



LUMASON[™]

(sulfur hexafluoride lipid-type A microspheres)
for injectable suspension

From Bracco Diagnostics Inc.—

A GLOBAL LEADER IN ENHANCED ECHOCARDIOGRAPHY

LUMASON FORMULARY KIT

Product Monograph
Safety Data Sheet
FDA Approval Letter
Prescribing Information

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Committed to You.[™]



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PRODUCT MONOGRAPH

Bracco Diagnostics Inc. is proud to introduce Lumason (sulfur hexafluoride lipid-type A microspheres) for injectable suspension to meet the demanding needs of echocardiography. Lumason is an ultrasound contrast agent indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.¹

Lumason, internationally known as SonoVue®, is an echo-enhancing agent that has been developed to meet the requirements of modern cardiac imaging practices. Lumason consists of a microsphere design that encapsulates inert sulfur hexafluoride gas in a phospholipid shell. Lumason is provided in a single patient-use kit. The Lumason kit provides all components necessary for reconstitution and requires no refrigeration. Lumason has been in use for over a decade in more than 30 countries. Lumason has been administered to more than 3 million patients and has an established safety and efficacy profile.

Bracco Diagnostics Inc. is committed to research and development that improves patient outcomes by providing important advances in diagnostic imaging. We are dedicated to providing imaging agents and solutions that improve diagnostic efficacy, patient safety, and cost effectiveness.

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INDICATIONS AND USAGE

Lumason is an ultrasound contrast agent indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

CONTRAINDICATIONS

Lumason is contraindicated in patients with:

- known or suspected right-to-left, bi-directional, or transient right-to-left cardiac shunts
- history of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in Lumason

Do not administer by intra-arterial injection.

IMPORTANT SAFETY 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)].**

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Manufactured for Bracco Diagnostics Inc., Monroe Township, NJ 08831 by Bracco Suisse SA, Plan-les-Quates 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).

LUMASON PROFILE AT A GLANCE

- Echocardiography is an important, portable, and noninvasive cardiac imaging modality. Contrast can provide left ventricle (LV) opacification and improve LV endocardial border delineation in patients with suboptimal quality of unenhanced baseline images.
- Lumason (sulfur hexafluoride lipid-type A microspheres) for injectable suspension 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 LV endocardial border.¹
- Lumason is a second-generation ultrasound contrast agent, which 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 consists of microscopically small microspheres (mean diameter range: 1.5–2.5 microns) surrounded and stabilized by a highly elastic membrane of phospholipids. The microspheres are filled with sulfur hexafluoride (SF₆), an inert gas with poor aqueous solubility that is slowly released from the microspheres in a liquid environment (blood) and then eliminated through the lungs .¹
- Lumason comes in a 3-part kit allowing for easy reconstitution and requires no refrigeration. Each kit contains a Lumason vial containing 25 mg lipid-type A lyophilized powder and 60.7 mg SF₆ headspace; 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, the reflected ultrasound signal provides a visual image that shows a contrast between the blood and the surrounding tissues, which may provide LV opacification and significantly improve the delineation of the LV endocardial border in patients with suboptimal echocardiograms.¹
- Pharmacokinetics: When administered to healthy volunteers at approximately 1 and 10 times the recommended doses, concentrations of the SF₆ gas component of Lumason in blood peaked within 1 to 2 minutes for both doses. The terminal half-life of SF₆ 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 SF₆ peaked at 1 to 4 minutes following Lumason administration. The cumulative recovery of SF₆ in expired air was 102 ± 18% (mean ± standard deviation), and the terminal half-life of SF₆ in blood was similar to that measured in healthy subjects.¹
- Elimination and metabolism: The SF₆ gas component of Lumason is eliminated via the lungs. SF₆ undergoes first-pass elimination within the pulmonary circulation, with approximately 40% to 50% SF₆ eliminated in the expired air during the first minute after Lumason injection. Because SF₆ undergoes little or no biotransformation, 88% of an administered dose is recovered unchanged in expired air.¹

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ECHOCARDIOGRAPHY IMAGE-ENHANCING AGENTS: AN INTRODUCTION

Cardiovascular disease is the leading cause of death in the United States. While the incidence of coronary heart disease has decreased over the past 40 years, CHD, including heart failure and valvular heart disease, is still the leading cause of death in the United States. In 2010, CHD was responsible for 1 of every 6 deaths, with 379,559 Americans dying of the disease.³ Because of the potential burden of CHD, safe, reliable, cost-effective, and convenient imaging modalities are needed to detect the condition and guide patient management.

Echocardiography may be the ideal primary imaging modality to detect or rule out suspected CHD. This sonographic technique uses ultrasound waves to produce dynamic diagnostic images of the heart and great vessels. Today, echocardiography has become the primary noninvasive imaging modality for the evaluation of cardiac anatomy, physiology, and function. This is because echocardiography provides real-time diagnostically useful information, has a good safety profile, is portable thereby allowing convenient imaging directly in the clinic (i.e., at bedside, in the intensive care unit or emergency department), and costs less than many other cardiac imaging modalities.⁴

In patients with obesity, pulmonary disease, or chest deformities, the critically ill, and the elderly, echocardiographic visualization can be suboptimal.^{5,6} The consequences of suboptimal images include inaccurate assessment of LV function, decreased diagnostic confidence, increased interobserver variability, misdiagnosis, and additional downstream testing.⁴ These concerns led to the development and successful implementation of enhanced ultrasound imaging.

INDICATIONS AND USAGE

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CONTRAINDICATIONS

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Microsphere echo-enhancing agents consist of encapsulated high-molecular-weight gas, the characteristics of which are distinct from those of surrounding blood cells and cardiac tissue.^{2,4} Echogenicity and harmonic properties of microsphere image-enhancing agents are a function of their nonlinear oscillation that allows them to reflect sound at both the fundamental frequency of the ultrasound source and at higher harmonics.^{4,7} Backscatter produced by these agents within the ultrasound field results in intense echocardiographic signals that are proportional to the blood volume, enhancing the LV cavity.⁴ Ultrasonic characteristics depend on the size of the microspheres, the outer shell composition, and the type of encapsulated gas.⁷ In general, increased shell elasticity leads to improved compression in an ultrasonic field and better resonance.⁴

Microsphere contrast agents oscillate as a result of the application of signal from insonation power at different mechanical indices, relying on harmonics to produce signal.⁸⁻¹⁰ Because of its highly compliant elastic shell, Lumason produces strong harmonics.⁸ At a low mechanical index microspheres remain static, backscattering the sound waves. As the insonation power increases, the microspheres begin to oscillate. At high MI, oscillation increases, disrupting and destroying the microspheres.⁸ The flexible phospholipid shell of Lumason starts oscillating at low MIs, resulting in a broad range of acoustic pressures that allow for continuous oscillation without destruction.⁸

Specific contrast modes have been developed by ultrasound machine manufacturers, typically involving markedly reduced insonation power (low-MI imaging) to optimize microsphere insonation and signal.¹¹ These low-MI modes allow continuous insonation of the microspheres, which keeps them oscillating thereby enabling real-time imaging of blood flow within parenchymal tissue.^{6,11} The oscillating microspheres create a specific echo signal with nonlinear characteristics and harmonic frequencies.⁶ A summary of microsphere-specific imaging modalities is provided in **Table 1**. The goal of all of these methods is to detect the echo from microspheres while suppressing tissue echo, relying on the unique nonlinear behavior of the microspheres in the acoustic field.⁶

Table 1. Microsphere-Specific Imaging Modes⁶

Imaging Mode	Also Known as	High MI	Low MI
Harmonic power Doppler	Harmonic color power angiography; power harmonics	Yes	No
Harmonic imaging	—	Yes	No
Ultraharmonic imaging	1.5 harmonic imaging	Yes	No
Pulse inversion	Phase inversion; coherent contrast imaging; pulse subtraction	Yes	Yes
Pulse inversion Doppler	Power pulse inversion	No	Yes
Amplitude modulation	Power modulation	No	Yes
Phase and amplitude modulation	Contrast pulse sequencing	No	Yes

MI=mechanical index.
Reproduced from Mulvagh SL, et al. *J Am Soc Echocardiogr.* 2008;21(11):1179-1201.

Ultrasound machines can detect specific low-MI echo signal despite the substantially reduced signal intensity (compared with conventional ultrasound) and distinguish it from the linear tissue signal (**Figure 1**).¹¹ This allows an effective separation of contrast agent signals from tissue signals, which can be displayed as a pure contrast agent image (**Figure 2**) or as an overlay or side-by-side images in combination with the anatomical tissue image.

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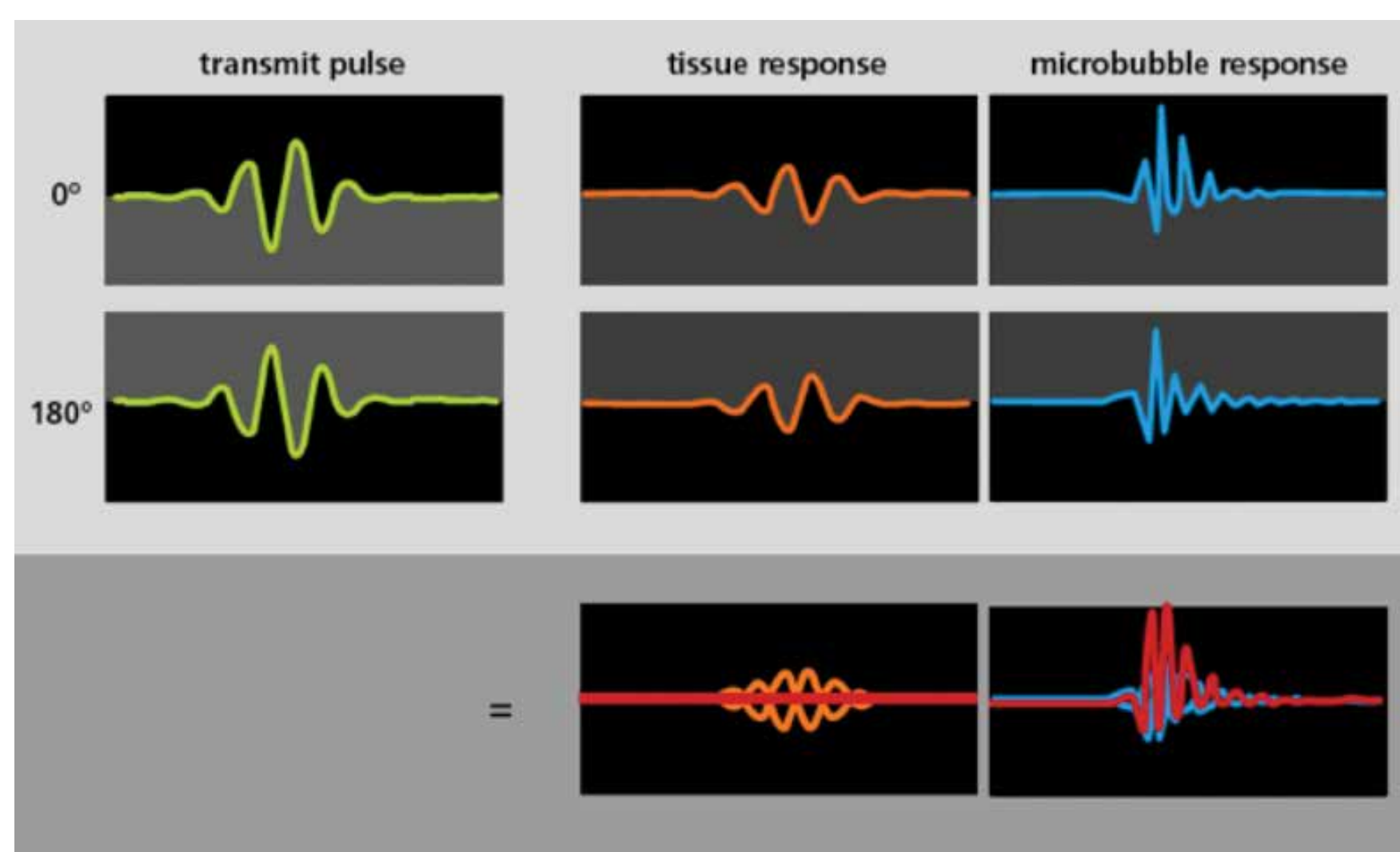


