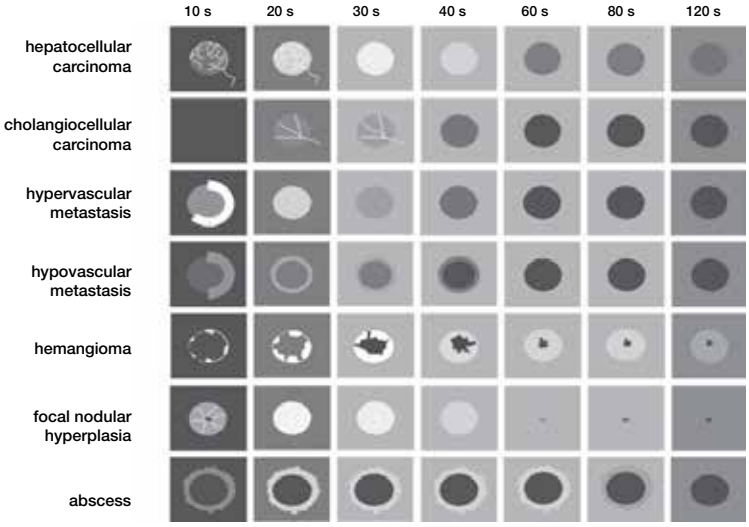

Figure 2. Schematic illustration of the enhancement pattern of focal liver lesions compared to surrounding normal liver tissue.[19]

The architecture of the supplying vessels and/or the pattern and temporal course of the enhancement allow the assessment of the benign or malignant nature of the focal liver lesion and, in many cases, a diagnosis of the lesion type.

Adapted from Greis C. Technological review: contrast-enhanced ultrasonography. In: *Contrast-Enhanced Ultrasound Modality: The New Diagnostic Imaging Tool*. Springer Press; 2008:5.

INDICATIONS AND USAGE[1]

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- in echocardiography to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border in adult patients with suboptimal echocardiograms
- in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients
- in ultrasonography of the urinary tract for the evaluation of suspected or known vesicoureteral reflux in pediatric patients

CONTRAINDICATIONS[1]

LUMASON is contraindicated in patients with:

- history of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in LUMASON

IMPORTANT SAFETY INFORMATION[1]

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following the injection of ultrasound contrast agents, including sulfur hexafluoride lipid microspheres *[see Warnings and Precautions (5.1)]*. Most serious reactions occur within 30 minutes of administration *[see Warnings and Precautions (5.1)]*.

- **Assess all patients for the presence of any condition that precludes administration *[see Contraindications (4)]*.**
- **Always have resuscitation equipment and trained personnel readily available *[see Warnings and Precautions (5.1)]*.**

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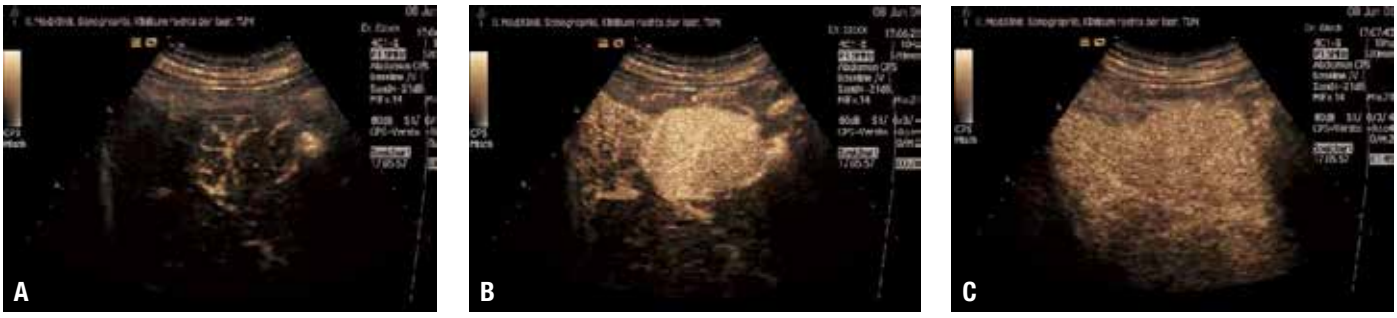
Figure 3. Enhancement pattern of a focal nodular hyperplasia after injection of LUMASON.

(A) In the early arterial phase the stellate vessels originating from the central artery are clearly visible. (B) A few seconds later the lesion is completely and intensely enhanced, indicating a strong arterial blood supply. (C) In the late phase the lesion shows no early wash-out of the contrast agent, indicating a conserved portal-venous blood supply – a sign of the benign character of the lesion.



Liver ultrasound images are courtesy of Dr. Stock, Clinic Rechts der Isar of the Technical University of Munich. Individual results may vary.

THE AMERICAN COLLEGE OF RADIOLOGY CEUS LI-RADS

The Liver Imaging Reporting and Data System (LI-RADS) was developed by the American College of Radiology (ACR) to standardize the categorization and reporting of CT and MRI liver findings from patients with cirrhosis or possessing other risk factors for developing hepatocellular carcinoma (HCC). LI-RADS helps ensure the use of consistent terminology, reduces imaging interpretation variability and errors, enhances communication with referring healthcare providers, and facilitates quality assurance and research.[30]

Acknowledging the importance of contrast-enhanced liver ultrasound, in 2014 the ACR convened a group of radiologists and hepatologists to develop CEUS LI-RADS. In June 2016, the ACR LI-RADS Steering Committee approved the first CEUS LI-RADS, and in 2017 the algorithm was updated. The system includes a lexicon of controlled terminology, schematic illustrations, and a categorization algorithm. CEUS LI-RADS will be updated as experience with this modality increases, technology improves, and in response to ultrasound user feedback.[30]

The CEUS LI-RADS uses the existing LI-RAD LR-1 thru LR-5 categorization system for reporting the likelihood of an observed lesion being benign or malignant. On the lowest end of the scale, LR-1 denotes a finding that is "definitely benign," while on the highest end of the scale LR-5 denotes a lesion that is "definitely HCC." Several other categorizations are included: LR-M, which denotes "probably or definitely malignant but not HCC specific"; LR-NC, which denotes "cannot be categorized due to image degradation or omission"; and LR-TIV, which denotes "tumor in vein." The CEUS LI-RADS algorithm utilizes a 4-step approach for lesion evaluation and confirmation.[30]

Specific indications for liver CEUS for patients at risk for HCC are reviewed in **Table 3**. CEUS LI-RADS also provides information on techniques and technical considerations, suggested imaging workup options and timing intervals for untreated observations, required and recommended reporting content, and imaging features. For more information about LI-RADS, including CEUS LI-RADS, please refer to https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS.

Table 3. Specific CEUS LI-RADS Indications for Patients at Risk for HCC[30]

Assess nodules ≥10 mm detected on ultrasound surveillance
Assess LR-3, LR-4, and LR-M observations detected on prior CT or MRI
Detect APHE when mistiming is suspected as the reason for its absence on prior CT or MRI
Assess biopsied observations with inconclusive histology
Guide biopsy or treatment of observations difficult to visualize with pre-contrast ultrasound
Help select appropriate observation(s) or observation component(s) for biopsy
Monitor changes in enhancement pattern over time for selected CEUS LR-3 or CEUS LR-4 observations
Differentiate tumor in vein ("tumor thrombus") from bland thrombus

APHE=arterial phase hyperenhancement; CEUS=contrast-enhanced ultrasound; CT=computed tomography; HCC=hepatocellular carcinoma; LI-RADS=Liver Imaging Reporting and Data System; MRI=magnetic resonance imaging.

INDICATION

LUMASON is an ultrasound contrast agent indicated for use in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients.[1]

INDICATIONS AND USAGE[1]
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CLINICAL STUDIES IN LIVER ULTRASOUND

Adults

A total of 499 patients with at least 1 focal liver lesion requiring characterization were evaluated in two studies (259 patients in Study A, 240 patients in Study B). Among these patients, there were 259 men and 240 women. The mean age was 56 years (range 19 to 93 years). The racial and ethnic representations were 74% Caucasian, 11% Black, 9% Hispanic, 5% Asian, and 1% other racial or ethnic groups. The mean weight was 80 kg (range 44 to 173 kg).

In both studies, prior to LUMASON administration, gray scale and Doppler (color or power imaging) ultrasound examinations of the target lesion were performed using commercially available ultrasound equipment and using standard techniques. Each patient received an intravenous injection of 2.4 mL LUMASON (up to 2 injections were allowed, 91% patients received 1 injection). Following LUMASON administration, ultrasound examination of the target lesion was carried out using contrast-specific imaging modes operating at MI ≤0.4. The probe was positioned to provide optimal visualization over the target lesion and was kept in the same position for at least 180 seconds.

Truth standard included histology/surgery, contrast CT, contrast MRI, and/or 6-month follow-up.

For each study, the interpretation of images was conducted by three independent readers who were blinded to clinical data. Lesions were characterized as malignant or benign. Separate blinded readers assessed the truth standard images.

Results of both studies demonstrated an improvement in characterization of focal liver lesions using LUMASON ultrasound compared to non-contrast ultrasound images. **Table 4** summarizes the efficacy results by reader.

Table 4. Diagnostic Performance of LUMASON Ultrasound for Characterization of Focal Liver Lesions[1]

Study A:

	Sensitivity (patients with malignant lesions) N = 119			Specificity (patients with benign lesions) N = 140		
	LUMASON %	Non-contrast %	Difference (95% CI)	LUMASON %	Non-contrast %	Difference (95% CI)
Reader 1	87*	49	38 (30, 54)	71	63	8 (–4, 21)
Reader 2	76*	35	41 (29, 52)	83*	54	29 (21, 44)
Reader 3	92*	16	76 (67, 84)	73*	22	51 (40, 61)

Study B:

	Sensitivity (patients with malignant lesions) N = 124			Specificity (patients with benign lesions) N = 116		
	LUMASON %	Non-contrast %	Difference (95% CI)	LUMASON %	Non-contrast %	Difference (95% CI)
Reader 4	65	53	12 (–1, 23)	72*	24	48 (35, 58)
Reader 5	61*	41	20 (7, 32)	67*	7	60 (50, 70)
Reader 6	47	66	–19 (–31, –7)	88*	59	29 (18, 40)

*Statistically significant improvement from non-contrast ($P<0.05$ based on McNemar's test).

Pediatric Patients

In one published study, 44 patients with an indeterminate focal liver lesion (23 males, 21 females, age range 4–18 years; median 11.5 years) were evaluated after intravenous bolus administration of 1.2 to 2.4 mL LUMASON. The findings of LUMASON ultrasound images were compared with CT, MRI, or histology. Specificity was 98% (43/44 patients).

PHARMACOECONOMIC ANALYSIS OF CEUS WITH LUMASON IN LIVER IMAGING

In 2012, the National Institute for Health and Care Excellence (NICE) in the United Kingdom published recommendations for use of CEUS with SonoVue (LUMASON in the United States) in liver imaging.[31] As part of this diagnostic guidance document, a de novo economic analysis was performed by an External Assessment Group. Three different models were used and in each, CEUS with SonoVue®/LUMASON was compared with contrast-enhanced CT and contrast-enhanced MRI. In addition, for each model, average costs, expected life years, and expected quality-adjusted life years (QALYs) for each technology were calculated.

