Bracco Diagnostics

# LUMASON™

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

**Rx ONLY**

Please see full prescribing information. A brief summary follows.

**WARNING: SERIOUS CARDIOPULMONARY REACTIONS**

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

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

## 1 INDICATIONS AND USAGE

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

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

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

## 2 DOSAGE AND ADMINISTRATION

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

**2.2 Recommended Dosage**

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

**Ultrasonography of the Liver**

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

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

**Ultrasonography of the Urinary Tract**

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

**2.3 Reconstitution Instructions**

- Inspect the Lumason kit and its components for signs of damage. Do not use the kit if the protective caps on the Lumason vial and prefilled syringe with 5 mL Sodium Chloride 0.9% Injection are not intact or if the kit shows other signs of damage.
- Under aseptic conditions, reconstitute Lumason by injecting the prefilled syringe with 5 mL Sodium Chloride 0.9% Injection into the Lumason vial using the following steps:
  1. Connect the plunger rod to the prefilled syringe barrel by screwing it clockwise into the syringe.
  2. Open the Mini-Spike blister and remove the syringe tip cap.
  3. Open the Mini-Spike green cap and connect the syringe to the MiniSpike by screwing it in clockwise.
  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.
  5. Empty the content of the syringe into the vlal by pushing on the plunger rod.
  6. Shake vigorously for 20 seconds, mixing all the contents in the vial. A homogeneous white milky liquid indicates formation of sulfur hexafluoride lipid microspheres.
  7. For preparation of doses greater than or equal to 1 mL, invert the system and slowly withdraw the intended volume of suspension into the syringe. For preparation of doses less than 1 mL, withdraw 2 mL of the reconstituted suspension into the 5 mL syringe and measure the volume of Lumason to inject by using the 0.2 mL graduations between the 1 mL and 2 mL marks.
  8. Unscrew the syringe from the Mini-Spike. Peel and remove the diluent label to display the reconstituted product label. For intravenous administration, immediately connect the syringe to a dose administration line (20 G) and administer as directed under the Administration Instructions. For intravesical administration, immediately connect the syringe to a sterile urinary catheter (6 french to 8 french) and administer as directed under the Administration Instructions.
- Following reconstitution, Lumason suspension contains 1.5 to 5.6 $x10^8$ microspheres/mL with 45 mcg/mL of sulfur hexafluoride.
- Use immediately after reconstitution. If the suspension is not used immediately after reconstitution, resuspend the microspheres for a few seconds by hand agitation before the suspension is drawn into the syringe. Reconstituted suspension within a vial may be used for up to 3 hours from the time of its reconstitution. Maintain the vial containing the reconstituted suspension at room temperature.

**2.4 Administration Instructions**

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

**Intravenous Administration**

Administer Lumason as an intravenous bolus injection.

**Intravesical Administration in Pediatric Patients**

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

## 4 CONTRAINDICATIONS

Lumason is contraindicated in patients with:

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

## 5 WARNINGS AND PRECAUTIONS

**5.1 Cardiopulmonary Reactions**

Serious cardiopulmonary reactions, including fatalities have occurred uncommonly during or shortly following administration of ultrasound contrast agents, including Lumason. These reactions typically occurred within 30 minutes of administration. The risk for these reactions may be increased among patients with unstable cardiopulmonary conditions (acute myocardial infarction, acute coronary artery syndromes, worsening or unstable congestive heart failure, or serious ventricular arrhythmias). Always have cardiopulmonary resuscitation personnel and equipment readily available prior to Lumason administration and monitor all patients for acute reactions.

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

**5.2 Hypersensitivity Reactions**

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

**5.3 Systemic Embolization**

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

**5.4 Ventricular Arrhythmia Related to High Mechanical Index**

High ultrasound mechanical index values may cause microsphere cavitation or rupture and lead to ventricular arrhythmias. Additionally, end-systolic triggering with high mechanical indices has been reported to cause ventricular arrhythmias.

Lumason is not recommended for use at mechanical indices greater than 0.8.

## 6 ADVERSE REACTIONS

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

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

**6.1 Clinical Trials Experience**

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

In completed clinical trials, a total of 6984 adult subjects (128 healthy volunteers and 6856 patients) received Lumason at cumulative doses ranging from 0.2 to 161 mL (mean 9.8 mL). Lumason was administered mainly as single or multiple injections; however, some subjects received infusion dosing. The majority (75%) of subjects received

Lumason at cumulative doses of 10 mL or less. There were 64% men and 36% women, with an average age of 59 years (range 17 to 99 years). A total of 79% subjects were Caucasian; 4% were Black; 16% were Asian; <1% were Hispanic; and <1% were in other racial groups or race was not reported.

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

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

**TABLE 1. ADVERSE REACTIONS IN PATIENTS* n = 6856**

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

*occurring in at least 0.2% of patients

**6.2 Postmarketing Experience**

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

## 8 USE IN SPECIFIC POPULATIONS

**8.1 Pregnancy**

**Risk Summary** There are no data with Lumason use in pregnant women to inform any drug-associated risks. No adverse developmental outcomes were observed in animal reproduction studies with administration of sulfur hexafluoride lipid-type A microspheres in pregnant rats and rabbits during organogenesis at doses up to at least 10 and 20 times, respectively, the maximum human dose of 4.8 mL based on body surface area (see Data).

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

**Data**

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

**8.2 Lactation**

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

**8.4 Pediatric Use**

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

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

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

**8.5 Geriatric Use**

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

## 17 PATIENT COUNSELING INFORMATION

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

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**Rx Only**

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

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

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