Figure 1. Principle of signal discrimination of tissue and microsphere response.¹¹

Two or more pulses are transmitted one after the other (green), differing in their form (e.g., inverted pulse, modulated power, etc). The responses from tissue (orange) transmit a linear response. The microspheres, on the other hand, start to oscillate in their particular resonance frequency and produce their own specific signal (blue) generating a nonlinear response. The linear responses from tissue are cancelled by the ultrasound machine, resulting in a suppression of tissue signals, while the nonlinear signals from microspheres are displayed selectively as contrast image (red).

Adapted from Porter TR, et al. *J Am Soc Echocardiogr.* 2014;27(8):797-810.



Figure 2. Pulse inversion image of LVO at low MI.⁶

Contrast echocardiography using the pulse inversion technique reveals uniform enhancement in the left ventricle.

LVO=left ventricular opacification; MI=mechanical index.

Reproduced from Mulvagh SL, et al. *J Am Soc Echocardiogr.* 2008;21(11):1179-1201.

INDICATIONS AND USAGE

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CONTRAINDICATIONS

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IMPORTANT SAFETY INFORMATION

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LUMASON PRODUCT CHARACTERISTICS

Lumason is a second-generation ultrasound contrast agent that has been developed to obtain an optimal backscattered signal over a broad frequency range, with good pressure stability and persistence in the blood stream. It consists of microscopically small microspheres (diameter 1.5–2.5 microns) surrounded and stabilized by a highly elastic membrane of phospholipids. The microspheres are filled with SF₆, an inert gas with poor aqueous solubility that is slowly released from the microspheres in a liquid environment (blood) and then eliminated through the lungs (**Figure 3**). This composition results in increased stability of the microspheres in the blood stream, along with rapid pulmonary elimination.^{1,2}

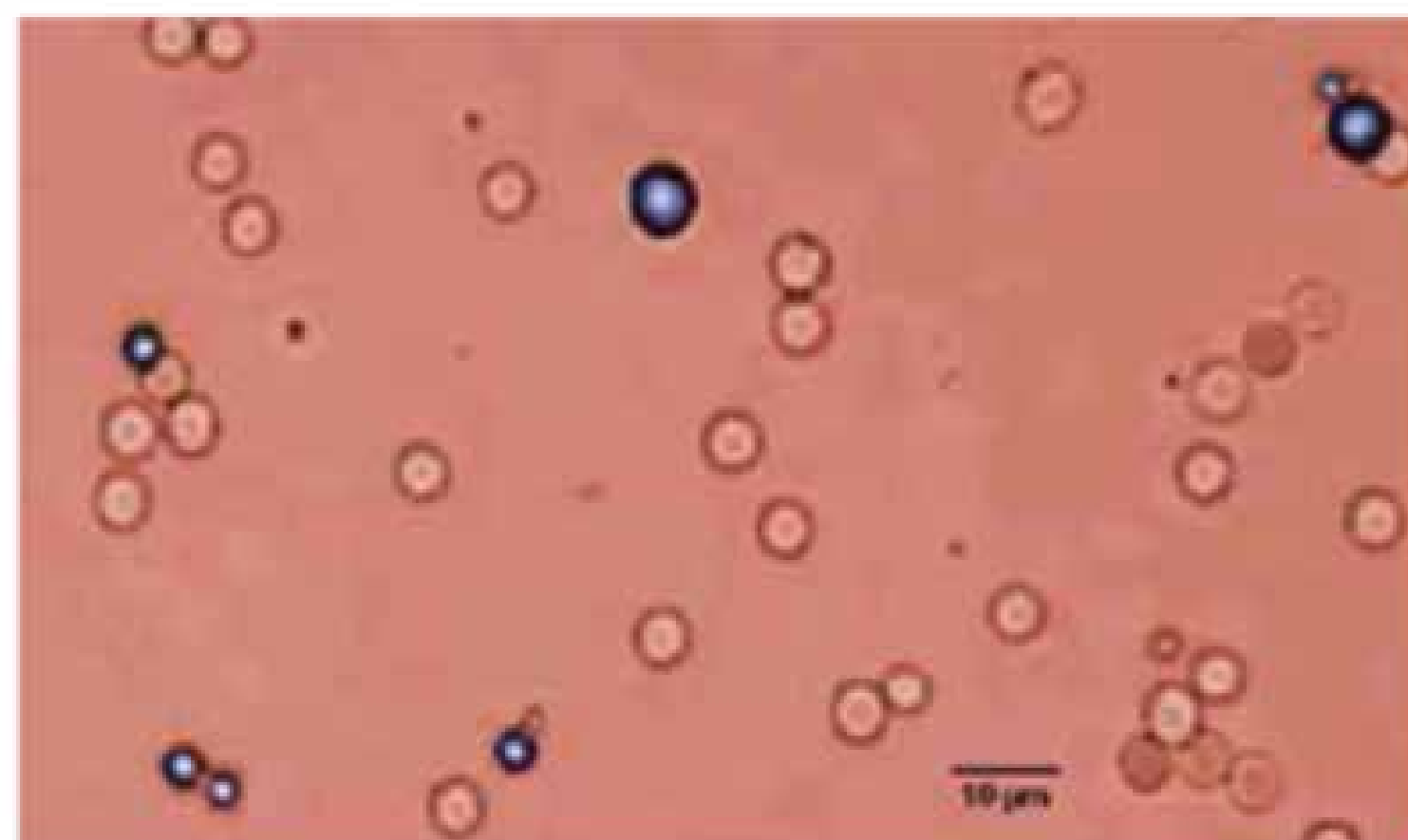


Figure 3. Schematic representation of the structure of Lumason microspheres (left) and the dispersion of the microspheres (blue) in blood (right, microscopic picture).

Gaseous microspheres (SF₆ gas) are surrounded by a monolayer membrane of phospholipids. Amphiphilic phospholipids are oriented with the hydrophilic phosphate groups (pink) outside, and the lipophilic fatty acid chains (purple) toward the inner lumen.

ACOUSTIC CHARACTERISTICS: MECHANISM OF ACTION

Within the blood, the acoustic impedance of Lumason microspheres is lower than that of the surrounding nonaqueous 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.¹ Resonance oscillations over a wide frequency range are obtained due to the size distribution of the Lumason microspheres, so that Lumason provides a good signal over the entire range of frequencies used for medical imaging (1-10 MHz).¹²

PHYSICOCHEMICAL PROPERTIES

Lumason microspheres are suspended in physiological 0.9% sodium chloride injection, USP (0.9% saline solution). Each milliliter of Lumason injectable suspension contains 1.5 to 5.6 × 10⁸ microspheres, 68 mcg SF₆ (12 mL), 0.038 mg distearoylphosphatidyl-choline (DSPC), 0.038 mg dipalmitoylphosphatidyl-glycerol sodium (DPPG-Na), 4.91 mg polyethylene glycol 4000, and 0.008 mg palmitic acid. The concentration of the SF₆ associated with the microspheres suspension is 45 µg/mL. Fifteen to twenty-three percent of the total lipids in the suspension are associated with the microspheres Table 2.¹

Table 2. Microsphere Characteristics¹

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

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Lumason is supplied as a single patient-use kit containing the following:

- a clear glass vial labeled as Lumason (sulfur hexafluoride lipid-type A microspheres) for injectable suspension, 25 mg lipid-type A/60.7 mg powder and headspace filled with sulfur hexafluoride,
- a prefilled syringe with 5 mL Sodium Chloride 0.9% Injection, USP (Diluent),
- a Mini-Spike.¹

Each Lumason vial is formulated as a 25 mg sterile, pyrogen-free lyophilized powder containing 24.56 mg polyethylene glycol 4000, 0.19 mg DSPC, 0.19 mg DPPG-Na, and 0.04 mg palmitic acid. The headspace of each vial contains 6.07 mg/mL ($\pm 2\%$) SF₆, or 60.7 mg per vial. Each prefilled syringe with 5 mL diluent 0.9% sodium chloride injection is sterile, nonpyrogenic, preservative free, and contains 9 mg sodium chloride per milliliter. 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 administration.¹

PHARMACODYNAMICS

Lumason is an inert image-enhancing agent and has no pharmacologic effect. The physical effect consists of the interaction between microspheres and ultrasound waves, which lead to the creation of a specific echo signal (contrast enhancement). The intensity of the contrast agent signal depends on the emitted insonation power, the insonation frequency, and the concentration of microspheres.^{8,13}

The recommended dose of Lumason provides useful echocardiographic signal intensity for 2 minutes after the injection. In clinical studies, echocardiography was conducted at an MI ≤ 0.8 in the majority of patients. Lumason microspheres are destroyed and contrast enhancement decreases as the MI increases.¹

INDICATIONS AND USAGE

Lumason is an ultrasound contrast agent indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

CONTRAINDICATIONS

Lumason is contraindicated in patients with:

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PHARMACOKINETICS

Lumason microspheres are transported in the body by the blood stream. They move freely through capillaries because they are smaller than red blood cells; however, they are large enough that they do not leave the vascular system (**Figure 4**). 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.^{14,15}