Model 1: Using the "Cirrhosis Surveillance" model, CEUS was shown to have the lowest discounted lifetime costs per person, followed by contrast-enhanced CT and contrast-enhanced MRI with gadolinium. Compared with CEUS, contrast-enhanced CT was as effective but more costly, whereas MRI with gadolinium was more effective, but much more costly.[31]

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- in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients
- in ultrasonography of the urinary tract for the evaluation of suspected or known vesicoureteral reflux in pediatric patients

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Model 2: With the "Potential Liver Metastases from Colorectal Cancer" model, using the different imaging techniques to investigate potential liver metastases from colorectal cancer, CEUS and contrast-enhanced CT were both cost-effective technologies, with equal expected costs and effectiveness. Contrast-enhanced MRI with gadolinium was more costly than either contrast-enhanced CT or CEUS.[31]

Model 3: Finally, using the "Incidentally Detected Focal Liver Lesions" model, the lower costs of CEUS, combined with slightly better test performance, meant that CEUS dominated both contrast-enhanced CT and contrast-enhanced MRI.[31]

Based on their economic analysis, NICE[31] has recommended that CEUS with SonoVue/LUMASON be used for:

- Characterizing incidentally detected focal liver lesion in adults in whom an unenhanced ultrasound scan is inconclusive. An unenhanced ultrasound scan in which a focal liver lesion is detected, but not characterized, is defined as inconclusive.
- Investigating potential liver metastases in adults if contrast-enhanced CT is not clinically appropriate, is not accessible, or is not acceptable to the person, and in whom an unenhanced ultrasound scan is unsatisfactory and contrast is needed for further diagnosis.
- Characterizing focal liver lesion in adults whose cirrhosis is being monitored if contrast-enhanced MRI is not clinically appropriate, is not accessible, or is not acceptable to the person, and when unenhanced ultrasound scan is inconclusive.

CONTRAST-ENHANCED ULTRASOUND OF THE URINARY TRACT IN CHILDREN

Vesicoureteral reflux (VUR) is a urinary tract abnormality common among neonates, infants, and children. VUR is characterized by retrograde flow of urine from the bladder into the ureter and toward the kidney.[32] VUR is found in approximately 1% of the pediatric population in the United States and Europe, and 20% to 50% of pediatric patients with recurrent urinary tract infections (UTIs) have VUR.[32,33] Recurrent UTIs associated with VUR may also be responsible for febrile UTIs and pyelonephritis, which may lead to permanent kidney damage in children.[34,35] Voiding cystourethrography and direct radionuclide cystography are commonly performed to diagnose VUR.[32] However, both of these modalities expose children to ionizing radiation in the genital area, and children with VUR may require serial imaging.[33] Contrast-enhanced ultrasonography of the urinary tract is emerging as a diagnostic tool to assess pediatric patients for VUR because it does not require exposure to ionizing radiation and has been reported to have diagnostic performance similar to that of voiding cystourethrography and direct radionuclide cystography.[33]

In December 2016, LUMASON became the only ultrasound contrast agent to obtain FDA approval for use in ultrasonography of the urinary tract (voiding ultrasonography) for the evaluation of suspected or known VUR in pediatric patients.

INDICATION

LUMASON is an ultrasound contrast agent indicated for use in ultrasonography of the urinary tract for the evaluation of suspected or known vesicoureteral reflux in pediatric patients.[1]

CLINICAL STUDIES IN ULTRASONOGRAPHY OF THE URINARY TRACT IN PEDIATRIC PATIENTS

The efficacy of LUMASON for the evaluation of pediatric patients with suspected or known vesicoureteral reflux was established in two published open-label single-center studies (A and B). Patients received 1 mL of LUMASON intravesically and underwent voiding urosonography (VUS). Patients were also evaluated with voiding cystourethrography (VCUG) as the reference standard. The presence or absence of urinary reflux with LUMASON ultrasound was compared to the radiographic reference standard.[1]

Study A evaluated 183 patients (94 male, 89 female; age 2 days - 44 months) with a total of 366 kidney-ureter units. The images were interpreted by one on-site reader, blinded to the reference standard. Out of 103 reference standard-positive images, LUMASON VUS was positive in 89 units and falsely negative in 14 units. In 263 units with negative reference standard, the LUMASON ultrasonography was negative in 226 and falsely positive in 37.[1]

Study B evaluated 228 patients (123 male, 105 female; age 6 days -13 years) with a total of 463 kidney-ureter units (some patients had more than 2 units). The images were interpreted independently by two on-site readers, blinded to the reference standard. Out of 71 reference standard-positive images, LUMASON ultrasonography was positive in 57 and falsely negative in 14. In 392 units with negative reference standard, LUMASON ultrasonography was negative in 302 and falsely positive in 90.[1]

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BOXED WARNING

IMPORTANT SAFETY INFORMATION

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It is important to note that in December 2016, the contraindication for patients with known or suspected right-to-left, bi-directional, or transient right-to-left cardiac shunts was removed from LUMASON.

WARNINGS AND PRECAUTIONS

Serious Cardiopulmonary Reactions

Serious cardiopulmonary reactions, including fatalities have occurred uncommonly during or shortly following administration of ultrasound contrast agents, including LUMASON. These reactions typically occurred within 30 minutes of administration. The risk for these reactions may be increased among patients with unstable cardiopulmonary conditions (acute myocardial infarction, acute coronary artery syndromes, worsening or unstable congestive heart failure, or serious ventricular arrhythmias). Always have cardiopulmonary resuscitation personnel and equipment readily available prior to LUMASON administration and monitor all patients for acute reactions.The reported reactions that may follow the administration of ultrasound contrast agents include: fatal cardiac or respiratory arrest, shock, syncope, symptomatic arrhythmias (atrial fibrillation, tachycardia, bradycardia, supraventricular tachycardia, ventricular fibrillation, and ventricular tachycardia), hypertension, hypotension, dyspnea, hypoxia, chest pain, respiratory distress, stridor, wheezing, loss of consciousness, and convulsions.

Hypersensitivity Reactions

Hypersensitivity reactions such as skin erythema, rash, urticaria, flushing, throat tightness, dyspnea, or anaphylactic shock have uncommonly been observed following the injection of LUMASON. These reactions may occur in patients with no history of prior exposure to sulfur hexafluoride lipid containing microspheres. Always have cardiopulmonary resuscitation personnel and equipment readily available prior to LUMASON administration and monitor all patients for hypersensitivity reactions.

Systemic Embolization

When administering LUMASON to patients with cardiac shunt, microspheres can bypass filtering by the lung and enter the arterial circulation. Assess patients with shunts for embolic phenomena following LUMASON administration. LUMASON is only for intravenous and/or intravesical administration; do not administer LUMASON by intra-arterial injection (see Dosage and Administration).

Ventricular Arrhythmia Related to High Mechanical Index

High ultrasound mechanical index values may cause microsphere cavitation or rupture and lead to ventricular arrhythmias. Additionally, end-systolic triggering with high mechanical indices has been reported to cause ventricular arrhythmias. LUMASON is not recommended for use at mechanical indices greater than 0.8.

INDICATIONS AND USAGE[1]
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IMPORTANT SAFETY INFORMATION[1]

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Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following the injection of ultrasound contrast agents, including sulfur hexafluoride lipid microspheres *[see Warnings and Precautions (5.1)]*. Most serious reactions occur within 30 minutes of administration *[see Warnings and Precautions (5.1)]*.
- **Assess all patients for the presence of any condition that precludes administration *[see Contraindications (4)]*.**
- **Always have resuscitation equipment and trained personnel readily available *[see Warnings and Precautions (5.1)]*.**

The risk for serious cardiopulmonary reactions may be increased among patients with unstable cardiopulmonary conditions (acute myocardial infarction, acute coronary artery syndromes, worsening or unstable congestive heart failure, or serious ventricular arrhythmias) *[see Warnings and Precautions (5.1)]*.[1]

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ADVERSE REACTIONS

The following serious adverse reactions are discussed in the Warnings and Precautions section:

- Cardiopulmonary reactions
- Hypersensitivity reactions

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

In completed clinical trials, a total of 6984 adult subjects (128 healthy volunteers and 6856 patients) received LUMASON at cumulative doses ranging from 0.2 to 161 mL (mean 9.8 mL). LUMASON was administered mainly as single or multiple injections; however, some subjects received infusion dosing. The majority (75%) of subjects received LUMASON at cumulative doses of 10 mL or less. There were 64% men and 36% women, with an average age of 59 years (range 17–99 years). A total of 79% subjects were Caucasian; 4% were Black; 16% were Asian; <1% were Hispanic; and <1% were in other racial groups or race was not reported.

In the clinical trials, serious adverse reactions were observed in 2 subjects: one who experienced a hypersensitivity-type rash and presyncope, and another who experienced anaphylactic shock shortly following LUMASON administration.

The most commonly reported adverse reactions among patients (occurring among at least 0.2% of patients) are listed in **Table 5**. Most adverse reactions were mild to moderate in intensity and resolved spontaneously.

Table 5. Adverse Reactions in Patients*[1] (n = 6856)	
Number (%) of Patients with Adverse Reactions	340 (5%)
Headache	65 (1%)
Nausea	37 (0.5%)
Dysgeusia	29 (0.4%)
Injection site pain	23 (0.3%)
Feeling hot	18 (0.3%)
Chest discomfort	17 (0.2%)
Chest pain	12 (0.2%)
Dizziness	11 (0.2%)
Injection site warmth	11 (0.2%)

*occurring in at least 0.2% of patients.

Postmarketing Experience

In the international postmarketing clinical experience and clinical trials, serious adverse reactions have uncommonly been reported following administration of LUMASON. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The serious adverse reactions include fatalities, especially in a pattern of symptoms suggestive of anaphylactoid/hypersensitivity reactions. Other serious reactions included arrhythmias and hypertensive episodes. These reactions typically occurred within 30 minutes of LUMASON administration.

USE IN SPECIFIC POPULATIONS

Pregnancy

There are no data with LUMASON use in pregnant women to inform any drug-associated risks. No adverse developmental outcomes were observed in animal reproduction studies with administration of sulfur hexafluoride lipid-type A microspheres in pregnant rats and rabbits during organogenesis at doses up to at least 10 and 20 times, respectively, the maximum human dose of 4.8 mL based on body surface area. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Lactation

There are no data on the presence of LUMASON in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUMASON and any potential adverse effects on the breastfed infant from LUMASON or from the underlying maternal condition.

Pediatric Use

Effectiveness in pediatric patients has been established for use in ultrasonography of the liver for characterization of focal liver lesions from adequate and well-controlled trials in adult patients and a clinical study of 44 pediatric patients. Safety of intravenous use of LUMASON was based on evaluation of published literature involving use of LUMASON in over 900 pediatric patients. Non-fatal anaphylaxis was reported in one pediatric patient.

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- in ultrasonography of the urinary tract for the evaluation of suspected or known vesicoureteral reflux in pediatric patients

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IMPORTANT SAFETY INFORMATION[1]

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- **Assess all patients for the presence of any condition that precludes administration *[see Contraindications (4)]*.**
- **Always have resuscitation equipment and trained personnel readily available *[see Warnings and Precautions (5.1)]*.**

The risk for serious cardiopulmonary reactions may be increased among patients with unstable cardiopulmonary conditions (acute myocardial infarction, acute coronary artery syndromes, worsening or unstable congestive heart failure, or serious ventricular arrhythmias) *[see Warnings and Precautions (5.1)]*.[1]

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Effectiveness in pediatric patients has been established for use in ultrasonography of the urinary tract for the evaluation of suspected or known of vesicoureteral reflux from two published studies comprising a total of 411 pediatric patients. Safety of intravesical use of LUMASON was based on evaluation of published literature involving use of LUMASON in over 6000 pediatric patients. No adverse reactions were reported.

Safety and effectiveness in pediatric patients have not been established for use in echocardiography.

Geriatric Use

Of the total number of 6856 adult patients in clinical studies of LUMASON, 39% were 65 and older, while 11% were 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly or younger patients, but greater sensitivity of some older individuals cannot be ruled out.

PATIENT COUNSELING INFORMATION

Advise patients to inform their healthcare provider if they develop any symptoms of hypersensitivity after LUMASON administration including rash, wheezing, or shortness of breath.

LUMASON DOSAGE AND ADMINISTRATION

IMPORTANT ADMINISTRATION INSTRUCTIONS

Do not administer LUMASON by intra-arterial injection (see Warnings and Precautions).

