

# Office of Clinical Pharmacology Review

---

<b>NDA or BLA Number</b>	203-684
<b>Link to EDR</b>	<a href="\\CDSESUB1\evsprod\NDA203684\203684.enx">\\CDSESUB1\evsprod\NDA203684\203684.enx</a>
<b>Submission Date</b>	June 29, 2016, SDN 93 September 16, 2016, SDN 104
<b>Submission Type</b>	Supplement-2 (Efficacy), 505(b)(2)
<b>Brand Name</b>	Lumason <sup>®</sup>
<b>Generic Name</b>	Sulfur hexafluoride (SF <sub>6</sub> ) lipid-type A microspheres for injectable suspension, for intravenous use
<b>Dosage Form and Strength</b>	Lumason (sulfur hexafluoride “SF <sub>6</sub> ” lipid-type A microspheres) for injectable suspension is supplied as a single patient-use kit as follows: <ul style="list-style-type: none"> <li>• One Lumason clear glass 10 mL vial containing 25 mg lipid-type A lyophilized powder with headspace fill of 60.7 mg of sulfur hexafluoride (SF<sub>6</sub>)</li> <li>• One prefilled syringe containing 5mL of Sodium Chloride 0.9% Injection, USP (Diluent)</li> <li>• One Mini-Spike</li> </ul> Lumason is for single use only.
<b>Route of Administration</b>	<b>Approved Indications:</b> intravenous <b>New Indication:</b> intravesical
<b>Indication (s)</b>	<b>Approved Indications:</b> Lumason is an ultrasound contrast agent indicated for use <ul style="list-style-type: none"> <li>• 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</li> <li>• in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients</li> </ul> <b>New Indication:</b> <ul style="list-style-type: none"> <li>• in ultrasonography of the (b) (4) urinary tract (b) (4) vesicoureteral reflux in pediatric patients</li> </ul>
<b>Applicant</b>	Bracco Diagnostics, Inc.
<b>Associated IND</b>	46,958 (first submitted December 23, 1994)
<b>OCP Review Team</b>	Sam Habet, R.Ph., Ph.D., Gene Williams, Ph.D.

**Table of Contents**

1. EXECUTIVE SUMMARY ..... 3

    1.1 Recommendations ..... 3

    1.2 Post-Marketing Requirements and Commitments ..... 3

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT ..... 4

    2.1 Pharmacology and Clinical Pharmacokinetics ..... 4

    2.2 Dosing and Therapeutic Individualization ..... 4

    2.3 Outstanding Issues ..... 5

    2.4 Summary of Labeling Recommendations ..... 5

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW ..... 5

    3.1 Overview of the Product and Regulatory Background ..... 5

    3.2 General Pharmacology and Pharmacokinetic Characteristics ..... 6

    3.3 Clinical Pharmacology Review Questions ..... 7

        3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness? ..... 7

        3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought? ..... 8

        3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors? ..... 9

## **1. EXECUTIVE SUMMARY**

Lumason® (sulfur hexafluoride-SF<sub>6</sub> lipid-type A microspheres) was initially approved by the FDA in October 10, 2014 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*”. Subsequently, on March 31, 2016, Lumason received FDA approval for use “*in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients.*”

In the current submission, the applicant is seeking an additional indication for use of Lumason during ultrasonography of the (b) (4) urinary tract in pediatric patients with known or suspected vesicoureteral reflux (VUR). The ultrasound procedure is called voiding urosonography (VUS) and encompasses examination of the urinary tract, including bladder, ureters, and urethra. The formulation used for VUS is the same formulation used for the approved indications.

This is a 505(b)(2) application based exclusively on literature reports. The four clinical studies reported used flat doses of 1 mL given intravesically, and the applicant proposes a flat dose of 1mL as the recommended dose for the package insert.

A lack of reporting of ineffective imaging provides support that the flat 1.0 mL dose is sufficient, but leaves open the question of whether lower doses might be equi-effective, especially for small children. No adverse events (AEs) were observed with the 1.0 mL dose and it is unlikely that intravesicular administration will result in significant systemic absorption of SF<sub>6</sub> due to the near complete voiding of SF<sub>6</sub> that occurs during VUS and the anatomical characteristics of the urinary bladder which act to limit drug absorption. Therefore, we conclude that an evaluation of lower doses is not needed.

### **1.1 Recommendations**

From the Clinical Pharmacology perspective, this supplemental NDA is approvable, provided an agreement can be reached on labeling.

### **1.2 Post-Marketing Requirements and Commitments**

From the Clinical Pharmacology perspective, no post-marketing requirements or commitments are indicated.