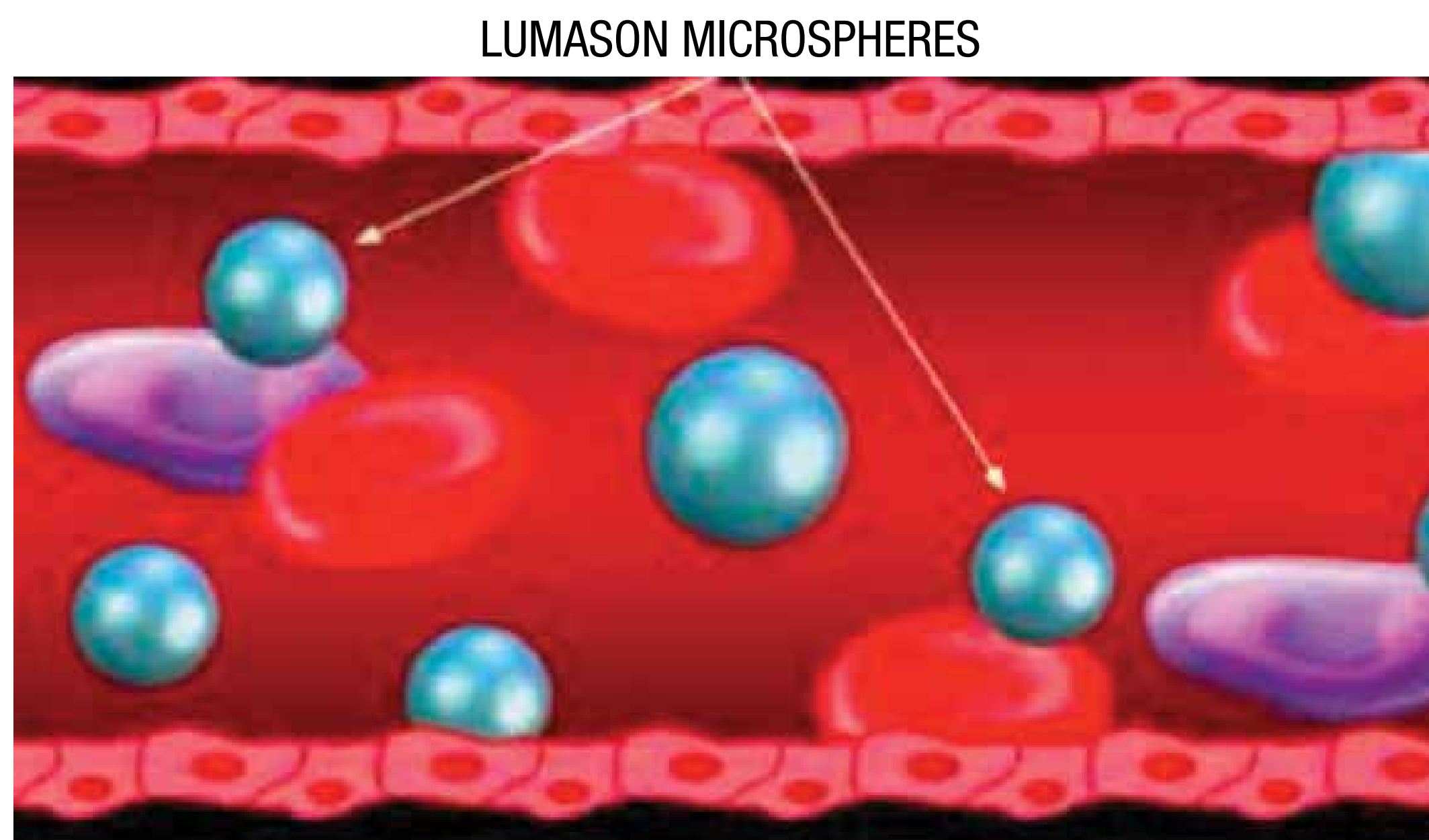


Figure 4. Schematic representation of Lumason microspheres in the vascular bed.

The microspheres cannot leave the intact vascular bed because of their size and thus exclusively enhance the intravascular compartment (blood pool contrast agent).

The pharmacokinetics of the SF₆ 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 SF₆ in blood peaked within 1 to 2 minutes for both doses. The terminal half-life of SF₆ 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 SF₆ 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 SF₆ were 341 L and 710 L 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 (SF₆) is via exhalation from the lungs. In a clinical study that examined SF₆ elimination 20 minutes after Lumason injection, the mean (\pm SD) cumulative recovery of SF₆ in expired air was 82% \pm 20% at the 0.03 mL/kg dose and 88% \pm 26% at the 0.3 mL/kg dose. SF₆ undergoes first-pass elimination within the pulmonary circulation; approximately 40% to 50% of the SF₆ content was eliminated in the expired air during the first minute after Lumason injection.

When metabolized, SF₆ undergoes little or no biotransformation; 88% of an administered dose is recovered unchanged in expired air.¹ (**Figure 5**) shows the elimination of SF₆ from blood and through exhalation.

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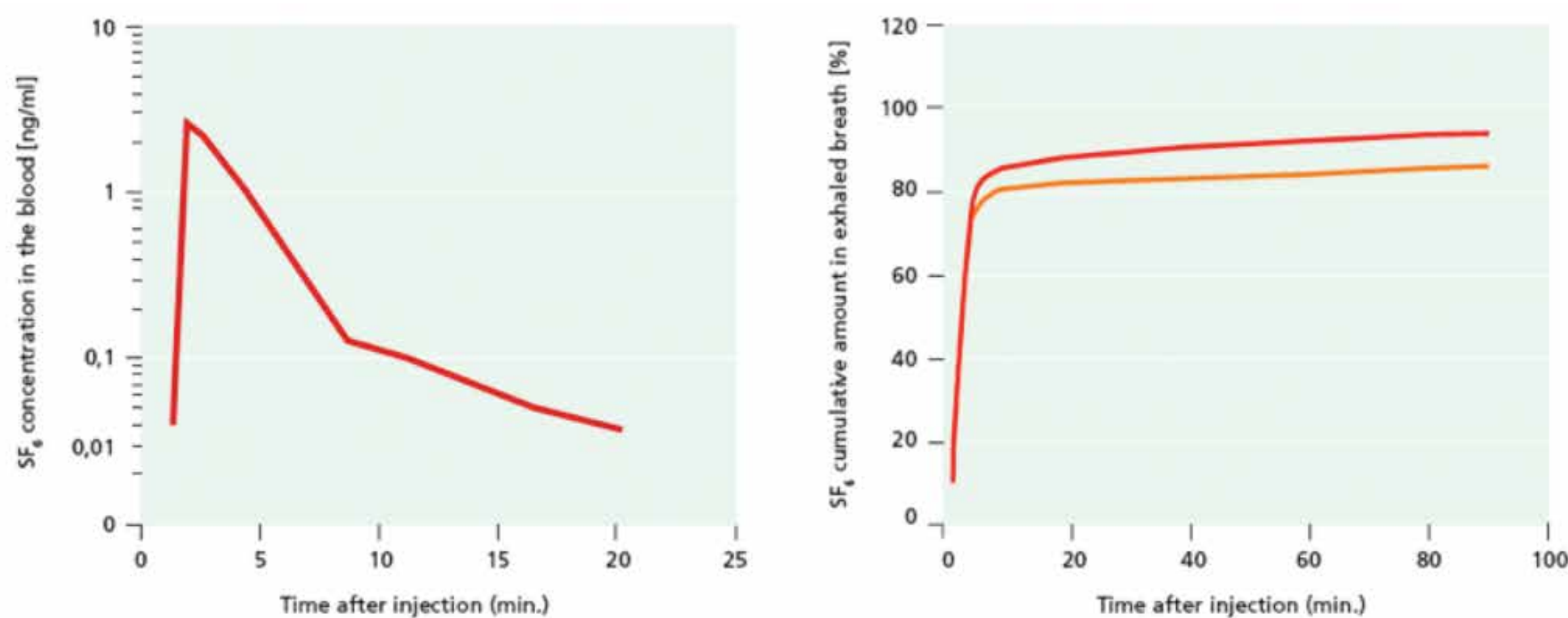


Figure 5. Elimination of SF₆ gas through exhalation.¹⁶

After an average of 20 minutes the complete dose of SF₆ is eliminated from the blood (left) and exhaled with the breath (right). The red curves correspond to a 10-fold clinical dose of Lumason, and the orange curve to a 1-fold clinical dose. SF₆=sulfur hexafluoride.

Adapted from Morel DR, et al. *Invest Radiol.* 2000;35(1):80-85.

PHARMACOKINETICS IN SPECIAL POPULATIONS

Pulmonary impairment

In a study of patients with pulmonary impairment, blood concentrations of SF₆ peaked at 1 to 4 minutes following Lumason administration. The cumulative recovery of SF₆ in expired air was 102% ± 18% (mean ± standard deviation), and the terminal half-life of SF₆ in blood was similar to that measured in healthy subjects.¹

INDICATIONS AND USAGE

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CLINICAL APPLICATION

LUMASON IMPROVES LEFT VENTRICULAR OPACIFICATION AND ENDOCARDIAL BORDER DELINEATION

Lumason is an ultrasound contrast agent indicated for use in patients with suboptimal echocardiograms to opacify the LV chamber and to improve the delineation of the LV endocardial border.¹

CLINICAL STUDIES IN ECHOCARDIOGRAPHY

A total of 191 patients with suspected cardiac disease and suboptimal noncontrast echocardiography received Lumason in 3 multicenter 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 22–96 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 92–405lb). 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 4 intravenous bolus injections of Lumason (0.5, 1, 2, and 4 mL) in randomized order. In Study C, each patient received 2 doses of Lumason (1 and 2 mL) in randomized order. All 3 studies assessed endocardial border delineation and left ventricular opacification. For each patient in each study, echocardiography with Lumason was compared with noncontrast (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 noncontrast echocardiographic images for each patient were evaluated by 2 independent reviewers, who were blinded to clinical information and the Lumason dose. Evaluation of the left ventricular endocardial border consisted of segment-based assessment involving 6 endocardial segments and using 2 apical views (2- and 4-chamber views)¹ (**Figure 6**).



Figure 6. Apical 2-chamber and 4-chamber views for assessment of EBD and LVO in Studies A, B, and C.

The apical **2-chamber** view is divided into 6 segments: basal, mid, and apical inferior (INF) and apical, mid, and basal anterior (ANT). The apical **4-chamber view** is divided into 6 segments: basal, mid-cavity (MID), and apical septal (SEPT) and apical, mid, and basal lateral (LAT). Using basal, mid, and apical as part of the name identifies the location along the long axis of the left ventricle from the apex to base. The circumferential locations are septal, lateral, inferior, and anterior.¹⁷

EBD=endocardial border definition; LVO=left ventricular opacification.