RECOMMENDED DOSAGE

Echocardiography

The recommended dose of LUMASON after reconstitution is 2 mL administered as an intravenous bolus injection during echocardiography. During a single examination, a second injection of 2 mL may be administered to prolong contrast enhancement. Follow each LUMASON injection with an intravenous flush using 5 mL of 0.9% Sodium Chloride Injection.

Ultrasonography of the Liver

Adults

The recommended dose of LUMASON after reconstitution in adult patients is 2.4 mL administered as an intravenous injection during ultrasonography of the liver. During a single examination, a second injection of 2.4 mL may be administered, if needed. Follow LUMASON injection with an intravenous flush using 5 mL of 0.9% Sodium Chloride Injection.

Pediatric Patients

The recommended dose of LUMASON after reconstitution in pediatric patients is 0.03 mL per kg administered as an intravenous injection during ultrasonography of the liver. During a single examination, a second injection of 0.03 mL per kg may be administered, if needed. Do not exceed 2.4 mL per injection. Follow LUMASON injection with an intravenous flush of 0.9% Sodium Chloride Injection.

Ultrasonography of the Urinary Tract

Pediatric Patients

The recommended dose of LUMASON after reconstitution is 1 mL. The bladder may be refilled with normal saline for a second cycle of voiding and imaging, without the need of a second LUMASON administration.

HOW SUPPLIED

LUMASON (sulfur hexafluoride lipid-type A microspheres) for injectable suspension is supplied as a single patient-use kit as follows:

- One LUMASON vial of 25 mg lipid-type A white lyophilized powder with headspace fill of 60.7 mg of sulfur hexafluoride
- One prefilled syringe containing 5 mL of Sodium Chloride 0.9% Injection, USP (Diluent)
- One Mini-Spike

Each kit is packaged in a clear plastic container.
(NDC 0270-7099-16) 5 Kits per carton.

STORAGE AND HANDLING

Store the kit at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) (see USP Controlled Room Temperature).

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LUMASON is contraindicated in patients with:
- history of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in LUMASON

IMPORTANT SAFETY INFORMATION[1]

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- **Assess all patients for the presence of any condition that precludes administration *[see Contraindications (4)]*.**
- **Always have resuscitation equipment and trained personnel readily available *[see Warnings and Precautions (5.1)]*.**

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LUMASON PREPARATION

RECONSTITUTION INSTRUCTIONS

LUMASON is supplied within a 3-part single patient-use kit containing the following:

- A LUMASON vial of 25 mg lipid-type A white lyophilized powder with headspace fill of 60.7 mg sulfur hexafluoride
- A prefilled syringe containing 5 mL Sodium Chloride 0.9% Injection, USP (Diluent),
- A Mini-Spike.

Glass vial

Prefilled syringe and its plunger rod

Mini-Spike

- Inspect the LUMASON kit and its components for signs of damage. Do not use the kit if the protective caps on the vial and prefilled syringe are not intact or if the kit shows other signs of damage.
- Under aseptic conditions, reconstitute LUMASON by injecting the prefilled syringe contents (5 mL Sodium Chloride 0.9% Injection) into the LUMASON vial using the following illustrated steps:

1. Connect the plunger rod to the prefilled syringe barrel by screwing it clockwise into the syringe (**PI, Figure 1**).

PI, Figure 1.

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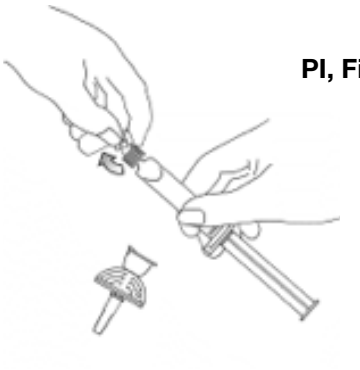
2. Open the Mini-Spike blister and remove the syringe tip cap (**PI, Figure 2**).



PI, Figure 2.

3. Open the Mini-Spike green cap and connect the syringe to the Mini-Spike by screwing it in clockwise (**PI, Figure 3**).

PI, Figure 3.

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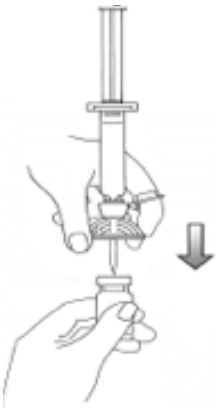
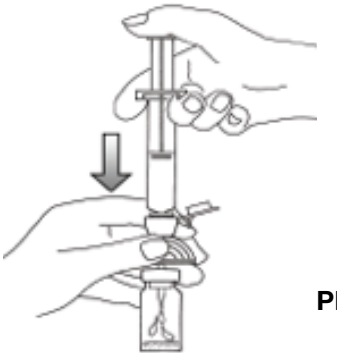
4. Remove the flip cap plastic protective cap from the vial, remove the Mini-Spike spike protection, and position the spike in the center of the rubber stopper of the vial. Press firmly inward until the spike is fully inserted in the stopper (**PI, Figure 4**).



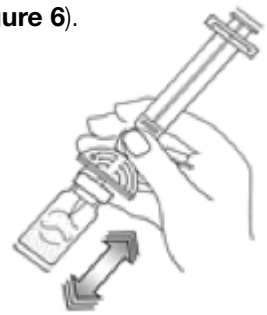
PI, Figure 4.

5. Empty the content of the syringe into the vial by pushing on the plunger rod (**PI, Figure 5**).



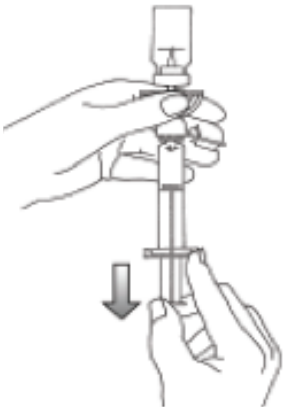
PI, Figure 5.

6. Shake vigorously for 20 seconds, mixing all the contents in the vial (**PI, Figure 6**). A homogeneous white milky liquid indicates formation of sulfur hexafluoride lipid microspheres.



PI, Figure 6.

7. For preparation of doses of greater than or equal to 1 mL, invert the system and slowly withdraw the intended volume of suspension into the syringe (**see PI, Figure 7**). For preparation of doses less than 1 mL, withdraw 2 mL of the reconstituted suspension into the 5 mL syringe and measure the volume of LUMASON to inject by using the 0.2 mL graduations between the 1 and 2 mL marks.



PI, Figure 7.

8. Unscrew the syringe from the Mini-Spike (**see PI, Figure 8**). Peel and remove the diluent label to display the reconstituted product label. For intravenous administration, immediately connect the syringe to a dose administration line (20 G) and administer as directed under the Administration Instructions below. For intravesical administration, immediately connect the syringe to a sterile urinary catheter (6F-8F) and administer as directed under the Administration Instructions below.

PI, Figure 8.

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- Following reconstitution, LUMASON suspension contains 1.5 to 5.6 $\times 10^8$ microspheres/mL with 45 mcg/mL of sulfur hexafluoride.
- Use immediately after reconstitution. If the suspension is not used immediately after reconstitution, resuspend the microspheres for a few seconds by hand agitation before the suspension is drawn into the syringe. Reconstituted suspension within a vial may be used for up to 3 hours from the time of its reconstitution. Maintain the vial containing the reconstituted suspension at room temperature.

ADMINISTRATION INSTRUCTIONS

Inspect visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The reconstituted suspension is milky-white, and does not contain visible particulate matter. Do not use the single-patient use vial for more than one patient.

- Intravenous administration
  1. Administer LUMASON as an intravenous bolus injection.
- Intravesical administration in pediatric patients
  1. Insert a sterile 6 french to 8 french urinary catheter into the bladder under sterile conditions;
  2. Empty the bladder of urine, and then fill the bladder with saline (sterile 0.9% sodium chloride solution) to approximately one third or half of its predicted total volume. The total bladder volume in children is calculated as [(age in years + 2) x 30] mL;
  3. Administer LUMASON as an intravesical bolus injection through the urinary catheter;
  4. Continue filling the bladder with saline until the patient has the urge to micturate or at the first sign of back pressure to the infusion.
  5. Immediately following the first voiding, the bladder may be refilled with normal saline for a second cycle of voiding and imaging, without the need of a second LUMASON administration.

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LUMASON®
(sulfur hexafluoride lipid-type A microspheres)
for injectable suspension, for intravenous use or intravesical use

From Bracco Diagnostics Inc.—

A GLOBAL LEADER IN ENHANCED ULTRASOUND

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SonoVue is a registered trademark of Bracco Suisse S.A.

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BRACCO
LIFE FROM INSIDE

SAFETY DATA SHEET

ACC. TO OSHA HCS

Trade name:
SonoVue (25 mg under sulfur hexafluoride gas) / LUMASON

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Ultrasound

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A GLOBAL LEADER IN ENHANCED ULTRASOUND

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BRACCO
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SAFETY DATA SHEET

ACC. TO OSHA HCS

Trade name:
SonoVue (25 mg under sulfur hexafluoride gas) / LUMASON

1 IDENTIFICATION

Product identifier

Sheet Code: 271
Trade name: SonoVue (25 mg under sulfur hexafluoride gas) / LUMASON
Chemical Name: For active, sulfur hexafluoride.
Synonyms: Sulfur hexafluoride microbubbles for injection.

How Supplied:
Kit consists of a clear glass vial containing 25 mg of lyophilized powder sealed under sulfur hexafluoride gas and capped, transfer system and a 5-mL vial of sterile physiological saline for reconstitution.

Relevant identified uses of the substance or mixture and uses advised against

We recommend that you use this product in a manner consistent with the listed use. If your intended use is not consistent with the stated use, please contact your sales or technical service representative.
Chemical Family: Inert gas containing sulfur and fluoride.

Molecular Formula: SF_6.*

CAS Number:
2551-62-4*
*Information pertains to sulfur hexafluoride.

Details of the supplier of the safety data sheet

Manufacturer/Supplier:
Bracco Diagnostics Inc.
P.O. Box 5225
Princeton, NJ 08543

Further Information Obtainable from:
B-Lands Consulting
WTC, 5 Place Robert Schuman, BP 1516
38025 Grenoble, FRANCE
Tel: +33 476 295 869
Fax: +33 476 295 870
services@reachteam.eu
www.reachteam.eu

Information department:
B-Lands Consulting
WTC, 5 Place Robert Schuman, BP 1516
38025 Grenoble, FRANCE
Tel: +33 476 295 869
Fax: +33 476 295 870
Email: clients@reachteam.eu
www.reachteam.eu

Emergency telephone number:
EMERGENCY CONTACT:
Health: 1-800-257-5181
U.S. Transport - Chemtrec: 1-800-424-9300
International Transport - Chemtrec: 1-703-527-3887

Emergency Overview:
Vials containing a sterile lyophilized white powder in the presence of sulfur hexafluoride gas.
See Health Effects and Toxicology sections for additional information.

2 HAZARD(S) IDENTIFICATION

Classification of the substance or mixture

The product is not classified according to the Globally Harmonized System (GHS).

Label elements

GHS label elements Not applicable.
Hazard pictograms Not applicable.
Signal word Not applicable.
Hazard statements Not applicable.

