Our commitment to you...

The ultrasound contrast agent LUMASON® (sulfur hexafluoride lipid-type A microspheres) for injectable suspension, known internationally as SonoVue®, was approved by the U.S. Food and Drug Administration (FDA) in 2014 for echocardiography, to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border, in adult patients with suboptimal echocardiograms.

Bracco Diagnostics Inc. is proud to introduce a second indication for LUMASON. As of March 2016, LUMASON was approved for use in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients.

LUMASON consists of microspheres that encapsulate an inert gas [sulfur hexafluoride (SF₆)] in a phospholipid shell. LUMASON is provided in a single-use, 3-part kit that includes all components necessary for reconstitution, and requires no refrigeration for storage or mechanical agitation for reconstitution.

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

Please see full Prescribing Information including boxed WARNING by clicking here.
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
• in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients

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

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)].
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Committed to Science,  
Committed to You™
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
• in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients

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LUMASON® (sulfur hexafluoride lipid-type A microspheres) for injectable suspension is a second-generation ultrasound contrast agent that has been developed to provide an optimal backscattered signal over a broad frequency range, with good pressure stability and persistence in the blood stream.1

LUMASON is characterized by a microsphere structure consisting of a low solubility gas (sulfur hexafluoride, SF₆) stabilized by a phospholipid shell.1

LUMASON is indicated: (1) in echocardiography for use in adult patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border, and (2) in ultrasonography of the liver for use in adult and pediatric patients to characterize focal liver lesions1

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

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 phases of signal intensity enhancement of the microvasculature.1

LUMASON is provided 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 with headspace filled with 60.7 mg of SF₆; a prefilled syringe containing 5 mL Sodium Chloride 0.9% Injection, USP (diluent); and a Mini-Spike.1

Mechanism of action (MOA): Within the blood, the acoustic impedance of LUMASON microspheres is lower than that of the surrounding nonaqueous tissue. When an ultrasound beam is reflected from the interface between the microspheres and the surrounding tissue, that reflected ultrasound signal provides a visual image that depicts contrast between the blood and the surrounding tissues.1

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.

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% of the 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 The phospholipid component of the microsphere shell is metabolized, re-entering the endogenous phospholipid metabolic pathway.3
CONTRAST-ENHANCED ULTRASOUND OF THE LIVER: AN INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) in the United States has tripled between 1975 and 2005, and it is now the third leading cause of cancer mortality worldwide.4 The American Cancer Society estimates that in 2016, about 39,230 new cases of liver cancer and intrahepatic bile duct (28,410 in men and 10,820 in women) will be diagnosed in the United States, and about 27,170 people (18,280 men and 8,890 women) will die of these cancers.5 Liver may also be the site of metastasis from virtually any primary cancer and represents the second most commonly involved organ in metastatic disease. Based on autopsy studies in Japan and the USA, up to 40% of patients with an extrahepatic primary tumour have hepatic metastases.6 In addition to considerations of patient-related risk factors, physical examination, and liver function tests, imaging plays a major role in noninvasive diagnosis of liver disease, including liver cancer, metastases and recurrences and for characterization of focal liver lesions.7,8 Since benign focal liver lesions are common in both the general population (prevalence of 5-10%) and patients with known malignancy, an accurate and reliable assessment of the nature of the hepatic lesion is critical in order to differentiate neoplastic lesions from benign abnormalities which might not require treatment.9 As a matter of fact, characterization of focal liver lesions is a frequently encountered challenge in clinical practice both in patients with neoplastic disease and in those with non-neoplastic disease.

Ultrasound is often used as the first-line imaging modality because it is noninvasive, cost-effective, and safe. Ultrasound may be followed by magnetic resonance (MRI) and/or computed tomography (CT) imaging, with or without contrast.10 Contrast-enhanced ultrasound (CEUS) has been shown to be more accurate than unenhanced ultrasound for diagnosis of focal liver lesions.11–16 In addition, CEUS has several advantages over contrast-enhanced MRI and CT imaging, including the ability to evaluate contrast enhancement of lesions in real time and the lack of exposure to ionizing radiation and iodine, therefore representing an imaging alternative for patients with renal function impairment.11,12,17

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
• in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients

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

Here, we describe the product’s characteristics, the clinical indication for characterization of focal liver lesions, its safety profile, and the pharmacoeconomics analysis of CEUS with LUMASON in liver imaging.