Reproduced from Cerqueira MD, et al. *Circulation*. 2002;105(4):539-542.

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Endocardial border delineation and duration of useful contrast effect

In all 3 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 2 additional endocardial border segments. **Table 3** demonstrates the improvement in endocardial border delineation after 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 3. Reduction in Percentage of Patients with Inadequate Border Delineation¹

Reader	Study A N = 76		Study B N = 62		Study C N = 53	
	Pre-injection	Post-injection	Pre-injection	Post-injection	Pre-injection	Post-injection
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 3 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 LVO are provided in **(Figure 7)**.

INDICATIONS AND USAGE

Lumason is an ultrasound contrast agent indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

CONTRAINDICATIONS

Lumason is contraindicated in patients with:

- known or suspected right-to-left, bi-directional, or transient right-to-left cardiac shunts
- history of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in Lumason

Do not administer by intra-arterial injection.

IMPORTANT SAFETY 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)].**

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)]).

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Left ventricular opacification

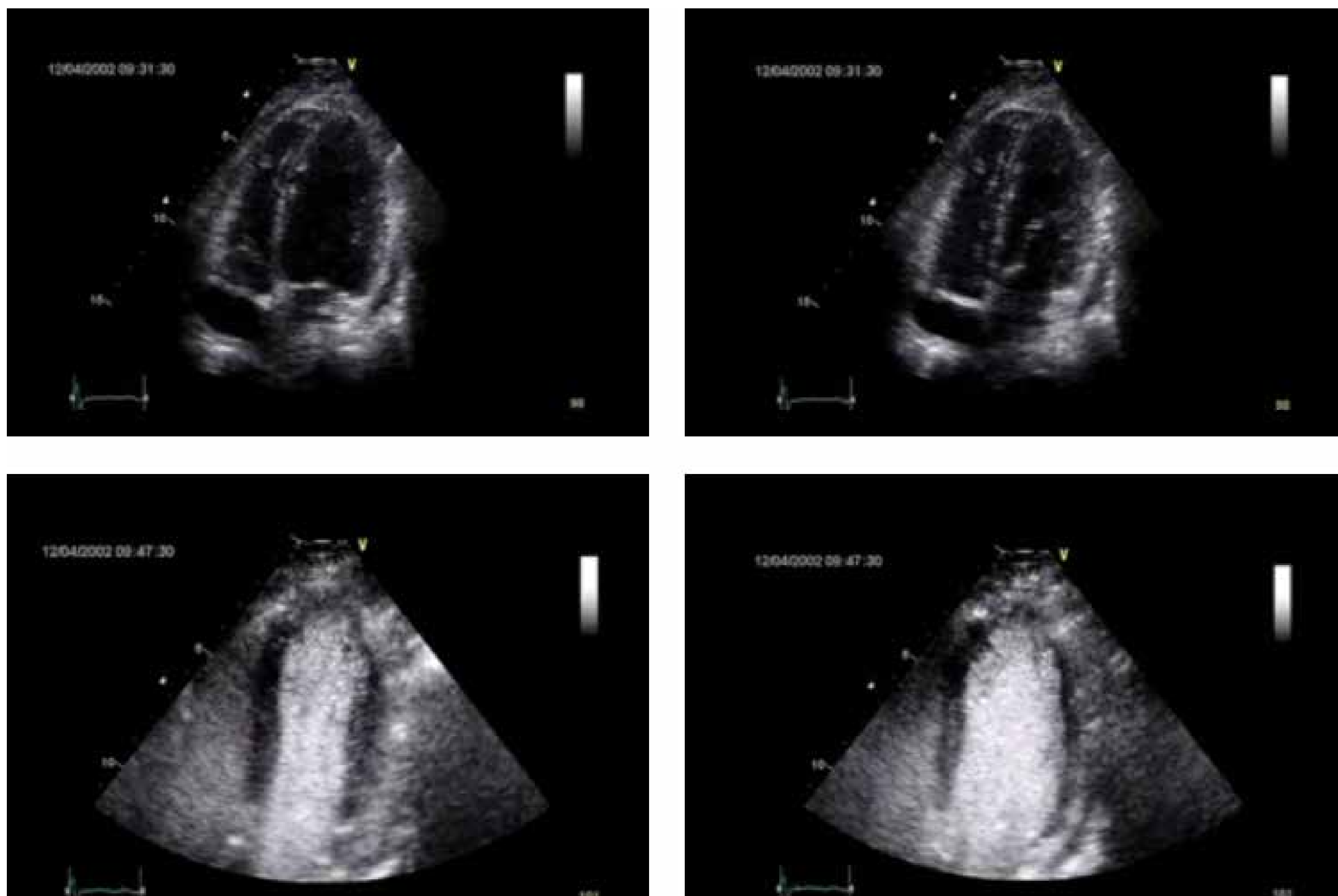


Figure 7. Echocardiography without and with Lumason.

Image of the apical 4-chamber view at end diastole (left) and end systole (right) without (top row) and with contrast enhancement (bottom row), respectively. After administration of Lumason, the left ventricle fills homogeneously with microspheres, including the spaces between intracavitary trabeculae and endocardium. Detectability of the endocardium is therefore significantly improved.

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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

INDICATIONS AND USAGE

Lumason is an ultrasound contrast agent indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

CONTRAINDICATIONS

Lumason is contraindicated in patients with:

- known or suspected right-to-left, bi-directional, or transient right-to-left cardiac shunts
- history of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in Lumason

Do not administer by intra-arterial injection.

IMPORTANT SAFETY 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)].**

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)]).

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DOSAGE AND ADMINISTRATION

Lumason is supplied within a single patient-use kit containing the following:

- a clear glass vial labeled as Lumason (sulfur hexafluoride lipid-type A microspheres) for injectable suspension, 25 mg lipid-type A/60.7 mg powder and headspace filled with sulfur hexafluoride,
- a prefilled syringe with 5 mL Sodium Chloride 0.9% Injection, USP (Diluent),
- a Mini-Spike.¹

Prior to Lumason reconstitution, inspect the kit and its components for signs of damage. Do not use the kit if the protective caps on the vial and the prefilled syringe are not intact or if the kit shows other signs of damage.¹ (See Reconstitution Section below.)

Each milliliter of reconstituted Lumason injectable suspension contains 1.5 to 5.6×10^8 microspheres, 68 mcg SF₆ (12 mL), 0.038 mg DSPC, 0.038 mg DPPG-Na, 4.91 mg polyethylene glycol 4000, and 0.008 mg palmitic acid.¹

RECOMMENDED DOSE

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.¹

CONTRAINDICATIONS

Lumason is contraindicated in patients with:

- known or suspected right-to-left, bidirectional, or transient right-to-left shunts
- history of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in Lumason

Do not administer by intra-arterial injection.¹

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SAFETY

ADVERSE REACTIONS

The following serious adverse reactions are discussed in the Warnings and Precautions section¹:

- Severe cardiopulmonary reactions
- Hypersensitivity reactions¹

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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.¹

In completed clinical trials, a total of 6307 adult subjects (128 healthy volunteers and 6179 patients) received Lumason at cumulative doses ranging from 0.2 to 161 mL (mean 10.5 mL). Lumason was administered mainly as single or multiple injections; however, some subjects received infusion dosing. Most subjects (73%) received Lumason at cumulative doses of 10 mL or less. There were 65% men and 35% women, with an average age of 59 years (range 17–99 years). A total of 4993 (79%) subjects were Caucasian, 192 (3%) Black, 1053 (17%) Asian, and 33 (<1%) Hispanic; 36 (<1%) were in other racial groups or race was not reported.¹

In the clinical trials, serious adverse reactions were observed in 2 subjects—one who experienced a hypersensitivity-type rash and near syncope symptoms and another who experienced anaphylactic shock shortly after Lumason administration.¹

INDICATIONS AND USAGE

Lumason is an ultrasound contrast agent indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

CONTRAINDICATIONS

Lumason is contraindicated in patients with:

- known or suspected right-to-left, bi-directional, or transient right-to-left cardiac shunts
- history of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in Lumason

Do not administer by intra-arterial injection.

IMPORTANT SAFETY 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)].**

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)]).

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The most commonly reported adverse reactions among patients (occurring among at least 0.2% of patients) are listed below

Table 4. Most adverse reactions were mild to moderate in intensity and resolved spontaneously.¹

Table 4. Adverse Reactions in Patients*¹	
n = 6179	
Number (%) of Patients with Adverse Reactions	302 (4.9%)
Headache	56 (0.9%)
Nausea	34 (0.6%)
Dysgeusia	19 (0.3%)
Injection site pain	18 (0.3%)
Chest discomfort	16 (0.3%)
Feeling hot	16 (0.3%)
Chest pain	11 (0.2%)
Injection site warmth	11 (0.2%)

*occurring in at least 0.2% of patients

Post-marketing experience

In international post-marketing clinical experience and ongoing clinical trials, serious adverse reactions have been uncommonly reported after 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 included 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.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).¹

WARNINGS AND PRECAUTIONS

Cardiopulmonary reactions

Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or shortly after the injection 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.¹

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.¹

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Anaphylactoid reactions

Anaphylactoid reactions such as skin erythema, rash, urticaria, flushing, throat tightness, dyspnea, or anaphylactic shock have been uncommonly observed after the injection of Lumason. These reactions may occur in patients with no history of prior exposure to SF₆ lipid-containing microspheres.¹

Systemic embolization

In patients with right-to-left, bidirectional, or transient right-to-left cardiac shunts, some intravenously injected SF₆ lipid-containing microspheres may bypass filtering by the lung and directly enter the arterial circulation. Occlusion of the microcirculation by these microspheres may result in tissue ischemia. Lumason is only for intravenous administration; do not administer Lumason by intra-arterial injection.¹

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.¹

PATIENT COUNSELING INFORMATION

Prior to administration of Lumason, instruct patients to inform their physician if they:

- are pregnant or nursing
- have a history of heart disease, respiratory diseases, or recent worsening of heart or lung conditions
- had prior reactions to Lumason¹

INDICATIONS AND USAGE

Lumason is an ultrasound contrast agent indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

CONTRAINDICATIONS

Lumason is contraindicated in patients with:

- known or suspected right-to-left, bi-directional, or transient right-to-left cardiac shunts
- history of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in Lumason

Do not administer by intra-arterial injection.

IMPORTANT SAFETY 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)].**

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)]).