Effects of Overexposure - Routes of Entry:
Inhalation:
Under normal conditions, this material is handled in closed vials and exposure by inhalation is not expected to occur. Sulfur hexafluoride is a gas that is absorbed following inhalation but rapidly exhaled.
Skin Contact:
Exposure may occur via skin contact if gloves and protective clothing are not worn. No information for absorption through skin.
Ingestion:
Ingestion of large quantities of this material in an occupational setting would not be expected to occur.
Ingestion of trace amounts of the material might occur if the material contacts hands and hands are not washed prior to eating, drinking or smoking.
The extent of systemic absorption of the powder and gas after ingestion is not known.
Note:
When prepared in a clinical setting, physiological saline for injection is added to the vial containing sulfur hexafluoride and lyophile. The resulting solution is intended for intravenous injection, under the care of a physician.
Additional Information:

Information pertaining to particular dangers for man and environment:

Negative Effects on the Health: See also Sections 11
Negative Effects on the Environment: See also Section 12
NFPA ratings (scale 0 - 4)

Health=0
Fire=0
Reactivity=0

HMIS-ratings (scale 0 - 4)

HEALTH	0	Health=0
FIRE	0	Fire=0
REACTIVITY	0	Reactivity=0

Results of PBT and vPvB assessment
PBT: Not applicable.
vPvB: Not applicable.

SAFETY DATA SHEET

ACC. TO OSHA HCS

Trade name:
SonoVue (25 mg under sulfur hexafluoride gas) / LUMASON

3 COMPOSITION/INFORMATION ON INGREDIENTS

Chemical characterization: Substances

Active Ingredient:			
CAS: 2551-62-4 EINECS: 219-854-2	sulphur hexafluoride		Press. Gas, H280
Impurities and stabilising additives:			
CAS: 67232-81-9	Sodium Dipalmitoylphosphatidylglycerol (DPPG)		
CAS: 816-94-4	Diasteroylphosphatidylcholine (DSPC)		
CAS: 57-10-3 EINECS: 200-312-9 RTECS: RT 4550000	palmitic acid, pure		

Chemical characterization: Mixtures

Description: Mixture: consisting of the following components.

Hazardous Components:				
CAS: 2551-62-4 EINECS: 219-854-2	sulphur hexafluoride		Press. Gas, H280	> 1%

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4 FIRST-AID MEASURES

Description of first aid measures

General information: No special measures required.
After Inhalation: Supply fresh air. If required, provide artificial respiration.
After Skin Contact:
Remove contaminated clothing.
Wash with water and rinse thoroughly for 5 minutes.
Seek medical attention if irritation (redness, itching or swelling) develops or persists.
After Eye Contact:
Wash with running water for several minutes holding the eyelids open.
If any symptoms of irritation develop and / or persist, consult your doctor.
After Swallowing:
Get medical attention immediately.
Vomiting may be induced only if a person is conscious and if ingestion has occurred within the past three hours.
Never induce vomiting in a person who is unconscious or experiencing convulsions.

Most important symptoms and effects, both acute and delayed See also Section 2 and 11.

Indication of any immediate medical attention and special treatment needed

No further relevant information available.
Means of Specific and Immediate Treatment to Keep at the Workplace: No special measures required.
Note to physicians: None.

5 FIRE-FIGHTING MEASURES

Extinguishing media

Suitable extinguishing agents: In case of fire, flood with Water

For safety reasons unsuitable extinguishing agents: Unknown.

Special hazards arising from the substance or mixture See also Section 10.
Hazardous Combustion Products:
Carbon Dioxide (CO_2)
In the absence of Oxygen: Carbon Monoxide (CO)
Hydrogen Fluoride (HF)
Sulfur Oxides (SOx)
Additional Information: Not Available

Advice for Firefighters

Evacuate personnel to an upwind direction, remove unneeded material and cool container(s) with water from a maximum distance.
Move container from fire area if you can do it without risk.
Protective Equipment:
Firefighters should wear adequate personal protective equipment with protection of respiratory tract (selfcontained breathing apparatus) (SCBA).
Wear flame and chemicals resistant clothing, boots and gloves (see Section 8).

6 ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures

Avoid inhalation of dust / fog.

[2]Wear protective equipment appropriate to the circumstances (see Section 8)

Environmental precautions: Do not allow product to reach sewage system or any water course.

Methods and material for containment and cleaning up:

Sweep material onto paper and place into a fiber drum for reclamation or disposal.

The spill area should be ventilated and decontaminated after material has been picked up.

Reference to other sections

See Section 7 for information on Safe Handling.

See Section 8 for information on Personal Protection Equipment.

See Section 13 for Disposal Information.

See Section 12 for Ecological Information.

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7 HANDLING AND STORAGE

Precautions for Safe Handling Avoid skin and eye contact.

Conditions for Safe Storage, including any Incompatibilities

Requirements to be met by Storerooms and Receptacles:

Store in a cool, dry place in tightly closed receptacles.

Container Requirements:

Kit consists of a clear glass vial, transfer system and a 5 mL of sterile physiological saline.

Five kits are provided per carton.

Storage Conditions: Store at 15-30 degrees C (59 to 86 degrees F).

Information about Storage in one Common Storage Facility: Not required.

Further information about storage conditions: None.

Specific end use(s) No further relevant information available.

8 EXPOSURE CONTROLS/PERSONAL PROTECTION

Additional information about design of technical systems: No further data; see item 7.

Control parameters

Components with limit values that require monitoring at the workplace:

2551-62-4 sulphur hexafluoride	
PEL (USA) REL (USA) TLV (USA)	6000 mg/m³, 1000 ppm 6000 mg/m³, 1000 ppm 5970 mg/m³, 1000 ppm
25322-68-3 Polyethylene glycol 4000	
OSHA-PEL (USA)	15 mg/m³
TLV-TWA (USA) WEEL (USA)	10 mg/m³ 10 mg/m³ Form: Aerosol

Additional information: The lists that were valid during the creation were used as basis.

Exposure controls

Appropriate Technical Controls: Provide adequate aspiration / ventilation in the workplace

Additional information about Design of Technical Facilities: No further data (see Section 7).

Personal protective equipment

General Protective and Hygienic Measures:

The usual precautionary measures for handling chemicals should be followed.

Wash hands before breaks and at the end of work.

Wear protective equipment (PPE) appropriate to the circumstances.

Do not eat, drink, smoke while working.

Provide appropriate ventilation.

Breathing Equipment:

Not anticipated for normal clinical environment.

In non-routine exposure conditions, where risk assessment shows air-purifying respirators are appropriate, use respirators and components tested and approved under appropriate government standards such as NIOSH (US) or CEN (EU).

Self-contained breathing apparatus should be available for emergency use.

8 EXPOSURE CONTROLS/PERSONAL PROTECTION (continued)

Protection of Hands:

Wear impervious gloves if the potential exists for dermal contact.

Material of Gloves:
Latex, Latex / Nitrile or Nitrile Gloves.
The selection of the suitable gloves does not only depend on the material, but also on further marks of quality and varies from manufacturer to manufacturer.
Selection of the glove material on consideration of the penetration times, rates of diffusion and the degradation.
The glove material has to be impermeable and resistant to the product/ the substance/ the mixture.

Penetration Time of Glove Material:
The exact break through time has to be found out by the manufacturer of the protective gloves and has to be observed.

Eye Protection:

Tightly sealed goggles

Body Protection:
In the case of high concentrations of dust, we recommend using lightweight disposable protective clothing

Limitation and Supervision of Exposure into the Environment: See also Section 7.
Additional Information about Design of Technical Systems: No further data; see Section 7.

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LUMASON is contraindicated in patients with:

- history of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in LUMASON

IMPORTANT SAFETY INFORMATION[1]

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following the injection of ultrasound contrast agents, including sulfur hexafluoride lipid microspheres *[see Warnings and Precautions (5.1)]*. Most serious reactions occur within 30 minutes of administration *[see Warnings and Precautions (5.1)]*.

- **Assess all patients for the presence of any condition that precludes administration *[see Contraindications (4)]*.**
- **Always have resuscitation equipment and trained personnel readily available *[see Warnings and Precautions (5.1)]*.**

The risk for serious cardiopulmonary reactions may be increased among patients with unstable cardiopulmonary conditions (acute myocardial infarction, acute coronary artery syndromes, worsening or unstable congestive heart failure, or serious ventricular arrhythmias) *[see Warnings and Precautions (5.1)]*.[1]

Please see full Prescribing Information for LUMASON including boxed **WARNING** in this document and at http://www.braccoimaging.com/us-en/products-and-solutions/contrast-enhanced-ultrasound/lumason/prescribing-information.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

LUMASON is manufactured for Bracco Diagnostics Inc., Monroe Township, NJ 08831 by Bracco Suisse S.A., Plan-les-Ouates Geneve, Switzerland (LUMASON lyophilized powder vial-25 mg lipid-type A/60.7 sulfur hexafluoride gas); Vetter Pharma-Fertigung GmbH & Co. KG, 88212 Ravensburg, Germany (Sodium Chloride 0.9% Injection, USP); B. Braun Melsungen AG, 34212 Melsungen, Germany (Mini-Spike).

1. LUMASON (sulfur hexafluoride lipid-type A microspheres) for injectable suspension, for intravenous use or intravesical use full Prescribing Information. Monroe Twp., NJ: Bracco Diagnostics Inc.; December 2016.

Bracco Diagnostics Inc. 259 Prospect Plains Road, Building H, Monroe Township, NJ 08831 USA
Phone: 609-514-2200 **Toll Free:** 1-877-272-2269 (U.S. only) **Fax:** 609-514-2446

9 PHYSICAL AND CHEMICAL PROPERTIES

Information on basic physical and chemical properties	Chemical Properties For polyethylene glycol 4000 (PEG 4000) unless indicated otherwise.
General Information	
Appearance:	
Form:	Powder
Color:	White
Odor:	PEG 4000: Mild Odor SF_6: Odorless
Odour threshold:	Not determined.
pH-value:	4.5 - 7.5 (of solution)
Flash point:	PEG 4000: Fp = 246 °C (Closed Cup) SF_6: Fp = Not Flammable.
Flammability (solid, gaseous):	Not determined.
Ignition temperature:	
Decomposition temperature:	Not determined.
Auto igniting:	Product is not selfigniting.
Danger of explosion:	Product does not present an explosion hazard.
Density at 20 °C:	1.108 g/cm³
Relative density	Not determined.
Vapour density	5.1 (SF_6; Air = 1.0)
Solubility in / Miscibility with	
Water:	PEG 4000: Soluble in Water SF_6: Slightly Soluble in Water
Partition coefficient (n-octanol/water):	Not determined.
Viscosity:	
Dynamic:	Not applicable.
Kinematic:	Not applicable.
Other information	No further relevant information available.

10 STABILITY AND REACTIVITY

Reactivity: There are not particular dangerous reactions with other substances in normal conditions of use.

Chemical stability: Stable under normal conditions.

Possibility of hazardous reactions: No dangerous reactions known.

Conditions to avoid: No further relevant information available.

Incompatible materials: No further relevant information available.

Hazardous decomposition products: No further relevant information available (See Section 5)

INDICATIONS AND USAGE[1]
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 patients with suboptimal echocardiograms
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11 TOXICOLOGICAL INFORMATION

Information on toxicological effects

Acute toxicity:

Toxicological Information for Active Ingredients:

LD/LC50 values that are relevant for classification:	
2551-62-4 sulphur hexafluoride	
LD50 ivn	5790 mg/kg (Rabbit)

Primary irritant effect:

By Inhalation:
Inhaling small amounts of sulfur hexafluoride or airborne dust from the powder would not be expected to produce symptoms.

By Ingestion:
Inadvertent ingestion of trace amounts of this material would not be expected to result in symptoms.

On the skin:
Material contains low concentration of components that are mild irritants or possible irritants.
It may have potential to cause mild irritation, however , moderate or severe irritation is not expected.

On the eyes:
May cause irritation. Significant exposure to cold sulfur hexafluoride gas can cause frostbite of the eye.