Figure 1. Schematic illustration of the enhancement pattern of focal liver lesions compared to surrounding normal liver tissue. The architecture of the supplying vessels and/or the pattern and temporal course of the enhancement allow the assessment of the benign or malignant nature of the focal liver lesion and, in many cases, a diagnosis of the lesion type.

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LUMASON PRODUCT CHARACTERISTICS

LUMASON DESCRIPTION

Each vial is formulated as a 25 mg sterile, pyrogen-free lyophilized powder containing 24.56 mg polyethylene glycol 4000, 0.19 mg distearoylphosphatidyl-choline (DSPC), 0.19 mg dipalmitoylphosphatidylglycerol sodium (DPPG-Na), and 0.04 mg palmitic acid. The headspace of each vial contains 6.07 mg/mL (±2%) sulfur hexafluoride (SF₆), or 60.7 mg per vial. Each prefilled syringe with 5 mL of diluent 0.9% Sodium Chloride Injection is sterile, nonpyrogenic, and preservative free containing 9 mg sodium chloride per mL. Upon reconstitution with 5 mL diluent, LUMASON is a milky white, homogeneous suspension containing sulfur hexafluoride lipid-type A microspheres. The suspension is isotonic and has a pH of 4.5 to 7.5; it is only for intravenous administration.

The sulfur hexafluoride lipid microspheres are composed of SF₆ gas in the core surrounded by an outer shell monolayer of phospholipids consisting of DSPC and DPPG-Na with palmitic acid as a stabilizer. Each milliliter of reconstituted LUMASON suspension contains 1.5 to 5.6 ×10⁸ 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 sulfur hexafluoride associated with the microspheres suspension is 45 mcg/mL. 15 to 23 percent of the total lipids in the suspension are associated with the microspheres. The sulfur hexafluoride lipid microsphere characteristics are listed in Table 1.

Table 1. Microsphere Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean diameter range</td>
<td>1.5–2.5 μm</td>
</tr>
<tr>
<td>Percent of microspheres ≤10 μm</td>
<td>≥99%</td>
</tr>
<tr>
<td>Upper size limit</td>
<td>100.0% ≤20 μm</td>
</tr>
</tbody>
</table>

MECHANISM OF ACTION

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

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

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 phases of signal intensity enhancement of the microvasculature.

PHARMACODYNAMIC PROPERTIES

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.
PHARMACOKINETIC PROPERTIES

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 (±SD) cumulative recovery of SF₆ in expired air was 82% ± 20% at the 0.03 mL/kg dose and 88% ± 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.¹

Metabolism

SF₆ undergoes little or no biotransformation; 88% of an administered dose is recovered unchanged in expired air.¹ While SF₆ is exhaled through the lungs, the phospholipid component of the microsphere shell is metabolized, re-entering the endogenous phospholipid metabolic pathway.³

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
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Figure 3. Below shows the pharmacokinetics of SF₆ after intravenous administration of LUMASON to healthy subjects.

**Figure 3.**

Median blood concentration of SF₆ (left) and mean cumulative elimination of SF₆ (right) after intravenous administration of LUMASON to healthy subjects. By 11 minutes, 80% to 90% of the administered 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;35:80-85. 31

**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 ± SD), and the terminal half-life of SF₆ in blood was similar to that measured in healthy subjects. ¹

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INDICATION

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

CLINICAL STUDIES

Adults

A total of 499 patients with at least 1 focal liver lesion requiring characterization were evaluated in 2 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 19–93 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 44–173 kg).

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

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
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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 with non-contrast ultrasound images. Table 2 summarizes the efficacy results by reader.