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LUMASON PREPARATION¹

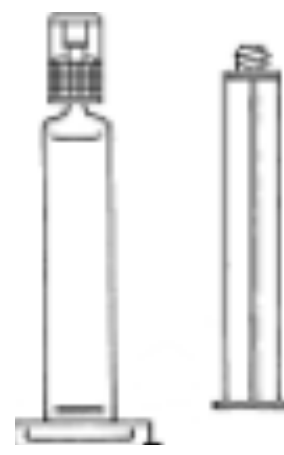
RECONSTITUTION

Lumason is supplied within a single patient-use kit containing the following:

- a clear glass vial labelled as Lumason (sulfur hexafluoride lipid-type A microspheres) for injectable suspension, 25 mg lipid-type A/60.7 mg powder and headspace filled with 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

Reconstitution steps

- Prior to Lumason reconstitution, inspect the 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.
- Perform all Lumason reconstitution steps under aseptic conditions. The Lumason vial and the prefilled syringe do not contain a bacteriostatic preservative.
- Lumason is reconstituted by injecting the prefilled syringe contents (5 mL Sodium Chloride 0.9% Injection, USP) 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 (**Figure 1**).



Figure 1.

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

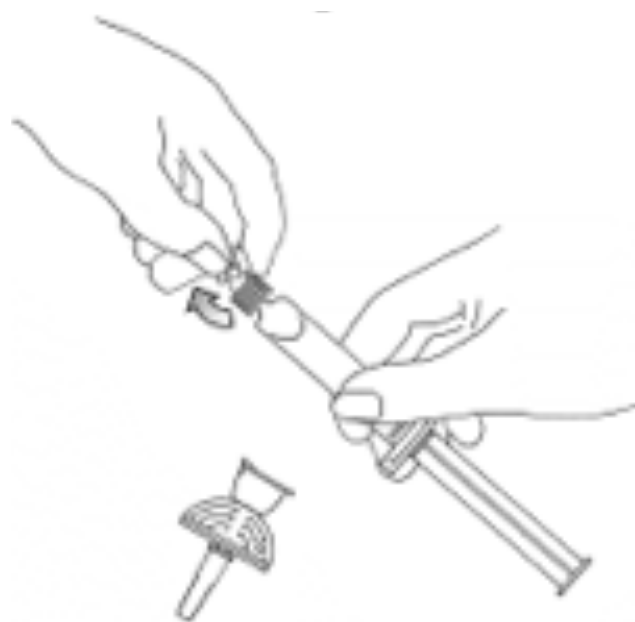


Figure 2.

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



Figure 3.

INDICATIONS AND USAGE

Lumason is an ultrasound contrast agent indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

CONTRAINDICATIONS

Lumason is contraindicated in patients with:

- known or suspected right-to-left, bi-directional, or transient right-to-left cardiac shunts
- history of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in Lumason

Do not administer by intra-arterial injection.

IMPORTANT SAFETY 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)].**

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)]).

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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 (**Figure 4**).

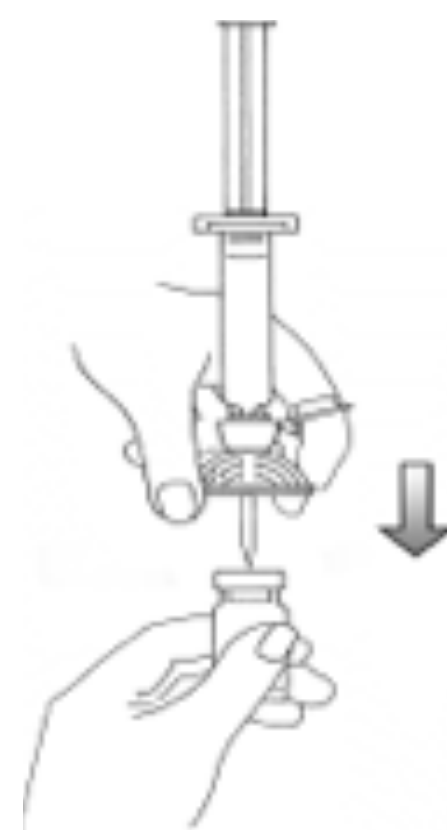


Figure 4.

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

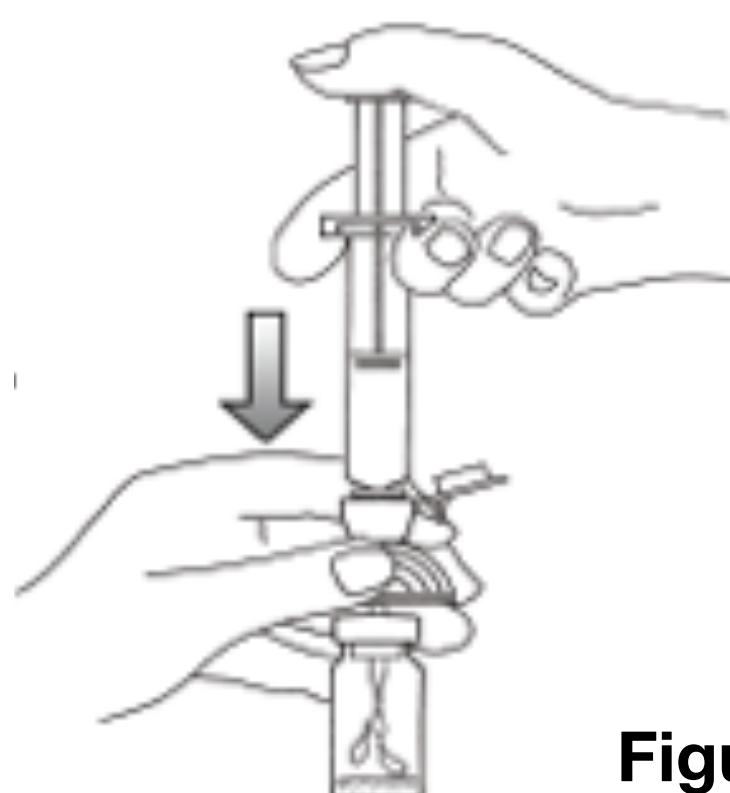


Figure 5.

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



Figure 6.

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7. Invert the system and slowly withdraw 2 mL of suspension into the syringe (**Figure 7**).

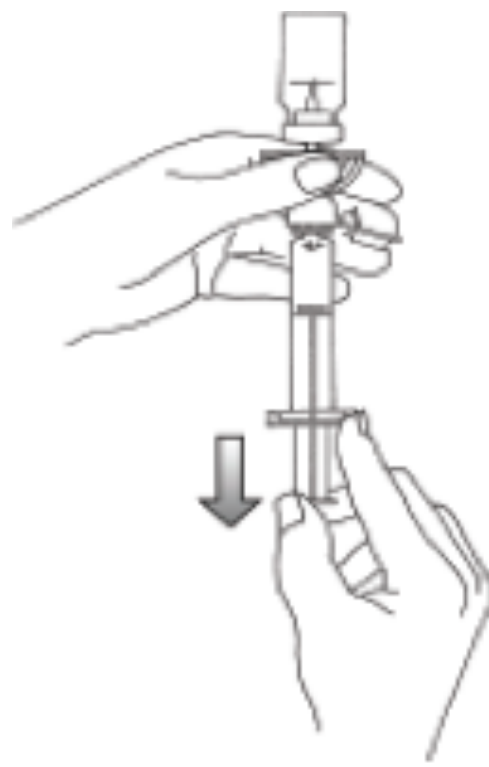


Figure 7.

8. Unscrew the syringe from the Mini-Spike (**Figure 8**).

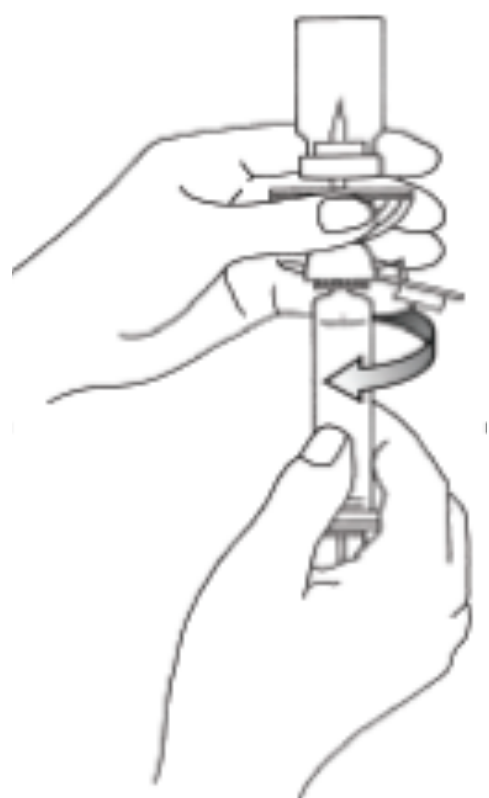


Figure 8.

Immediately connect the syringe to the dose administration line (20 G) and administer as directed under Administration section.

INDICATIONS AND USAGE

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CONTRAINDICATIONS

Lumason is contraindicated in patients with:

- known or suspected right-to-left, bi-directional, or transient right-to-left cardiac shunts
- history of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in Lumason

Do not administer by intra-arterial injection.

IMPORTANT SAFETY 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)].**

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)]).

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Administration

- Administer Lumason as an intravenous bolus injection.
- The milky white Lumason suspension should be used immediately after reconstitution. If the suspension is not used immediately after reconstitution, the microspheres should be resuspended by a few seconds of hand agitation before the suspension is withdrawn into the syringe. Reconstituted suspension within a vial may be used for up to 3 hours from the time of its reconstitution, after the microspheres have been resuspended by hand agitation prior to withdrawal of the suspension into the syringe. Maintain the vial containing the reconstituted suspension at room temperature.
- Lumason is for single use only. Unused portions of the reconstituted suspension must be discarded in accordance with regulations dealing with the disposal of such materials. Syringe and other materials used should be properly disposed of after single use.

DOSAGE FORMS AND STRENGTHS

Lumason (sulfur hexafluoride lipid-type A microspheres) for injectable suspension is a 3-part single patient-use kit comprised of:

- one Lumason vial containing 25 mg of lipid-type A sterile 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),
- a Mini-Spike.

Following reconstitution with the provided diluent, Lumason suspension contains 1.5 to 5.6×10^8 microspheres/mL with 45 mcg/mL of sulfur hexafluoride.¹

STORAGE AND HANDLING

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

Lumason is for single use only. Lumason does not contain an antimicrobial preservative and the suspension should be used within 3 hours after reconstitution. The microspheres should be resuspended by a few seconds of hand agitation before the product is withdrawn into the syringe.

Store the reconstituted Lumason at room temperature in the supplied product vial.¹

Please see full Prescribing Information including boxed **WARNING** by clicking [here](#).

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INDICATIONS AND USAGE

Lumason is an ultrasound contrast agent indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

CONTRAINDICATIONS

Lumason is contraindicated in patients with:

- known or suspected right-to-left, bi-directional, or transient right-to-left cardiac shunts
- history of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in Lumason

Do not administer by intra-arterial injection.

IMPORTANT SAFETY 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)].