CMR effects (carcinogenicity, mutagenicity and toxicity for reproduction):

Sensitization:
This material may act as a sensitizer (allergen) for those persons who are allergic to the formulation or components in the formulation.
Germ Cell Mutagenicity:
A number of in vitro and in vivo mutagenicity studies did not show mutagenicity for SonoVue.
Carcinogenicity: Not Available.
Reproductive Toxicity:
Reproduction studies with SonoVue in rats and rabbits at daily doses up to 17 times and 35 times the normal dose, respectively, did not show impaired fertility or harm to the fetus.
Specific Target Organ Toxicity
Single Exposure (STOT - SE): No further relevant information available
Repeated Exposure (STOT - RE): No further relevant information available
Aspiration Hazard: No further relevant information available

Other information (about experimental toxicology):
SonoVue did not cause acute toxicity in monkeys when administered intravenously at a dose at least 139 times the human exposure based upon body surface area.
Subacute to Chronic Toxicity: No harmful effects are expected from SonoVue under normal use conditions.

11 TOXICOLOGICAL INFORMATION (continued)

Carcinogenic Categories

IARC (International Agency for Research on Cancer)
None of the ingredients is listed.

NTP (National Toxicology Program)
None of the ingredients is listed.

OSHA-Ca (Occupational Safety & Health Administration)
None of the ingredients is listed.

Additional toxicological information:

Contact with small quantities of material for short periods is not expected to result in pharmacologic or toxic effects.
The safety of SonoVue in patients with cardiac shunts has not been studied. Extreme caution should be exercised when considering administration of SonoVue to patients with congenital heart defects.
Significant exposure to cold sulfur hexafluoride gas can cause frostbite.

Any Eventual Delayed Effect after Prolonged Exposure:
Repeated and prolonged exposure to skin may cause skin irritation.

INDICATIONS AND USAGE[1]
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 patients with suboptimal echocardiograms
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Please see full Prescribing Information for LUMASON including boxed **WARNING** in this document and at http://www.braccoimaging.com/us-en/products-and-solutions/contrast-enhanced-ultrasound/lumason/prescribing-information.

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Phone: 609-514-2200 **Toll Free:** 1-877-272-2269 (U.S. only) **Fax:** 609-514-2446

12 ECOLOGICAL INFORMATION

Toxicity

Aquatic toxicity: No further relevant information available.

Persistence and degradability No further relevant information available.

Bioaccumulative potential No further relevant information available.

Mobility in soil: No further relevant information available.

General notes:
Generally not hazardous for water.
Avoid transfer into the environment.

Results of PBT and vPvB assessment
PBT: Not applicable.
vPvB: Not applicable.

Other adverse effects No further relevant information available.
Additional Information: Use according to good working practice.

13 DISPOSAL CONSIDERATIONS

Waste treatment methods:

Recommendation:
Must not be disposed of together with household garbage. Do not allow product to reach sewage system.
Reutilise if possible or contact a waste processors for recycling or safe disposal.

Uncleaned packagings:
Recommendation: Dispose in accordance with national, state, local or applicable country regulations.
Recommended cleansing agent: Water, if necessary with cleansing agents.

14 TRANSPORT INFORMATION

UN-Number **DOT, ADR, ADN, IMDG, IATA**	Void
UN proper shipping name **DOT, ADR, ADN, IMDG, IATA**	Void
Transport hazard class(es) **ADR, ADN, IMDG, IATA** **Class**	Void
Packing group **DOT, ADR, IMDG, IATA**	Void
Environmental hazards: **Marine pollutant:**	No
Special precautions for user	Not applicable.
Transport in bulk according to Annex II of MARPOL73/78 and the IBC Code	Not applicable.
UN "Model Regulation":	-

INDICATIONS AND USAGE[1]

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Phone: 609-514-2200 **Toll Free:** 1-877-272-2269 (U.S. only) **Fax:** 609-514-2446

15 REGULATORY INFORMATION

Safety, health and environmental regulations/legislation specific for the substance or mixture

Sara

Section 355 (extremely hazardous substances):	
None of the ingredients is listed.	
Section 313 (Specific toxic chemical listings):	
None of the ingredients is listed.	
TSCA (Toxic Substances Control Act):	
2551-62-4	sulphur hexafluoride
25322-68-3	Polyethylene glycol 4000
57-10-3	palmitic acid, pure

Proposition 65

Chemicals known to cause cancer:
None of the ingredients is listed.

Chemicals known to cause reproductive toxicity for females:
None of the ingredients is listed.

Chemicals known to cause reproductive toxicity for males:
None of the ingredients is listed.

Chemicals known to cause developmental toxicity:
None of the ingredients is listed.

Carcinogenic categories

EPA (Environmental Protection Agency)
None of the ingredients is listed.

TLV (Threshold Limit Value established by ACGIH)
None of the ingredients is listed.

NIOSH-Ca (National Institute for Occupational Safety and Health)
None of the ingredients is listed.

GHS label elements Not applicable.
Hazard pictograms Not applicable.
Signal word Not applicable.
Hazard statements Not applicable.

16 OTHER INFORMATION

This information is based on our present knowledge. However, this shall not constitute a guarantee for any specific product features and shall not establish a legally valid contractual relationship.

Significant Dangers:

Relevant phrases
H280 Contains gas under pressure; may explode if heated.
Training Hints:
All persons handling this product should be informed on the existence of the hazard, on any possible risk they might be subjected to and about all required protective measures to prevent such a damage or to reduce the exposition.

WARNINGS:
Diagnostic agents are intended for use under direction of a physician and/or under the conditions of use described on the label and in the product's package insert. As a general precaution, personnel who handle drug substances should avoid contact (ingestion, inhalation, skin and eye contact) with these substances.

Department issuing SDS:
B-Lands Consulting
WTC, 5 Place Robert Schuman, BP 1516
38025 Grenoble, FRANCE
Tel: +33 476 295 869
Fax: +33 476 295 870
services@reachteam.eu
www.reachteam.eu
Date of preparation / last revision 11/07/2014 / -

Abbreviations and acronyms:
RID: Règlement international concernant le transport des marchandises dangereuses par chemin de fer (Regulations Concerning the International Transport of Dangerous Goods by Rail)
ICAO: International Civil Aviation Organisation
ADR: Accord européen sur le transport des marchandises dangereuses par Route (European Agreement concerning the International Carriage of Dangerous Goods by Road)
IMDG: International Maritime Code for Dangerous Goods
IATA: International Air Transport Association
ACGIH: American Conference of Governmental Industrial Hygienists
EINECS: European Inventory of Existing Commercial Chemical Substances
ELINCS: European List of Notified Chemical Substances
CAS: Chemical Abstracts Service (division of the American Chemical Society)
NFPA: National Fire Protection Association (USA)
HMIS: Hazardous Materials Identification System (USA)
LC50: Lethal concentration, 50 percent
LD50: Lethal dose, 50 percent
Press. Gas: Gases under pressure: Liquefied gas
*** Data compared to the previous version altered.**
- data updating on the basis of the latest amendments.
- adaptation of the form according to Regulation 1907/2006/CE.

Please see full Prescribing Information for LUMASON including boxed **WARNING** in this document and at http://www.braccoimaging.com/us-en/products-and-solutions/contrast-enhanced-ultrasound/lumason/prescribing-information.

Ultrasound

LUMASON®

(sulfur hexafluoride lipid-type A microspheres)
for injectable suspension, for intravenous use or intravesical use

From Bracco Diagnostics Inc.—
A GLOBAL LEADER IN ENHANCED ULTRASOUND

FDA APPROVAL LETTERS

Please see full Prescribing Information for LUMASON including boxed **WARNING** in this document and at http://www.braccoimaging.com/us-en/products-and-solutions/contrast-enhanced-ultrasound/lumason/prescribing-information.

BRACCO
LIFE FROM INSIDE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203684

NDA APPROVAL

Bracco Diagnostics Inc.
Attention: Melanie Benson
Director, U.S. Regulatory Operations
259 Prospect Plains Road, Bldg. H
Monroe Township, NJ 08831

Dear Ms. Benson:

Please refer to your New Drug Application (NDA) dated December 21, 2011, received December 21, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lumason (sulfur hexafluoride lipid-type A microspheres) for injectable suspension.

We acknowledge receipt of your amendments dated January 27, February 9 and 27, March 2, April 19 and 26, May 10, June 19, July 23, September 13, December 7 and 14, 2012; January 7, May 31 (2), August 19, September 13 and 25, November 12, 2013; April 11, May 9, June 9, June 18, September 5 and 29, 2014.

The April 11, 2014, submission constituted a complete response to our November 27, 2013, action letter.

This new drug application provides for the use of Lumason (sulfur hexafluoride lipid-type-A microspheres) for injectable suspension for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for*

Content of Labeling Technical Qs and As, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 203684**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Frank Lutterodt
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 5483, Room: 5483
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

ADVISORY COMMITTEE

Your application for Lumason (sulfur hexafluoride lipid-type A microspheres) for injectable suspension was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease. Furthermore, outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth to less than 9 years because necessary studies are impossible or highly impracticable. This is because the number of pediatric patients younger than 9 years of age with poor non-contrast echocardiography is small.

We are deferring submission of your pediatric study for ages 9 to 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This required study is listed below.

2803-1 Deferred pediatric study under PREA: 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).

Draft Protocol Submitted:	February 25, 2014
Final Protocol Submission:	October 31, 2014
Study Completion (Including Blinded Read):	December 31, 2017
Final Report Submission:	May 31, 2018

Submit the protocol(s) to your IND 046958, with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Frank Lutterodt, Regulatory Project Manager, at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Charles Ganley, M.D.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHARLES J GANLEY
10/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203684/S-001

SUPPLEMENT APPROVAL

Bracco Diagnostics Inc.
Attention: Melanie Benson
Director, US Regulatory Operations
259 Prospect Plains Road, Building H
Monroe Township, NJ 08831

Dear Ms. Benson:

Please refer to your Supplemental New Drug Application (sNDA) dated June 4, 2015, received June 4, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lumason; (Sulfur Hexafluoride Lipid-Type A Microspheres) for Injectable Suspension.

We acknowledge receipt of your amendments dated June 22, July 10, October 21, 23, and 29, November 6, 18, and 24, December 17, and 18, 2015; and February 22, March 3 (2), 4, 16, 17, 21, 28, 30, and 31, 2016.

This new drug application provides for the use of Lumason; (Sulfur Hexafluoride Lipid-Type A Microspheres) for Injectable Suspension for use in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert,) with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your June 4, 2015, submission containing final printed carton and container labels.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:
Modupe Fagbami
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 5439
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code 20903 *if shipping via United States Postal Service (USPS).*
Use zip code 20993 *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have fulfilled the pediatric study requirements for all relevant pediatric age groups for this application.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Modupe Fagbami, Regulatory Project Manager, at (301) 796-1348.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LIBERO L MARZELLA
03/31/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA203684/S-002

SUPPLEMENT APPROVAL

Bracco Diagnostics Inc.
Attention: Melanie Benson
Director, US Regulatory Operations
259 Prospect Plains Road, Building H
Monroe Township, NJ 08831

Dear Ms. Benson:

Please refer to your Supplemental New Drug Application (sNDA) dated June 29, 2016, received June 29, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lumason (Sulfur Hexafluoride Lipid-Type A Microspheres) for Injectable Suspension.

This Prior Approval supplemental new drug application provides for the use of Lumason in ultrasonography of the urinary tract for the evaluation of suspected or known vesicoureteral reflux in pediatric patients.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Modupe Fagbami
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 5439
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code 20903 *if shipping via United States Postal Service (USPS).*
Use zip code 20993 *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have fulfilled the pediatric study requirements for all relevant pediatric age groups for this application.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Modupe Fagbami, Regulatory Project Manager, at (301) 796-1348.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Content of Labeling

INDICATIONS AND USAGE[1]

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 patients with suboptimal echocardiograms
- in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients
- in ultrasonography of the urinary tract for the evaluation of suspected or known vesicoureteral reflux in pediatric patients

CONTRAINDICATIONS[1]

LUMASON is contraindicated in patients with:

- history of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in LUMASON

IMPORTANT SAFETY INFORMATION[1]

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following the injection of ultrasound contrast agents, including sulfur hexafluoride lipid microspheres *[see Warnings and Precautions (5.1)]*. Most serious reactions occur within 30 minutes of administration *[see Warnings and Precautions (5.1)]*.