### Table 2. Diagnostic Performance of LUMASON Ultrasound for Characterization of Focal Liver Lesions

#### Study A:

<table>
<thead>
<tr>
<th>Reader</th>
<th>LUMASON % (patients with malignant lesions)</th>
<th>Non-contrast %</th>
<th>Difference (95% CI)</th>
<th>Specificity (patients with benign lesions)</th>
<th>LUMASON %</th>
<th>Non-contrast %</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 1</td>
<td>87*</td>
<td>49</td>
<td>38 (30, 54)</td>
<td>71</td>
<td>63</td>
<td>8 (–4, 21)</td>
<td></td>
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<tr>
<td>Reader 2</td>
<td>76*</td>
<td>35</td>
<td>41 (29, 52)</td>
<td>83*</td>
<td>54</td>
<td>29 (21, 44)</td>
<td></td>
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<tr>
<td>Reader 3</td>
<td>92*</td>
<td>16</td>
<td>76 (67, 84)</td>
<td>73*</td>
<td>22</td>
<td>51 (40, 61)</td>
<td></td>
</tr>
</tbody>
</table>

#### Study B:

<table>
<thead>
<tr>
<th>Reader</th>
<th>LUMASON % (patients with malignant lesions)</th>
<th>Non-contrast %</th>
<th>Difference (95% CI)</th>
<th>Specificity (patients with benign lesions)</th>
<th>LUMASON %</th>
<th>Non-contrast %</th>
<th>Difference (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Reader 4</td>
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<td>53</td>
<td>12 (–1, 23)</td>
<td>72*</td>
<td>24</td>
<td>48 (35, 58)</td>
<td></td>
</tr>
<tr>
<td>Reader 5</td>
<td>61*</td>
<td>41</td>
<td>20 (7, 32)</td>
<td>67*</td>
<td>7</td>
<td>60 (50, 70)</td>
<td></td>
</tr>
<tr>
<td>Reader 6</td>
<td>47</td>
<td>66</td>
<td>–19 (–31, –7)</td>
<td>88*</td>
<td>59</td>
<td>29 (18, 40)</td>
<td></td>
</tr>
</tbody>
</table>

*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 boys, 21 girls, age range 4–18 years; median 11.5 years) were evaluated after intravenous bolus administration of 1.2 to 2.4 mL LUMASON. The findings of LUMASON ultrasound images were compared with CT, MRI, or histology. Specificity was 98% (43 of 44 patients).

## IMPORTANT SAFETY INFORMATION

### BOXED WARNING

**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)].

Please see full Prescribing Information including boxed WARNING by clicking here.
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

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.

The reported reactions that may follow the administration of ultrasound contrast agents include fatal cardiac or respiratory arrest, shock, syncope, symptomatic arrhythmias (atrial fibrillation, tachycardia, bradycardia, supraventricular tachycardia, ventricular fibrillation, and ventricular tachycardia), hypertension, hypotension, dyspnea, hypoxia, chest pain, respiratory distress, stridor, wheezing, loss of consciousness, and convulsions.

Hypersensitivity reactions

Hypersensitivity reactions such as skin erythema, rash, urticaria, flushing, throat tightness, dyspnea, or anaphylactic shock have 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.

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
- in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients

CONTRAINDICATIONS

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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.

ADVERSE REACTIONS

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

- Cardiopulmonary reactions
- Hypersensitivity reactions

Clinical trials experience

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

In completed clinical trials, a total of 6,984 adult subjects (128 healthy volunteers and 6,856 patients) received LUMASON at cumulative doses ranging from 0.2 to 161 mL (mean 9.8 mL). LUMASON was administered mainly as single or multiple injections; however, some subjects received infusion dosing. The majority (75%) of subjects received LUMASON at cumulative doses of 10 mL or less. There were 64% men and 36% women, with an average age of 59 years (range 17–99 years). A total of 79% subjects were Caucasian; 4% were Black; 16% were Asian; <1% were Hispanic; and <1% were in other racial groups or race was not reported.

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

The most commonly reported adverse reactions among patients (occurring among at least 0.2% of patients) are listed in Table 3. Most adverse reactions were mild to moderate in intensity and resolved spontaneously.

<table>
<thead>
<tr>
<th>Table 3. Adverse Reactions in Patients*¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 6856</td>
</tr>
<tr>
<td>Number (%), of Patients with Adverse Reactions</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Dysgeusia</td>
</tr>
<tr>
<td>Injection site pain</td>
</tr>
<tr>
<td>Feeling hot</td>
</tr>
<tr>
<td>Chest discomfort</td>
</tr>
<tr>
<td>Chest pain</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Injection site warmth</td>
</tr>
</tbody>
</table>

*occurring in at least 0.2% of patients

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**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).