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Lumason is a trademark of Bracco Diagnostics Inc.
SonoVue is a registered trademark of Bracco Suisse SA.

Manufactured for:

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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15-011515

LUMASON™

(sulfur hexafluoride lipid-type A microspheres)
for injectable suspension

From Bracco Diagnostics Inc.—

A GLOBAL LEADER IN ENHANCED ECHOCARDIOGRAPHY

SAFETY DATA SHEET

acc. to OSHA HCS

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

Please see full Prescribing Information including boxed **WARNING** by clicking [here](#).

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INDICATIONS AND USAGE

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CONTRAINDICATIONS

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

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WARNING: SERIOUS CARDIOPULMONARY REACTIONS

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SAFETY DATA SHEET

Trade name:

SonoVue (25 mg under sulfur hexafluoride gas) / Lumason

ACC. TO OSHA HCS

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: SF₆.*

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.

Please see full Prescribing Information including boxed **WARNING** by clicking [here](#).

SAFETY DATA SHEET

ACC. TO OSHA HCS

Trade name:

SonoVue (25 mg under sulfur hexafluoride gas) / Lumason

2 HAZARD(S) IDENTIFICATION

Classification of the substance or mixture

Classification according to Regulation (EC) No 1272/2008

The product is not classified according to the CLP regulation.

Classification according to Directive 67/548/EEC or Directive 1999/45/EC Not applicable.

Information concerning particular hazards for human and environment:

The product does not have to be labelled due to the calculation procedure of international guidelines.

Classification system:

The classification was made according to the latest editions of international substances lists, and expanded upon from company and literature data.

Label elements

Labelling according to Regulation (EC) No 1272/2008 Void

Hazard pictograms Void

Signal word Void

Hazard statements Void

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.

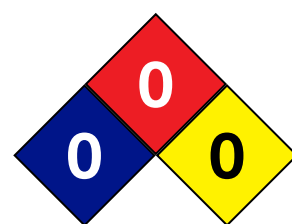
Information pertaining to particular dangers for man and environment:

Negative Effects on the Health: See also Sections 11

Negative Effects on the Environment: See also Section 12

Classification system:

NFPA ratings (scale 0 - 4)



Health=0

Fire=0

Reactivity=0

HMIS-ratings (scale 0 - 4)

HEALTH Health=0

FIRE Fire=0

REACTIVITY Reactivity=0

Results of PBT and vPvB assessment

PBT: Not applicable.

vPvB: Not applicable.

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SAFETY DATA SHEET


Trade name:

SonoVue (25 mg under sulfur hexafluoride gas) / Lumason

ACC. TO OSHA HCS

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%

INDICATIONS AND USAGE

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CONTRAINDICATIONS

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WARNING: SERIOUS CARDIOPULMONARY REACTIONS

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SAFETY DATA SHEET

Trade name:

SonoVue (25 mg under sulfur hexafluoride gas) / Lumason

ACC. TO OSHA HCS

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 (CO₂)

In the absence of Oxygen: Carbon Monoxide (CO)

Hydrogen Fluoride (HF)

Sulfur Oxides (SO_x)

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

(self-contained breathing apparatus) (SCBA).

Wear flame and chemicals resistant clothing, boots and gloves (see Section 8).

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SAFETY DATA SHEET

Trade name:

SonoVue (25 mg under sulfur hexafluoride gas) / Lumason

ACC. TO OSHA HCS

6 ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment and emergency procedures

Avoid inhalation of dust / fog.

²Wear 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.

INDICATIONS AND USAGE

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SAFETY DATA SHEET

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SonoVue (25 mg under sulfur hexafluoride gas) / Lumason

ACC. TO OSHA HCS

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)	6000 mg/m ³ , 1000 ppm
REL (USA)	6000 mg/m ³ , 1000 ppm
TLV (USA)	5970 mg/m ³ , 1000 ppm
25322-68-3 Polyethylene glycol 4000	
OSHA-PEL (USA)	15 mg/m ³
TLV-TWA (USA)	10 mg/m ³
WEEL (USA)	10 mg/m ³ 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.

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SAFETY DATA SHEET

Trade name:

SonoVue (25 mg under sulfur hexafluoride gas) / Lumason

ACC. TO OSHA HCS

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.

INDICATIONS AND USAGE

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CONTRAINDICATIONS

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SAFETY DATA SHEET

ACC. TO OSHA HCS

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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/cm ³
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.

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SAFETY DATA SHEET

Trade name:

SonoVue (25 mg under sulfur hexafluoride gas) / Lumason

ACC. TO OSHA HCS

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

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SAFETY DATA SHEET

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SonoVue (25 mg under sulfur hexafluoride gas) / Lumason

ACC. TO OSHA HCS

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.

Please see full Prescribing Information including boxed **WARNING** by clicking [here](#).

SAFETY DATA SHEET

Trade name:

SonoVue (25 mg under sulfur hexafluoride gas) / Lumason

ACC. TO OSHA HCS

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

Lumason is an ultrasound contrast agent indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

CONTRAINDICATIONS

Lumason is contraindicated in patients with:

- known or suspected right-to-left, bi-directional, or transient right-to-left cardiac shunts
- history of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in Lumason

Do not administer by intra-arterial injection.

IMPORTANT SAFETY 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)].**

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)]).

Please see full Prescribing Information including boxed **WARNING** by clicking [here](#).

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.

Manufactured for Bracco Diagnostics Inc., Monroe Township, NJ 08831 by Bracco Suisse SA, Plan-les-Quates 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).

SAFETY DATA SHEET

Trade name:

SonoVue (25 mg under sulfur hexafluoride gas) / Lumason

ACC. TO OSHA HCS

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.

Please see full Prescribing Information including boxed **WARNING** by clicking [here](#).

SAFETY DATA SHEET

Trade name:

SonoVue (25 mg under sulfur hexafluoride gas) / Lumason

ACC. TO OSHA HCS

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

Lumason is an ultrasound contrast agent indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

CONTRAINDICATIONS

Lumason is contraindicated in patients with:

- known or suspected right-to-left, bi-directional, or transient right-to-left cardiac shunts
- history of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in Lumason

Do not administer by intra-arterial injection.

IMPORTANT SAFETY 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)].

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)]).

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Manufactured for Bracco Diagnostics Inc., Monroe Township, NJ 08831 by Bracco Suisse SA, Plan-les-Quates 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).

SAFETY DATA SHEET

Trade name:

SonoVue (25 mg under sulfur hexafluoride gas) / Lumason

ACC. TO OSHA HCS

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.

Please see full Prescribing Information including boxed **WARNING** by clicking [here](#).

SAFETY DATA SHEET

Trade name:

SonoVue (25 mg under sulfur hexafluoride gas) / Lumason

ACC. TO OSHA HCS

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 including boxed **WARNING** by clicking [here](#).

INDICATIONS AND USAGE

Lumason is an ultrasound contrast agent indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

CONTRAINDICATIONS

Lumason is contraindicated in patients with:

- known or suspected right-to-left, bi-directional, or transient right-to-left cardiac shunts
- history of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in Lumason

Do not administer by intra-arterial injection.

IMPORTANT SAFETY 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)].

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- **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)]).

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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 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).

Lumason is a trademark of Bracco Diagnostics Inc.

SonoVue is a registered trademark of Bracco Suisse SA.

Manufactured for:

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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15-011515

LUMASON[™]

(sulfur hexafluoride lipid-type A microspheres)
for injectable suspension

From Bracco Diagnostics Inc.—

A GLOBAL LEADER IN ENHANCED ECHOCARDIOGRAPHY

FDA APPROVAL LETTER

Please see full Prescribing Information including boxed **WARNING** by clicking [here](#).



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



LUMASON[™]

(sulfur hexafluoride lipid-type A microspheres)
for injectable suspension

From Bracco Diagnostics Inc.—

A GLOBAL LEADER IN ENHANCED ECHOCARDIOGRAPHY

PRESCRIBING INFORMATION

Please see full Prescribing Information including boxed **WARNING** by clicking [here](#).

Committed to Science,
Committed to You.[™]



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
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).

INDICATIONS AND USAGE

Lumason is an ultrasound contrast agent indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border (1).

DOSAGE AND ADMINISTRATION

- Intended for single use (2)
- Recommended dose after reconstitution is 2 mL administered as an intravenous bolus injection during echocardiography (2)
- During a single examination, a second injection of 2 mL may be administered to prolong contrast enhancement (2)
- Follow each injection with an intravenous flush using 5 mL of 0.9% Sodium Chloride Injection (2)

DOSAGE FORMS AND STRENGTHS

Injectable suspension supplied as a 3-part kit:

- Lumason vial containing 25 mg of lipid-type A lyophilized powder and headspace fill of 60.7 mg sulfur hexafluoride (3)
- Prefilled syringe containing 5 mL Sodium Chloride 0.9% Injection, USP (Diluent) (3)
- Mini-Spike (3)

Following reconstitution with 5mL diluent, Lumason injectable suspension contains 1.5 to 5.6 x10⁸ microspheres/mL with 45 mcg/mL of sulfur hexafluoride. (3)

CONTRAINDICATIONS

- Known or suspected right-to-left, bi-directional, or transient right-to-left cardiac shunts (4)
- 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)
- Anaphylactoid 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

Original: 10/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dose
- 2.2 Lumason Reconstitution
- 2.3 Imaging Guidelines

3 DOSAGE FORMS AND STRENGTHS

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12 CLINICAL PHARMACOLOGY

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- 14.1 Echocardiography
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17 PATIENT COUNSELING INFORMATION

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

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

Lumason is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

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.

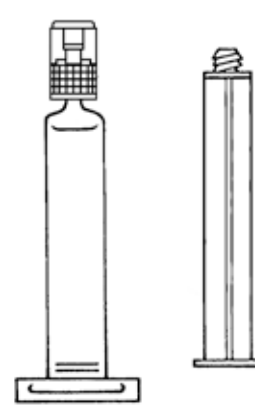
2.2 Lumason Reconstitution

Lumason is supplied within a kit containing the following:

- a clear glass vial labeled as Lumason (sulfur hexafluoride lipid-type A microspheres) for injectable suspension, 25 mg lipid-type A /60.7 mg powder and headspace filled with sulfur hexafluoride,
- a prefilled syringe with 5 mL Sodium Chloride 0.9% Injection, USP, (Diluent),
- a Mini-Spike.



Glass vial



Prefilled syringe and its plunger rod



Mini-Spike

Reconstitution steps:

- Prior to Lumason reconstitution, inspect the 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.
- Perform all Lumason reconstitution steps under aseptic conditions. The Lumason vial and the prefilled syringe do not contain a bacteriostatic preservative.
- Lumason is reconstituted by injecting the prefilled syringe contents (5 mL Sodium Chloride 0.9% Injection, USP) 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).