- **Assess all patients for the presence of any condition that precludes administration *[see Contraindications (4)]*.**
- **Always have resuscitation equipment and trained personnel readily available *[see Warnings and Precautions (5.1)]*.**

The risk for serious cardiopulmonary reactions may be increased among patients with unstable cardiopulmonary conditions (acute myocardial infarction, acute coronary artery syndromes, worsening or unstable congestive heart failure, or serious ventricular arrhythmias) *[see Warnings and Precautions (5.1)]*.[1]

Please see full Prescribing Information for LUMASON including boxed **WARNING** in this document and at http://www.braccoimaging.com/us-en/products-and-solutions/contrast-enhanced-ultrasound/lumason/prescribing-information.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

LUMASON is manufactured for Bracco Diagnostics Inc., Monroe Township, NJ 08831 by Bracco Suisse S.A., Plan-les-Ouates Geneve, Switzerland (LUMASON lyophilized powder vial-25 mg lipid-type A/60.7 sulfur hexafluoride gas); Vetter Pharma-Fertigung GmbH & Co. KG, 88212 Ravensburg, Germany (Sodium Chloride 0.9% Injection, USP); B. Braun Melsungen AG, 34212 Melsungen, Germany (Mini-Spike).

Bracco Diagnostics Inc. 259 Prospect Plains Road, Building H, Monroe Township, NJ 08831 USA
Phone: 609-514-2200 **Toll Free:** 1-877-272-2269 (U.S. only) **Fax:** 609-514-2446

Ultrasound

LUMASON®

(sulfur hexafluoride lipid-type A microspheres)
for injectable suspension, for intravenous use or intravesical use

From Bracco Diagnostics Inc.—
A GLOBAL LEADER IN ENHANCED ULTRASOUND

PRESCRIBING INFORMATION

Please see full Prescribing Information for LUMASON including boxed **WARNING** in this document and at http://www.braccoimaging.com/us-en/products-and-solutions/contrast-enhanced-ultrasound/lumason/prescribing-information.

BRACCO
LIFE FROM INSIDE

Bracco Diagnostics

Lumason®

(sulfur hexafluoride lipid-type A microspheres) for injectable suspension, for intravenous use or intravesical use

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LUMASON® safely and effectively. See full prescribing information for LUMASON.

LUMASON (sulfur hexafluoride lipid-type A microspheres) for injectable suspension, for intravenous use or intravesical use
Initial U.S. Approval: 2014

WARNING: SERIOUS CARDIOPULMONARY REACTIONS
See full prescribing information for complete boxed warning
Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following the injection of ultrasound contrast agents, including sulfur hexafluoride lipid microspheres (5.1). Most serious reactions occur within 30 minutes of administration (5.1).
- **Assess all patients for the presence of any condition that precludes administration (4).**
- **Always have resuscitation equipment and trained personnel readily available (5.1).**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	12/2016
Dosage and Administration (2)	12/2016
Contraindications (4)	12/2016
Warnings and Precautions (5.3)	12/2016

----------INDICATIONS AND USAGE----------
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 patients with suboptimal echocardiograms (1)
- in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients (1)
- in ultrasonography of the urinary tract for the evaluation of suspected or known vesicoureteral reflux in pediatric patients (1)

--------DOSAGE AND ADMINISTRATION--------
Avoid intra-arterial injection (2.1, 5.3)
See Full Prescribing Information for reconstitution instructions (2.3)
For intravenous injection:
- Echocardiography: After reconstitution, administer 2 mL as an intravenous injection in adult patients (2.2, 2.4)
- Ultrasonography of the liver in adults: After reconstitution, administer 2.4 mL as an intravenous injection (2.2, 2.4)
- Ultrasonography of the liver in pediatric patients: After reconstitution, administer 0.03 mL per kg as an intravenous injection, up to a maximum of 2.4 mL per injection (2.2, 2.4)
- May repeat dose one time during a single examination (2.2, 2.4)
- Follow each injection with an intravenous flush of 0.9% Sodium Chloride Injection (2.2, 2.4)

For intravesical administration in pediatric patients:
- Ultrasonography of the urinary tract: After reconstitution, administer 1 mL via sterile 6-8F urinary catheter. Bladder should be first emptied and then partially filled with saline before injection of Lumason (2.2, 2.4)
- After Lumason administration, continue filling the bladder with saline until the patient has the urge to micturate or at the first sign of back pressure to the infusion (.2.4)

------DOSAGE FORMS AND STRENGTHS------
- For 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 (3)

----------CONTRAINDICATIONS----------
- History of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in Lumason (4)

--------WARNINGS AND PRECAUTIONS--------
- Cardiopulmonary reactions, including fatalities. Always have resuscitation equipment and trained personnel readily available (5.1)
- Hypersensitivity reactions (5.2)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥ 0.5%) are headache and nausea (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Bracco Diagnostics Inc at 1-800-257-5181 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION

December 2016

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: SERIOUS CARDIOPULMONARY REACTIONS

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following the injection of ultrasound contrast agents, including sulfur hexafluoride lipid microspheres *[see Warnings and Precautions (5.1)]*. Most serious reactions occur within 30 minutes of administration *[see Warnings and Precautions (5.1)]*.
Assess all patients for the presence of any condition that precludes administration *[see Contraindications (4)]*.
- **Always have resuscitation equipment and trained personnel readily available *[see Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

Echocardiography
Lumason is indicated 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.

Ultrasonography of the Liver
Lumason is indicated for use with ultrasound of the liver in adult and pediatric patients to characterize focal liver lesions.

Ultrasonography of the Urinary Tract
Lumason is indicated for use in ultrasonography of the urinary tract in pediatric patients for the evaluation of suspected or known vesicoureteral reflux.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions
Do not administer Lumason by intra-arterial injection *[see Warnings and Precautions (5.3)]*.

2.2 Recommended Dosage

Echocardiography
The recommended dose of Lumason after reconstitution is 2 mL administered as an intravenous bolus injection during echocardiography. During a single examination, a second injection of 2 mL may be administered to prolong contrast enhancement. Follow each Lumason injection with an intravenous flush using 5 mL of 0.9% Sodium Chloride Injection.

Ultrasonography of the Liver
Adults
The recommended dose of Lumason after reconstitution in adult patients is 2.4 mL administered as an intravenous injection during ultrasonography of the liver. During a single examination, a second injection of 2.4 mL may be administered, if needed. Follow Lumason injection with an intravenous flush using 5 mL of 0.9% Sodium Chloride Injection.
Pediatric Patients
The recommended dose of Lumason after reconstitution in pediatric patients is 0.03 mL per kg administered an intravenous injection during ultrasonography of the liver. During a single examination, a second injection of 0.03 mL per kg may be administered, if needed. Do not exceed 2.4 mL per injection. Follow Lumason injection with an intravenous flush of 0.9% Sodium Chloride Injection.

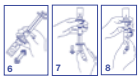
Ultrasonography of the Urinary Tract
Pediatric Patients
The recommended dose of Lumason after reconstitution is 1 mL. The bladder may be refilled with normal saline for a second cycle of voiding and imaging, without the need of a second Lumason administration.

2.3 Reconstitution Instructions

Contents of Lumason Kit

- Inspect the Lumason kit and its components for signs of damage. Do not use the kit if the protective caps on the Lumason vial and prefilled syringe with 5 mL Sodium Chloride 0.9% Injection are not intact or if the kit shows other signs of damage.
- Under aseptic conditions, reconstitute Lumason by injecting the prefilled syringe with 5 mL Sodium Chloride 0.9% Injection into the Lumason vial using the following illustrated steps:

1. Connect the plunger rod to the prefilled syringe barrel by screwing it clockwise into the syringe (see Figure 1).
2. Open the Mini-Spike blister and remove the syringe tip cap (see Figure 2).
3. Open the Mini-Spike green cap and connect the syringe to the Mini-Spike by screwing it in clockwise (see Figure 3).
4. Remove the flip cap plastic protective cap from the vial, remove the Mini-Spike spike protection and position the spike in the center of the rubber stopper of the vial. Press firmly inward until the spike is fully inserted in the stopper (see Figure 4).
5. Empty the content of the syringe into the vial by pushing on the plunger rod (see Figure 5).



6. Shake vigorously for 20 seconds, mixing all the contents in the vial (see Figure 6). A homogeneous white milky liquid indicates formation of sulfur hexafluoride lipid microspheres.
7. For preparation of doses greater than or equal to 1 mL, invert the system and slowly withdraw the intended volume of suspension into the syringe (see Figure 7). For preparation of doses less than 1 mL, withdraw 2 mL of the reconstituted suspension into the 5 mL syringe and measure the volume of Lumason to inject by using the 0.2 mL graduations between the 1 mL and 2 mL marks.
8. Unscrew the syringe from the Mini-Spike (see Figure 8). Peel and remove the diluent label to display the reconstituted product label. For intravenous administration, immediately connect the syringe to a dose administration line (20 G) and administer as directed under the Administration Instructions below. For intravesical administration, immediately connect the syringe to a sterile urinary catheter (6 french to 8 french) and administer as directed under the Administration Instructions below.

- Following reconstitution, Lumason suspension contains 1.5 to 5.6 x10^8 microspheres/mL with 45 mcg/mL of sulfur hexafluoride.
- Use immediately after reconstitution. If the suspension is not used immediately after reconstitution, resuspend the microspheres for a few seconds by hand agitation before the suspension is drawn into the syringe. Reconstituted suspension within a vial may be used for up to 3 hours from the time of its reconstitution. Maintain the vial containing the reconstituted suspension at room temperature.

2.4 Administration Instructions
Inspect visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The reconstituted suspension is milky-white, and does not contain visible particulate matter. Do not use the single-patient use vial for more than one patient.

Intravenous Administration
Administer Lumason as an intravenous bolus injection.

Intravesical Administration in Pediatric Patients
1. Insert a sterile 6 french to 8 french urinary catheter into the bladder under sterile conditions;
2. Empty the bladder of urine, and then fill the bladder with saline (sterile 0.9% sodium chloride solution) to approximately one third or half of its predicted total volume. The total bladder volume in children is calculated as [(age in years + 2) x 30] mL;
3. Administer Lumason as an intravesical bolus injection through the urinary catheter;
4. Continue filling the bladder with saline until the patient has the urge to micturate or at the first sign of back pressure to the infusion.
5. Immediately following the first voiding, the bladder may be refilled with normal saline for a second cycle of voiding and imaging, without the need of a second Lumason administration

2.5 Imaging Guidelines

Echocardiography
After baseline non-contrast echocardiography is complete, Adjust the mechanical index for the ultrasound device to 0.8 or lower. Continue ultrasound imaging following Lumason injection.

Ultrasonography of the Liver
After identification of the target focal lesion on non-contrast ultrasound examination, hold transducer still while switching scanner to low mechanical index (≤ 0.4) contrast-specific imaging. Continue ultrasound imaging following Lumason injection.

Ultrasonography of the Urinary Tract
After baseline non-contrast ultrasound examination of the kidney and bladder, switch the scanner to low mechanical index (≤0.4) contrast specific imaging. Perform continuous alternate ultrasound imaging of the bladder, ureters, and kidneys during filling and voiding of the bladder.

3 DOSAGE FORMS AND STRENGTHS

For injectable suspension: Lumason is supplied as a 3-part single-patient use kit comprised of:
- one Lumason clear vial containing 25 mg of lipid-type A sterile white lyophilized powder with headspace filled with 60.7 mg of sulfur hexafluoride gas
- one prefilled syringe containing 5 mL Sodium Chloride 0.9% Injection, USP (Diluent)
- one Mini-Spike

Following reconstitution, Lumason is a homogeneous, milky white suspension containing1.5 to 5.6 x10^8 microspheres/mL with 45 mcg/mL of sulfur hexafluoride.