---

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USE IN SPECIFIC POPULATIONS

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.

Nursing mothers

It is not known whether LUMASON is excreted in human milk. Based on the rapid clearance of LUMASON, nursing mothers should be advised to pump and discard breast milk once after the drug’s administration. Because many drugs are excreted in human milk, caution should be exercised when LUMASON is administered to a nursing woman.

Pediatric use

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

Geriatric use

Of the total number of 6,856 adult patients in clinical studies of LUMASON, 39% were 65 and older, while 11% were 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly or younger patients, but greater sensitivity of some older individuals cannot be ruled out.

PATIENT COUNSELING INFORMATION

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

PHARMACOECONOMIC ANALYSIS OF CEUS WITH LUMASON IN LIVER IMAGING

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

Please see full Prescribing Information including boxed WARNING by clicking here.
Model 1: Using the “Cirrhosis Surveillance” model, CEUS was shown to have the lowest discounted lifetime costs per person, followed by contrast-enhanced CT and contrast-enhanced MRI with gadolinium. Compared with CEUS, contrast-enhanced CT was as effective but more costly, whereas MRI with gadolinium was more effective, but much more costly.32

Model 2: With the “Potential Liver Metastases from Colorectal Cancer” model, using the different imaging techniques to investigate potential liver metastases from colorectal cancer, CEUS and contrast-enhanced CT were both cost-effective technologies, with equal expected costs and effectiveness. Contrast-enhanced MRI with gadolinium was more costly than either contrast-enhanced CT or CEUS.32

Model 3: Finally, using the “Incidentally Detected Focal Liver Lesions” model, the lower costs of CEUS, combined with slightly better test performance, meant that CEUS dominated both contrast-enhanced CT and contrast-enhanced MRI.32

Based on their economic analysis, NICE32 has recommended that CEUS with SonoVue/LUMASON be used for:

• Characterizing incidentally detected focal liver lesion in adults in whom an unenhanced US scan is inconclusive. An unenhanced ultrasound scan in which a focal liver lesion is detected, but not characterized, is defined as inconclusive.

• Investigating potential liver metastases in adults if contrast-enhanced CT is not clinically appropriate, is not accessible, or is not acceptable to the person, and in whom an unenhanced ultrasound scan is unsatisfactory and contrast is needed for further diagnosis.

• Characterizing focal liver lesion in adults whose cirrhosis is being monitored if contrast-enhanced MRI is not clinically appropriate, is not accessible, or is not acceptable to the person, and when unenhanced ultrasound scan is inconclusive.

INDICATIONS AND USAGE

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• in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients

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

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 DOSAGE AND ADMINISTRATION

RECOMMENDED DOSE FOR ULTRASOUND OF THE LIVER

- Ultrasonography of the liver in adults: After reconstitution, administer 2.4 mL as an intravenous injection
- 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
- May repeat dose one time during a single examination
- Follow each injection with an intravenous flush of 0.9% Sodium Chloride Injection

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
- Prefilled syringe containing 5 mL Sodium Chloride 0.9% Injection, USP (Diluent)
- Mini-Spike

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
LUMASON PREPARATION

RECONSTITUTION

LUMASON is supplied within a 3-part 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 of sulfur hexafluoride,
• A prefilled syringe containing 5 mL Sodium Chloride 0.9% Injection, USP (Diluent),
• A Mini-Spike.

INDICATIONS AND USAGE

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IMPORTANT SAFETY INFORMATION:

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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 (PI, Figure 1).

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

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

Please see full Prescribing Information including boxed WARNING by clicking here.
4. Remove the flip cap plastic protective cap from the vial, remove the Mini-Spike spike protection, and position the spike in the center of the rubber stopper of the vial. Press firmly inward until the spike is fully inserted in the stopper (PI, Figure 4).

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

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

![PI, Figure 6.]

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

![PI, Figure 7.]

8. Unscrew the syringe from the Mini-Spike (see PI, Figure 8). Peel and remove the diluent label to display the reconstituted product label.

![PI, Figure 8.]

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

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