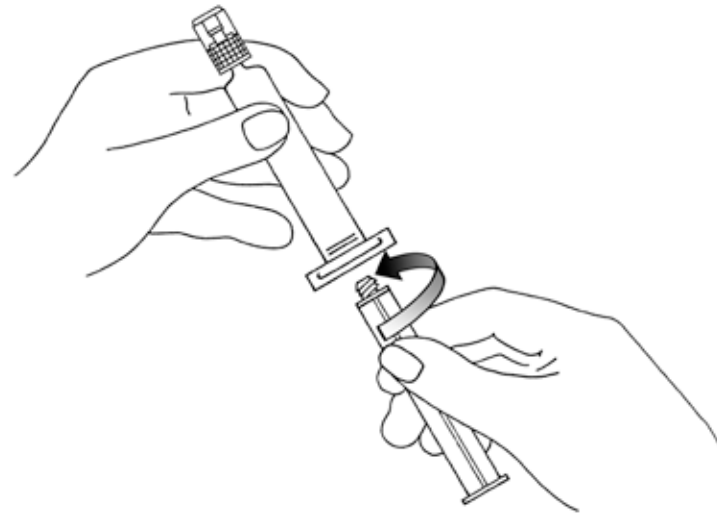


Figure 1.

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

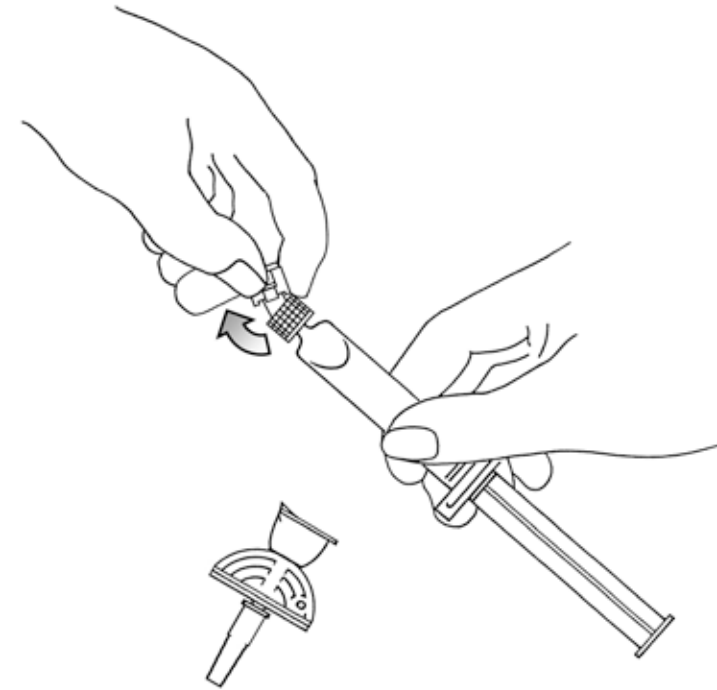


Figure 2.

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

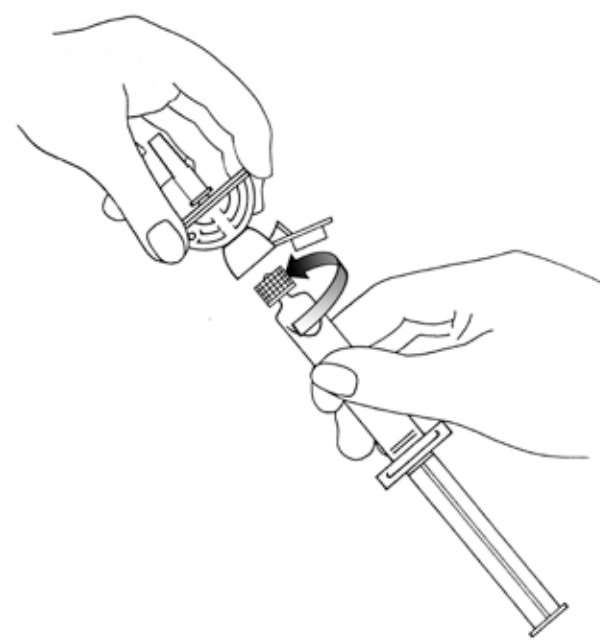


Figure 3.

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).

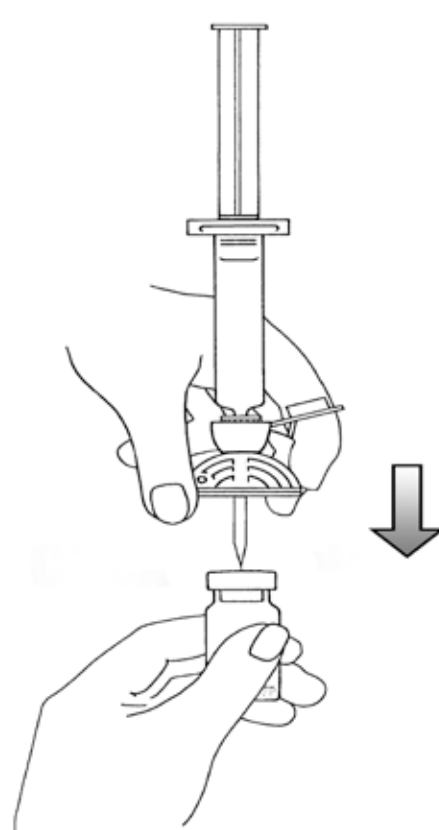


Figure 4.

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

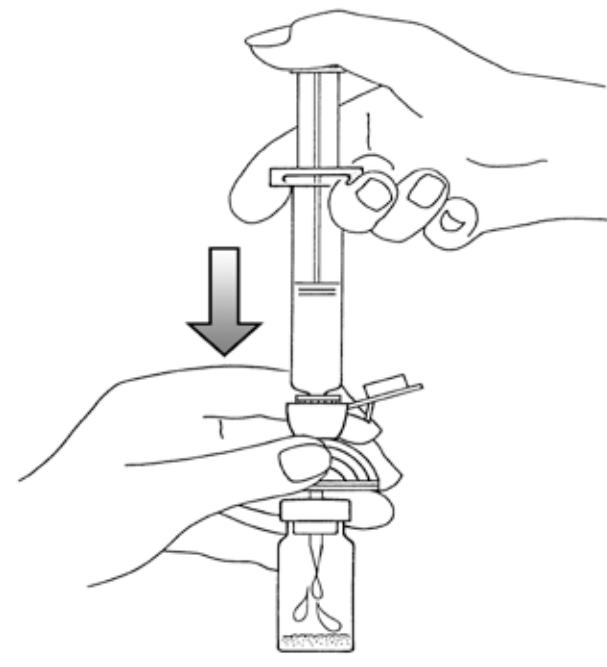


Figure 5.

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.



Figure 6.

7. Invert the system and slowly withdraw 2 mL of suspension into the syringe (see Figure 7).

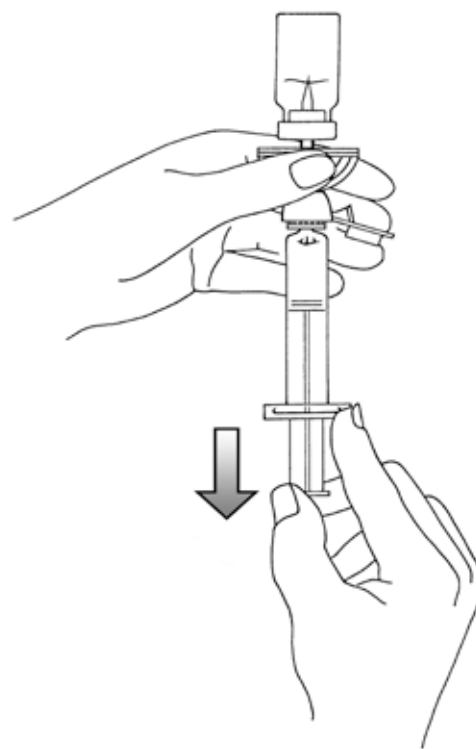


Figure 7.

8. Unscrew the syringe from the Mini-Spike (see Figure 8). Immediately connect the syringe to the dose administration line (20 G) and administer as directed under *Administration* section below.

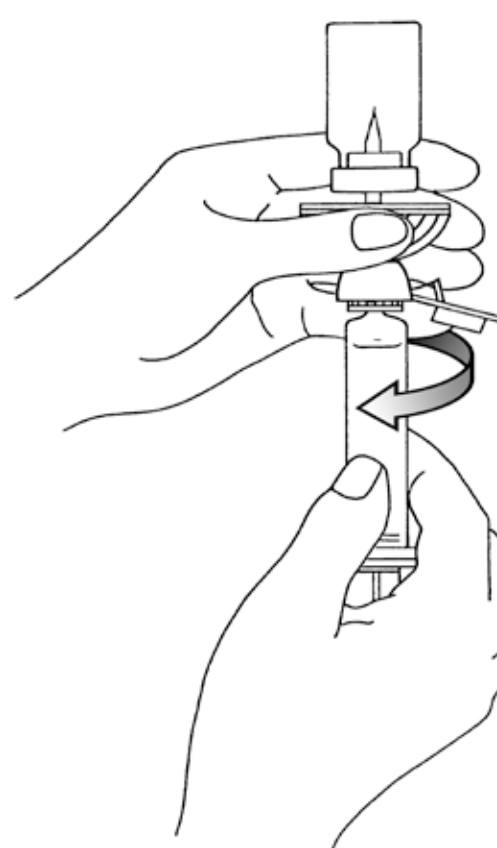


Figure 8.

Administration:

- Administer Lumason as an intravenous bolus injection.
- The milky white Lumason suspension should be used immediately after reconstitution. If the suspension is not used immediately after reconstitution, the microspheres should be resuspended by a few seconds of hand agitation before the suspension is withdrawn into the syringe. Reconstituted suspension within a vial may be used for up to 3 hours from the time of its reconstitution, after the microspheres have been resuspended by hand agitation prior to withdrawal of the suspension into the syringe. Maintain the vial containing the reconstituted suspension at room temperature.
- Lumason is for single use only. Unused portions of the reconstituted suspension must be discarded after one use in accordance with regulations dealing with the disposal of such materials. Syringe and other materials used should also be properly disposed of after single use.

2.3 Imaging Guidelines

After baseline non-contrast echocardiography is complete, the mechanical index for the ultrasound device should be adjusted to 0.8 or lower. Ultrasound imaging is then continued following Lumason injection.

3 DOSAGE FORMS AND STRENGTHS

Lumason (sulfur hexafluoride lipid-type A microspheres) for injectable suspension is a 3-part kit comprised of:

- one Lumason vial containing 25 mg of lipid-type A sterile 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 with the provided diluent, Lumason suspension contains 1.5 to 5.6×10^8 microspheres/mL with 45 mcg/mL of sulfur hexafluoride.