4 CONTRAINDICATIONS

Lumason is contraindicated in patients with:
- history of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in Lumason

5 WARNINGS AND PRECAUTIONS

5.1 Serious Cardiopulmonary Reactions
Serious cardiopulmonary reactions, including fatalities have occurred uncommonly during or shortly following administration of ultrasound contrast agents, including Lumason. These reactions typically occurred within 30 minutes of administration. The risk for these reactions may be increased among patients with unstable cardiopulmonary conditions (acute myocardial infarction, acute coronary artery syndromes, worsening or unstable congestive heart failure, or serious ventricular arrhythmias). Always have cardiopulmonary resuscitation personnel and equipment readily available prior to Lumason administration and monitor all patients for acute reactions. The reported reactions that may follow the administration of ultrasound contrast agents include: fatal cardiac or respiratory arrest, shock, syncope, symptomatic arrhythmias (atrial fibrillation, tachycardia, bradycardia, supraventricular tachycardia, ventricular fibrillation, and ventricular tachycardia), hypertension, hypotension, dyspnea, hypoxia, chest pain, respiratory distress, stridor, wheezing, loss of consciousness, and convulsions.

5.2 Hypersensitivity Reactions
Hypersensitivity reactions such as skin erythema, rash, urticaria, flushing, throat tightness, dyspnea, or anaphylactic shock have uncommonly been observed following the injection of Lumason. These reactions may occur in patients with no history of prior exposure to sulfur hexafluoride lipid containing microspheres. Always have cardiopulmonary resuscitation personnel and equipment readily available prior to Lumason administration and monitor all patients for hypersensitivity reactions.

5.3 Systemic Embolization
When administering Lumason to patients with cardiac shunt, microspheres can bypass filtering by the lung and enter the arterial circulation. Assess patients with shunts for embolic phenomena following Lumason administration. Lumason is only for intravenous and/or intravesical administration; do not administer Lumason by intra-arterial injection *[see Dosage and Administration (2.1)]*.

5.4 Ventricular Arrhythmia Related to High Mechanical Index
High ultrasound mechanical index values may cause microsphere cavitation or rupture and lead to ventricular arrhythmias. Additionally, end-systolic triggering with high mechanical indices has been reported to cause ventricular arrhythmias.
Lumason is not recommended for use at mechanical indices greater than 0.8.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:
- Cardiopulmonary reactions *[see Warnings and Precautions (5.1)]*
- Hypersensitivity reactions *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
In completed clinical trials, a total of 6984 adult subjects (128 healthy volunteers and 6856 patients) received Lumason at cumulative doses ranging from 0.2 to 161 mL (mean 9.8 mL). Lumason was administered mainly as single or multiple injections; however, some subjects received infusion dosing. The majority (75%) of subjects received Lumason at cumulative doses of 10 mL or less. There were 64% men and 36% women, with an average age of 59 years (range 17 to 99 years). A total of 79% subjects were Caucasian; 4% were Black; 16% were Asian; <1% were Hispanic; and <1% were in other racial groups or race was not reported.
In the clinical trials, serious adverse reactions were observed in 2 subjects; one who experienced a hypersensitivity-type rash and presyncope and another who experienced anaphylactic shock shortly following Lumason administration.
The most commonly reported adverse reactions among patients (occurring among at least 0.2% of patients) are listed below (Table 1). Most adverse reactions were mild to moderate in intensity and resolved spontaneously.

Table 1. Adverse Reactions in Patients*
n = 6856

Number (%) of Patients with Adverse Reactions	340 (5%)
Headache	65 (1%)
Nausea	37 (0.5%)
Dysgeusia	29 (0.4%)
Injection site pain	23 (0.3%)
Feeling Hot	18 (0.3%)
Chest discomfort	17 (0.2%)
Chest pain	12 (0.2%)
Dizziness	11 (0.2%)
Injection Site Warmth	11 (0.2%)

*occurring in at least 0.2% of patients

6.2 Postmarketing Experience
In the international postmarketing clinical experience and clinical trials, serious adverse reactions have uncommonly been reported following administration of Lumason. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The serious adverse reactions include fatalities, especially in a pattern of symptoms suggestive of anaphylactoid/hypersensitivity reactions. Other serious reactions included arrhythmias and hypertensive episodes. These reactions typically occurred within 30 minutes of Lumason administration.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
There are no data with Lumason use in pregnant women to inform any drug-associated risks. No adverse developmental outcomes were observed in animal reproduction studies with administration of sulfur hexafluoride lipid-type A microspheres in pregnant rats and rabbits during organogenesis at doses up to at least 10 and 20 times, respectively, the maximum human dose of 4.8 mL based on body surface area (see Data).
In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Lumason was administered intravenously to rats at doses of 0.2, 1, and 5 mL/kg (approximately 0.4, 2, and 10 times the recommended maximum human dose of 4.8 mL, respectively, based on body surface area); Lumason doses were administered daily for about 30 consecutive days, from two weeks before pairing until the end of organogenesis. Lumason was administered intravenously to rabbits at doses of 0.2, 1, and 5 mL/kg (approximately 0.8, 4, and 20 times the recommended maximum human dose, respectively, based on body surface area); Lumason doses were administered daily from gestation day 6 to day 19 inclusive. No significant findings on the fetus were observed.

8.2 Lactation

Risk Summary

There are no data on the presence of Lumason in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Lumason and any potential adverse effects on the breastfed infant from Lumason or from the underlying maternal condition.

8.4 Pediatric Use

Ultrasonography of the Liver

Effectiveness in pediatric patients has been established for use in ultrasonography of the liver for characterization of focal liver lesions from adequate and well controlled trials in adult patients and a clinical study of 44 pediatric patients *[see Clinical Studies (14)]*. Safety of intravenous use of Lumason was based on evaluation of published literature involving use of Lumason in over 900 pediatric patients. Non-fatal anaphylaxis was reported in one pediatric patient.

Ultrasonography of the Urinary Tract

Effectiveness in pediatric patients has been established for use in ultrasonography of the urinary tract for the evaluation of suspected or known vesicoureteral reflux from two published studies comprising a total of 411 pediatric patients *[see Clinical Studies (14)]*. Safety of intravesical use of Lumason was based on evaluation of published literature involving use of Lumason in over 6000 pediatric patients. No adverse reactions were reported.

Echocardiography

Safety and effectiveness in pediatric patients have not been established for use in echocardiography.

8.5 Geriatric Use

Of the total number of 6856 adult patients in clinical studies of Lumason, 39% were 65 and over, while 11% were 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly or younger patients, but greater sensitivity of some older individuals cannot be ruled out.

11 DESCRIPTION

Lumason (sulfur hexafluoride lipid-type A microspheres) for injectable suspension, for intravenous or intravesical use is used to prepare the ultrasound contrast agent. The single-patient use kit contains the following three items:

1) one clear glass 10 mL vial containing 25 mg of white lyophilized powder lipid-type A, 60.7 mg of sulfur hexafluoride gas and capped with a blue flip-cap
2) one prefilled syringe containing 5 mL Sodium Chloride 0.9% Injection, USP (Diluent)
3) one Mini-Spike

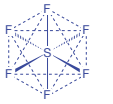
Each vial is formulated as a 25 mg sterile, pyrogen-free lyophilized powder containing 24.56 mg of polyethylene glycol 4000, 0.19 mg of distearoylphosphatidyl-choline (DSPC), 0.19 mg of dipalmitoylphosphatidylglycerol sodium (DPPG-Na) and 0.04 mg of palmitic acid. The headspace of each vial contains 6.07 mg/mL (± 2 %) sulfur hexafluoride, SF_6, or 60.7 mg per vial.

Each prefilled syringe with 5 mL of diluent 0.9% Sodium Chloride Injection is sterile, nonpyrogenic, preservative free containing 9 mg sodium chloride per mL.

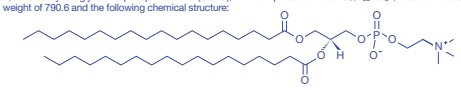
Upon reconstitution with 5mL diluent, Lumason is a milky white, homogeneous suspension containing sulfur hexafluoride lipid-type A microspheres. The suspension is isotonic and has a pH of 4.5 to 7.5.

The sulfur hexafluoride lipid microspheres are composed of SF_6 gas in the core surrounded by an outer shell monolayer of phospholipids consisting DSPC and DPPG-Na with palmitic acid as a stabilizer.

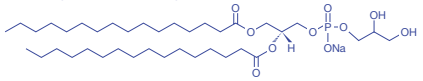
Sulfur hexafluoride has a molecular weight of 145.9 and the following chemical structure:



1,2-Distearoyl-*sn*-glycero-3-phosphocholine (DSPC), with empirical formula $C_{44}H_{88}NO_8P$, has a molecular weight of 790.6 and the following chemical structure:



1,2-Dipalmitoyl-*sn*-glycero-3-phospho-*rac*-glycerol sodium (DPPG-Na), with empirical formula $C_{38}H_{74}NaO_{10}P$, has a molecular weight of 745 and the following chemical structure:



Each milliliter of reconstituted Lumason suspension contains 1.5 to 5.6 x 10^8 microspheres, 68 mcg SF_6 (12 mcL), 0.038 mg DSPC, 0.038 mg DPPG-Na, 4.91 mg polyethylene glycol 4000 and 0.008 mg palmitic acid. The sulphur hexafluoride associated with the microspheres suspension is 45 mcg/mL. Fifteen to twenty three percent of the total lipids in the suspension are associated with the microspheres.

The sulfur hexafluoride lipid microsphere characteristics are listed in Table 2:

Table 2. Microsphere Characteristics

Mean diameter range	1.5 – 2.5 µm
Percent of microspheres ≤ 10 µm	≥ 99%
Upper size limit	100.0% ≤ 20 µm

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Within the blood, the acoustic impedance of Lumason microspheres is lower than that of the surrounding non-aqueous tissue. Therefore, an ultrasound beam is reflected from the interface between the microspheres and the surrounding tissue. The reflected ultrasound signal provides a visual image that shows a contrast between the blood and the surrounding tissues.

For ultrasonography of the urinary tract in pediatric patients, the intravesically administered Lumason microspheres increase signal intensity of fluids within the urethra, bladder, ureters, and renal pelvis.

12.2 Pharmacodynamics

Lumason provides useful echocardiographic signal intensity for two minutes after intravenous injection. Lumason microspheres are destroyed and contrast enhancement decreases as the mechanical index increases (values of 0.8 or less are recommended).

For ultrasonography of the liver, Lumason provides dynamic patterns of differential signal intensity enhancement between focal liver lesions and liver parenchyma during the arterial, portal venous, and late phase of signal intensity enhancement of the microvasculature.

In ultrasonography of the urinary tract, Lumason facilitates the detection of reflux of fluid from the bladder into the ureters.

Pulmonary Hemodynamic Effects

The effect of Lumason 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. This study did not assess the effect of Lumason on visualization of cardiac or pulmonary structures.

12.3 Pharmacokinetics

The pharmacokinetic of the SF_6 gas component of Lumason was evaluated in 12 healthy adult subjects. After intravenous bolus injections of 0.03 mL/kg and 0.3 mL/kg of Lumason, corresponding to approximately 1 and 10 times the recommended doses, concentrations of SF_6 in blood peaked within 1 to 2 minutes for both doses. The terminal half-life of SF_6 in blood was approximately 10 minutes for the 0.3 mL/kg dose. The area-under-the-curve of SF_6 was dose-proportional over the dose range studied.

Distribution

In a study of healthy subjects, the mean values for the apparent steady-state volume of distribution of SF_6 following intravenous administration, were 341 mcL and 710 mcL for Lumason doses of 0.03 mL/kg and 0.3 mL/kg, respectively. Preferential distribution to the lung is likely responsible for these values.

