

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).

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

Indications and Usage (1)	3/2016
Dosage and Administration (2)	3/2016

-----INDICATIONS AND USAGE-----

Lumason is an ultrasound contrast agent indicated for use

- in echocardiography to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border in adult patients with suboptimal echocardiograms (1)
- in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients (1)

-----DOSAGE AND ADMINISTRATION-----

- Echocardiography: After reconstitution, administer 2 mL as an intravenous injection in adult patients (2.2)

- Ultrasonography of the liver in adults: After reconstitution, administer 2.4 mL as an intravenous injection (2.2)
- Ultrasonography of the liver in pediatric patients: After reconstitution, administer 0.03 mL per kg as an intravenous injection, up to a maximum of 2.4 mL per injection (2.2)
- May repeat dose one time during a single examination (2.2)
- Follow each injection with an intravenous flush of 0.9% Sodium Chloride Injection (2.2)

-----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)

-----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)
- Hypersensitivity reactions (5.2)

-----ADVERSE REACTIONS-----

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

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

See 17 for PATIENT COUNSELING INFORMATION

3/2016

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

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

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

1 INDICATIONS AND USAGE

Echocardiography

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

Ultrasonography of the Liver

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

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

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

2.2 Recommended Dose

Echocardiography

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

Ultrasonography of the Liver

Adults

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

Pediatric Patients

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

2.3 Administration

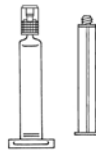
Contents of Lumason Kit

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

Lumason Reconstitution Steps:

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

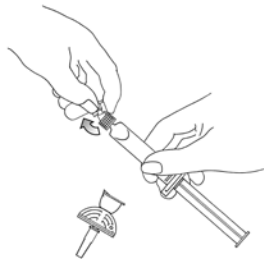


Figure 2.

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).

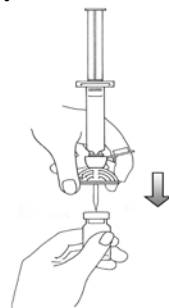


Figure 4.

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

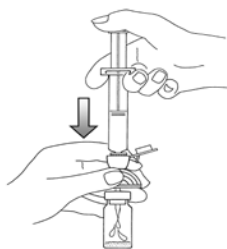


Figure 5.

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.

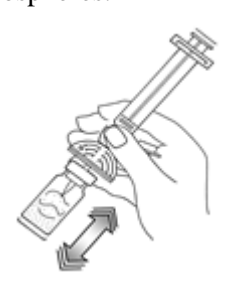


Figure 6.

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

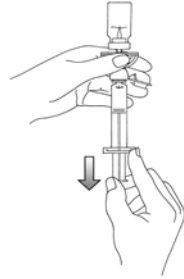


Figure 7.

8. Unscrew the syringe from the Mini-Spike (see Figure 8). Peel and remove the diluent label to display the reconstituted product label. Immediately connect the syringe to the dose administration line (20 G) and administer as directed under *Lumason Administration* section below.

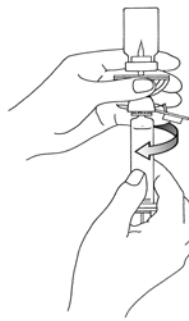


Figure 8.

Lumason Administration:

- Administer Lumason as an intravenous bolus injection.
- Use immediately after reconstitution. If the suspension is not used immediately after reconstitution, resuspend the microspheres for a few seconds by hand agitation before the suspension is drawn into the syringe. Reconstituted suspension within a vial may be used for up to 3 hours from the time of its reconstitution. Maintain the vial containing the reconstituted suspension at room temperature.
- Lumason is for single use only. Discard unused portions of the reconstituted suspension 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.

2.4 Imaging Guidelines

Echocardiography

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.

Ultrasonography of the Liver

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

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 Hypersensitivity Reactions

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

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:

- Cardiopulmonary reactions [see Warnings and Precautions (5.1)]
- Hypersensitivity reactions [see Warnings and Precautions (5.2)]

6.1 Clinical Trials Experience

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

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

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

The most commonly reported adverse reactions among patients (occurring among at least 0.2% of patients) are listed below (Table 1). Most adverse reactions were mild to moderate in intensity and resolved spontaneously.

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

*occurring in at least 0.2% of patients

6.2 Postmarketing Experience

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

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 for use in echocardiography.

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

8.5 Geriatric Use

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

11 DESCRIPTION

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

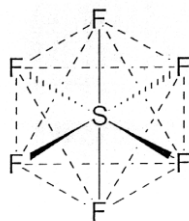
Each vial is formulated as a 25 mg sterile, pyrogen-free lyophilized powder containing 24.56 mg of polyethylene glycol 4000, 0.19 mg of distearoylphosphatidyl-choline (DSPC), 0.19 mg of dipalmitoylphosphatidylglycerol sodium (DPPG-Na) and 0.04 mg of palmitic acid. The headspace of each vial contains 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.

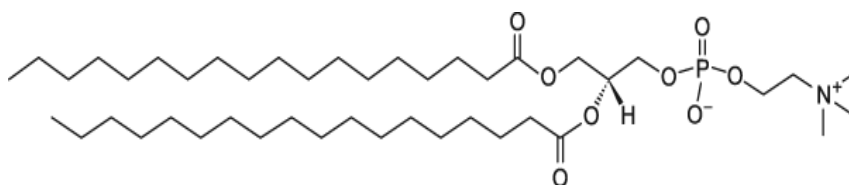
Upon reconstitution with 5mL diluent, Lumason is a milky white, homogeneous suspension containing sulfur hexafluoride lipid-type A microspheres. The suspension is isotonic and has a pH of 4.5 to 7.5; it is only for intravenous administration.

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.

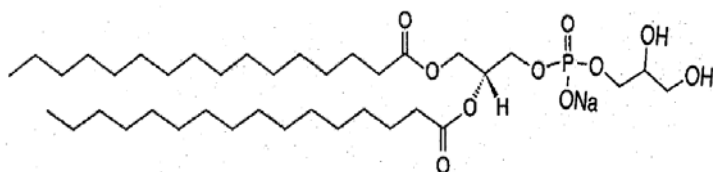
Sulfur hexafluoride has a molecular weight of 145.9 and the following chemical structure:



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

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

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

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 $82 \pm 20\%$ (SD) at the 0.03 mL/kg dose and $88 \pm 26\%$ (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

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

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

Left Ventricular Opacification

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

Ultrasonography of the Liver

Adults

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

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

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

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

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

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

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

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

Pediatric patients:

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

14.3 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

Lumason is a registered trademark of Bracco Diagnostics Inc.

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 mg sulfur hexafluoride gas)

Vetter Pharma-Fertigung GmbH & Co. KG

88212 Ravensburg, Germany (Sodium Chloride 0.9% Injection, USP)

B. Braun Melsungen AG

34212 Melsungen, Germany (Mini-Spike)