4 CONTRAINDICATIONS

Lumason is contraindicated in patients with:

- known or suspected right-to-left, bi-directional, or transient right-to-left cardiac shunts
- history of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in Lumason

Do not administer by intra-arterial injection.

5 WARNINGS AND PRECAUTIONS

5.1 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 Anaphylactoid Reactions

Anaphylactoid 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.

5.3 Systemic Embolization

In patients with right-to-left, bi-directional, or transient right-to-left cardiac shunts, some intravenously injected sulfur hexafluoride lipid containing microspheres may bypass filtering by the lung and directly enter the arterial circulation. Occlusion of the microcirculation by these microspheres may result in tissue ischemia. Lumason is only for intravenous administration; do not administer Lumason by intra-arterial injection.

5.4 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.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Severe 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 6307 adult subjects (128 healthy volunteers and 6179 patients) received Lumason at cumulative doses ranging from 0.2 to 161 mL (mean 10.5 mL). Lumason was administered mainly as single or multiple injections; however, some subjects received infusion dosing. The majority (73%) of subjects received Lumason at cumulative doses of 10 mL or less. There were 65% men and 35% women, with an average age of 59 years (range 17 to 99 years). A total of 4993 (79%) subjects were Caucasian; 192 (3%) were Black; 1053 (17%) were Asian; 33 (< 1%) were Hispanic; and 36 (<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 near syncope symptoms 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 = 6179	
Number (%) of Patients with Adverse Reactions	302 (4.9%)
Headache	56 (0.9%)
Nausea	34 (0.6%)
Dysgeusia	19 (0.3%)
Injection site pain	18 (0.3%)
Chest discomfort	16 (0.3%)
Feeling Hot	16 (0.3%)
Chest pain	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 on-going 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.

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)*]).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of Lumason in pregnant women. Reproduction studies have been performed in animals at doses up to at least 8 and 17 times the human dose based on body surface area (in rats and rabbits, respectively). These studies revealed no evidence of impaired fertility or harm to the fetus due to Lumason. Because animal reproduction studies are not always predictive of human response, Lumason should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether Lumason is excreted in human milk. Based on the rapid clearance of Lumason, advise nursing mothers to pump and discard breast milk once after the drug's administration [*see Clinical Pharmacology (12)*]. Because many drugs are excreted in human milk, caution should be exercised when Lumason is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of 6179 adult patients in clinical studies of Lumason, 39% were 65 and over. 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 is used to prepare the ultrasound contrast agent. The single use kit contains the following three items:

- 1) one clear glass 10 mL vial containing 25 mg of 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

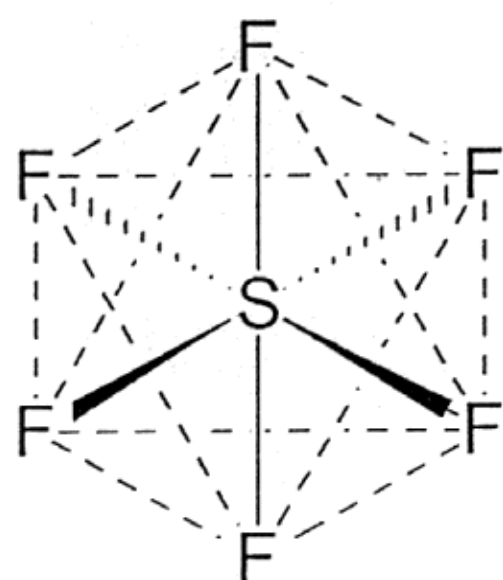
Each vial is formulated as a 25 mg sterile, pyrogen-free lyophilized powder containing 24.56 mg of polyethylene glycol 4000, 0.19 mg of distearoylphosphatidyl-choline (DSPC), 0.19 mg of dipalmitoylphosphatidylglycerol sodium (DPPG-Na) and 0.04 mg of palmitic acid. The headspace of each vial contains 6.07 mg/mL ($\pm 2\%$) sulfur hexafluoride, SF₆, 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.

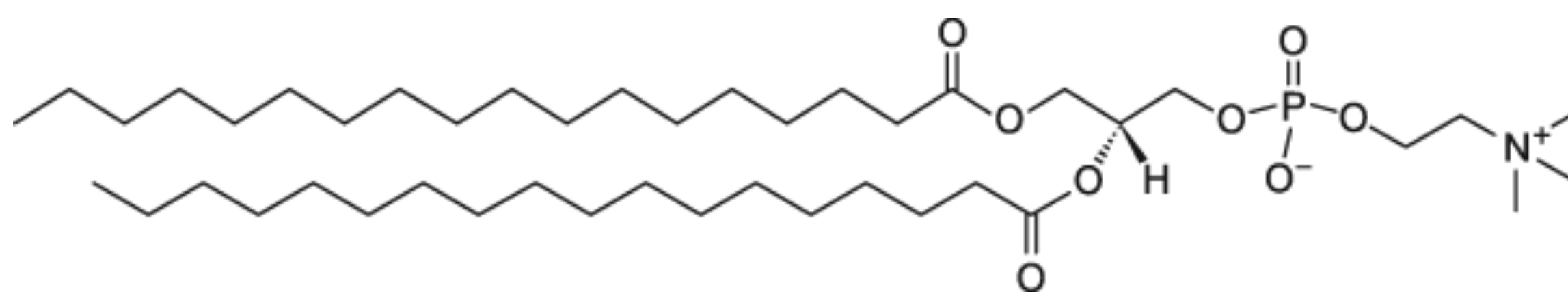
Upon reconstitution with 5mL diluent, Lumason is a milky white, homogeneous suspension containing sulfur hexafluoride lipid-type A microspheres. The suspension is isotonic and has a pH of 4.5 to 7.5; it is only for intravenous administration.

The sulfur hexafluoride lipid microspheres are composed of SF₆ gas in the core surrounded by an outer shell monolayer of phospholipids consisting DSPC and DPPG-Na with palmitic acid as a stabilizer.

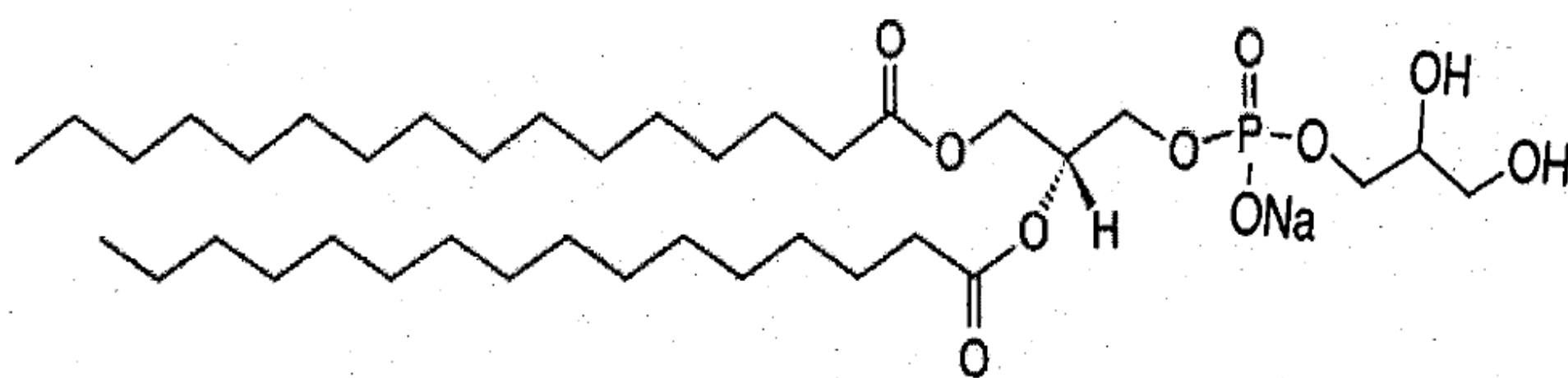
Sulfur hexafluoride has a molecular weight of 145.9 and the following chemical structure:



1,2-Distearoyl-*sn*-glycero-3-phosphocholine (DSPC), with empirical formula C₄₄H₈₈NO₈P, 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 C₃₈H₇₄NaO₁₀P, has a molecular weight of 745 and the following chemical structure:



Each milliliter of reconstituted Lumason suspension contains 1.5 to 5.6×10^8 microspheres, 68 mcg SF₆ (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.

12.2 Pharmacodynamics

A recommended dose of Lumason provides useful echocardiographic signal intensity for two minutes after the injection.

In clinical studies, echocardiography was conducted at a mechanical index (MI) ≤ 0.8 in the majority of patients. Lumason microspheres are destroyed and contrast enhancement decreases as the MI increases.

12.3 Pharmacokinetics

The pharmacokinetic of the SF₆ 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 SF₆ in blood peaked within 1 to 2 minutes for both doses. The terminal half-life of SF₆ 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 SF₆ 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 SF₆ were 341 L and 710 L 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

The SF₆ component of Lumason is eliminated via the lungs. In a clinical study that examined SF₆ elimination twenty minutes following Lumason injection, the mean cumulative recovery of SF₆ 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.

SF₆ undergoes first pass elimination within the pulmonary circulation; approximately 40% to 50% of the SF₆ content was eliminated in the expired air during the first minute following Lumason injection.

Metabolism

SF₆ undergoes little or no biotransformation; 88% of an administered dose is recovered unchanged in expired air.

Pharmacokinetics in Special Populations

Pulmonary Impairment:

In a study of patients with pulmonary impairment, blood concentrations of SF₆ peaked at 1 to 4 minutes following Lumason administration. The cumulative recovery of SF₆ in expired air was 102 ± 18% (mean ± standard deviation), and the terminal half-life of SF₆ 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.

Reader	Study A N = 76		Study B N = 62		Study C N = 53	
	Pre- injection	Post- injection	Pre- injection	Post- injection	Pre- injection	Post- injection
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 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.

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 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 before and after reconstitution at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Lumason is for single use only. Lumason does not contain an antimicrobial preservative and the suspension should be used within 3 hours after reconstitution. The microspheres should be resuspended by a few seconds of hand agitation before the product is withdrawn into the syringe [see *Dosage and Administration (2.2)*].

Store the reconstituted Lumason at room temperature in the supplied product vial.

17 PATIENT COUNSELING INFORMATION

Prior to administration of Lumason, instruct patients to inform their physician if they:

- are pregnant or nursing
- have a history of heart disease, respiratory diseases, or recent worsening of heart or lung conditions
- had prior reactions to Lumason

Rx only

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

Manufactured for:
Bracco Diagnostics Inc.
Monroe Twp., NJ 08831

By:
BRACCO Suisse SA
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)