Elimination

Following intravenous administration, the SF_6 component of Lumason is eliminated via the lungs. In a clinical study that examined SF_6 elimination twenty minutes following Lumason injection, the mean cumulative recovery of SF_6 in expired air was 82 ± 20% (SD) at the 0.03 mL/kg dose and 88 ± 26% (SD) at the 0.3 mL/kg dose. SF_6 undergoes first pass elimination within the pulmonary circulation; approximately 40% to 50% of the SF_6 content was eliminated in the expired air during the first minute following Lumason injection.

Metabolism

SF_6 undergoes little or no biotransformation; following intravenous administration., 88% of an administered dose is recovered unchanged in expired air.

Pharmacokinetics in Specific Populations

Pulmonary Impairment:

In a study of patients with pulmonary impairment, blood concentrations of SF_6 peaked at 1 to 4 minutes following intravenous Lumason administration. The cumulative recovery of SF_6 in expired air was 102 ± 18% (mean ± standard deviation), and the terminal half-life of SF_6 in blood was similar to that measured in healthy subjects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies were performed to evaluate the carcinogenic potential of Lumason. No evidence of genotoxicity was found in the following studies conducted with Lumason: 1) a bacterial mutagenesis (Ames) assay, 2) an *in vitro* human lymphocyte chromosome aberration assay, and 3) an *in vivo* mouse micronucleus assay. No impairment of fertility was observed in rats receiving Lumason at doses up to 8 times the human dose based on body surface area.

14 CLINICAL STUDIES

14.1 Echocardiography

A total of 191 patients with suspected cardiac disease and suboptimal non-contrast echocardiography received Lumason in three multi-center controlled clinical trials (76 patients in Study A, 62 patients in Study B, and 53 patients in Study C). Among these patients, there were 127 men and 64 women. The mean age was 59 years (range 22 to 96 years). The racial and ethnic representations were 79% Caucasian, 16% Black, 4% Hispanic, < 1% Asian, and < 1% 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 whom 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. Patients with NYHA Class IV heart failure were not included in these studies.

In Studies A and B, each patient received four intravenous bolus injections of Lumason (0.5, 1, 2, and 4 mL), in randomized order. In Study C, each patient received two doses of Lumason (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 Lumason 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 the Lumason dose. Evaluation of left ventricular endocardial border consisted of segment based assessment involving six endocardial segments and using two apical views (2- and 4 chamber views).

Endocardial Border Delineation and Duration of Useful Contrast Effect

In all three studies, administration of Lumason improved left ventricular endocardial border delineation. The majority of the patients who received a 2.0 mL dose of Lumason had improvement in endocardial border delineation manifested as visualization of at least two additional endocardial border segments. Table 3 demonstrates the improvement in endocardial border delineation following Lumason administration as a reduction in percentage of patients with inadequate border delineation in at least one pair of adjacent segments (combined 2-chamber and 4-chamber view). The results are shown by reader.

Table 3. Reduction in Percentage of Patients with Inadequate Border Delineation

Reader	Study A N = 76		Study B N = 62		Study C N = 53	
	Non-contrast	Lumason	Non-contrast	Lumason	Non-contrast	Lumason
A	60 (79%)	22 (33%)	31 (50%)	12 (19%)	12 (23%)	10 (19%)
B	62 (82%)	29 (37%)	54 (87%)	6 (10%)	45 (85%)	20 (38%)

Following the first appearance of contrast within the left ventricle the mean duration of useful contrast effect ranged from 1.7 to 3.1 minutes.

Left Ventricular Opacification

In all three studies, complete left ventricular opacification was observed in 52% to 80% of the patients following administration of a 2.0-mL dose of Lumason. The studies did not sufficiently assess the effect of Lumason upon measures of left ventricular ejection fraction and wall motion.

14.2 Ultrasonography of the Liver

Adults

A total of 499 patients with at least 1 focal liver lesion requiring characterization were evaluated in two studies (259 patients in Study A, 240 patients in Study B). Among these patients, there were 259 men and 240 women. The mean age was 56 years (range 19 to 93 years). The racial and ethnic representations were 74% Caucasian, 11% Black, 9% Hispanic, 5% Asian, and 1% other racial or ethnic groups. The mean weight was 80 kg (range 44 to 173 kg).

In both studies, prior to Lumason administration, gray scale and Doppler (color or power imaging) ultrasound examinations of the target lesion were performed using commercially available ultrasound equipment and using standard techniques. Each patient received an intravenous injection of 2.4 mL of Lumason (up to 2 injections were allowed, 91% patients received 1 injection). Following Lumason administration, ultrasound examination of the target lesion was carried out using contrast-specific imaging modes operating at MI ≤ 0.4. The probe was positioned to provide optimal visualization over the target lesion and was kept in the same position for at least 180 seconds.

Truth standard included: histology/surgery, contrast CT, contrast MRI, and/or 6 month follow-up.

For each study, the interpretation of images was conducted by three independent readers who were blinded to clinical data. Lesions were characterized as malignant or benign. Separate blinded readers assessed the truth standard images.

Results of both studies demonstrated an improvement in characterization of focal liver lesions using Lumason ultrasound compared to non-contrast ultrasound images. Table 4 summarizes the efficacy results by reader.

Table 4. Diagnostic Performance of Lumason Ultrasound for Characterization of Focal Liver Lesions

Study A:						
	Sensitivity (patients with malignant lesions) N=119			Specificity (patients with benign lesions) N=140		
	Lumason %	Non-contrast %	Difference (95% CI)	Lumason %	Non-contrast %	Difference (95% CI)
Reader 1	87*	49	38 (30, 54)	71	63	8 (-4, 21)
Reader 2	76*	35	41 (29, 52)	83*	54	29 (21, 44)
Reader 3	92*	16	76 (67, 84)	73*	22	51 (40, 61)
Study B:						
	Sensitivity (patients with malignant lesions) N=124			Specificity (patients with benign lesions) N=116		
	Lumason %	Non-contrast %	Difference (95% CI)	Lumason %	Non-contrast %	Difference (95% CI)
Reader 4	65	53	12 (-1, 23)	72*	24	48 (35, 58)
Reader 5	61*	41	20 (7, 32)	67*	7	60 (50, 70)
Reader 6	47	66	-19 (-31, -7)	88*	59	29 (18, 40)

*Statistically significant improvement from non-contrast (p<0.05 based on McNemar's test)

Pediatric patients

In one published study, 44 patients with an indeterminate focal liver lesion (23 males, 21 females, age range: 4-18 years, median 11.5 years) were evaluated after intravenous bolus administration of 1.2 to 2.4 mL of Lumason. The findings of Lumason ultrasound images were compared to CT, MRI or histology. Specificity was 98% (43/44 patients).

14.3 Ultrasonography of the Urinary Tract

Pediatric Patients

The efficacy of Lumason for the evaluation of pediatric patients with suspected or known vesicoureteral reflux was established in two published open-label single center studies (A and B). Patients received 1 mL of Lumason intravesically and underwent voiding urosonography (VUS). Patients were also evaluated with voiding cystourethrography (VCUG) as the reference standard. The presence or absence of urinary reflux with Lumason ultrasound was compared to the radiographic reference standard.

Study A evaluated 183 patients (94 male, 89 female; age 2 days - 44 months) with a total of 366 kidney-ureter units. The images were interpreted by one on-site reader, blinded to the reference standard. Out of 103 reference standard-positive images, Lumason VUS was positive in 89 units and falsely negative in 14 units. In 263 units with negative reference standard, the Lumason ultrasonography was negative in 226 and falsely positive in 37.

Study B evaluated 228 patients (123 male, 105 female; age 6 days -13 years) with a total of 463 kidney-ureter units (some patients had more than 2 units). The images were interpreted independently by two on-site readers, blinded to the reference standard.. Out of 71 reference standard positive images, Lumason ultrasonography was positive in 57 and falsely negative in 14. In 392 units with negative reference standard, Lumason ultrasonography was negative in 302 and falsely positive in 90.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Lumason (sulfur hexafluoride lipid-type A microspheres) for injectable suspension is supplied as a single patient-use kit as follows:

- One Lumason vial of 25 mg lipid-type A white lyophilized powder with headspace fill of 60.7 mg of sulfur hexafluoride
- One prefilled syringe containing 5mL of Sodium Chloride 0.9% Injection, USP (Diluent)
- One Mini-Spike

Each kit is packaged in a clear plastic container.
(NDC 0270-7099-16) 5 Kits per carton

16.2 Storage and Handling

Store the kit at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise patients to inform their healthcare provider if they develop any symptoms of hypersensitivity after LUMASON administration including rash, wheezing, or shortness of breath.

Manufactured for:
Bracco Diagnostics Inc.
Monroe Township, NJ 08831
by
BRACCO Suisse SA
Plan-les-Ouates Geneve, Switzerland (Lumason lyophilized powder vial-25 mg lipid-type A/60.7 mg sulfur hexafluoride gas)

Vetter Pharma-Fertigung GmbH & Co. KG
88212 Ravensburg, Germany (Sodium Chloride 0.9% Injection, USP)

B. Braun Melsungen AG
34212 Melsungen, Germany (Mini-Spike)

This product is covered by US Patent No. 5,686,060

Revised December 2016

CL68D04

LUMASON®
(sulfur hexafluoride lipid-type A microspheres)
for injectable suspension, for intravenous use or intravesical use

INDICATIONS AND USAGE[1]
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 patients with suboptimal echocardiograms
- in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients
- in ultrasonography of the urinary tract for the evaluation of suspected or known vesicoureteral reflux in pediatric patients

CONTRAINDICATIONS[1]
LUMASON is contraindicated in patients with:
- history of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in LUMASON

IMPORTANT SAFETY INFORMATION[1]

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following the injection of ultrasound contrast agents, including sulfur hexafluoride lipid microspheres *[see Warnings and Precautions (5.1)]*. Most serious reactions occur within 30 minutes of administration *[see Warnings and Precautions (5.1)]*.
- **Assess all patients for the presence of any condition that precludes administration *[see Contraindications (4)]*.**
- **Always have resuscitation equipment and trained personnel readily available *[see Warnings and Precautions (5.1)]*.**

The risk for serious cardiopulmonary reactions may be increased among patients with unstable cardiopulmonary conditions (acute myocardial infarction, acute coronary artery syndromes, worsening or unstable congestive heart failure, or serious ventricular arrhythmias) *[see Warnings and Precautions (5.1)]*.[1]

Please see full Prescribing Information for LUMASON including boxed **WARNING** in this document and at http://www.braccoimaging.com/us-en/products-and-solutions/contrast-enhanced-ultrasound/lumason/prescribing-information.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

LUMASON is manufactured for Bracco Diagnostics Inc., Monroe Township, NJ 08831 by Bracco Suisse S.A., Plan-les-Ouates Geneve, Switzerland (LUMASON lyophilized powder vial-25 mg lipid-type A/60.7 sulfur hexafluoride gas); Vetter Pharma-Fertigung GmbH & Co. KG, 88212 Ravensburg, Germany (Sodium Chloride 0.9% Injection, USP); B. Braun Melsungen AG, 34212 Melsungen, Germany (Mini-Spike).

1. LUMASON (sulfur hexafluoride lipid-type A microspheres) for injectable suspension, for intravenous use or intravesical use full Prescribing Information. Monroe Twp., NJ: Bracco Diagnostics Inc.; December 2016.

Bracco Diagnostics Inc. 259 Prospect Plains Road, Building H, Monroe Township, NJ 08831 USA
Phone: 609-514-2200 **Toll Free:** 1-877-272-2269 (U.S. only) **Fax:** 609-514-2446

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Please see full Prescribing Information for LUMASON including boxed **WARNING** in this document and at http://www.braccoimaging.com/us-en/products-and-solutions/contrast-enhanced-ultrasound/lumason/prescribing-information.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

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Committed **to You.**™

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