## **2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT**

### **2.1 Pharmacology and Clinical Pharmacokinetics**

The active ingredient in Lumason is sulfur hexafluoride lipid microspheres composed of SF<sub>6</sub> gas in their core. The acoustic impedance of Lumason microspheres is lower than that of the surrounding non-aqueous tissue. Therefore, an ultrasound beam is reflected from the interface between the microspheres and the surrounding tissue. The reflected ultrasound signal provides a visual image that shows a contrast between the blood and the surrounding tissues.

For the proposed indication for the use of Lumason during VUS, Lumason is administered through a catheter into the bladder and ultrasound imaging is acquired during filling of the bladder and voiding. No pharmacokinetics data have been collected following intravesical administration. The following information, acquired after intravenous administration, is summarized from the approved package insert.

Following Lumason administration, SF<sub>6</sub> undergoes first pass elimination within the pulmonary circulation; approximately 45% of the SF<sub>6</sub> content was eliminated in expired air during the first minute following injection. At twenty minutes following Lumason injection, the mean cumulative recovery of SF<sub>6</sub> in expired air was 82%.

At a dose of 0.03 mL/kg, which approximates the clinical dose of 2 -2.4 mL, the terminal half-life of SF<sub>6</sub> in blood could not be estimated. At a dose of 0.3 mL/kg, the terminal half-life of SF<sub>6</sub> was approximately 10 minutes.

### **2.2 Dosing and Therapeutic Individualization**

The approved recommended doses are 2.0 mL IV for echocardiography in adult patients, 2.4 mL IV for ultrasonography of the liver in adult patients, and 0.03 mg/kg IV for ultrasonography of the liver in pediatric patients. The use of weight-based dosing for pediatric patients is the only example of individualization of dose in the approved package insert.

The proposed dose for the proposed indication of ultrasonography of the (b) (4) urinary tract in children is 1 mL administered into the bladder via catheter. Prior to dosing, (b) (4) saline is administered. No reports of ineffective imaging or technical artifacts were reported in any of the trials, even though the same 1.0 mL dose was used in newborns, infants and older children.

A lack of reporting of ineffective imaging provides support that the flat 1.0 mL dose is sufficient, but leaves open the question of whether lower doses might be equi-effective, especially for small children. We conclude that an exploration of lower doses is not needed, as no AEs were observed with the 1.0 mL dose and it is unlikely that intravesical administration will result in significant systemic absorption of SF<sub>6</sub> (see **3.2 General Pharmacology and Pharmacokinetic Characteristics**).

## 2.3 Outstanding Issues

There are no outstanding issues.

## 2.4 Summary of Labeling Recommendations

Labeling negotiations with the applicant have yet to occur. We have the following recommendations:

- The addition to section **12.3 Pharmacokinetics** that pertains to the mechanism of action following intravesical administration should be moved from section **12.3 Pharmacokinetics** to section **12.1 Mechanism of Action**.
- The language describing the healthy subject study performed in 12 healthy subjects should not include (b) (4).
- The sentence stating that (b) (4) should be deleted.
- The header titled “Pharmacokinetics in (b) (4) Populations” should be changed to “Pharmacokinetics in Specific Populations.”

## **3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW**

### **3.1 Overview of the Product and Regulatory Background**

Lumason was initially approved by the FDA on October 10, 2014 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”. It was subsequently approved on March 31, 2016 for use “in ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients.”

Within the blood, the acoustic impedance of Lumason microspheres is lower than that of the surrounding non-aqueous tissue. Therefore, an administered 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.

Lumason (sulfur hexafluoride lipid-type A microspheres) is provided as a powder. The powder is reconstituted with saline prior to administration resulting in a final microsphere concentration of approximately 5 mg/mL. The recommended doses are 2.0 mL IV for echocardiography in adult patients, 2.4 mL IV for ultrasonography of the liver in adult patients, and 0.03 mg/kg IV for ultrasonography of the liver in pediatric patients. The use of weight-based dosing for pediatric patients is the only example of individualization of dose in the approved package insert. The proposed dose for the currently proposed indication of ultrasonography of the (b) (4) urinary tract in children is 1 mL administered into the bladder via catheter. Prior to dosing, (b) (4) saline is administered. An excerpt from section **2.2 Recommended Dose** of the proposed package insert is reproduced (indented).

Empty the bladder of urine, and then fill the bladder with saline (normal sterile 0.9% sodium chloride solution) to approximately one third or half of its predicted total volume [(age in years + 2) x 30] mL. (b) (4) Lumason (b) (4) continue filling the bladder with saline until the patient has the urge to micturate or (b) (4) the first (b) (4) sign of back pressure to the infusion. 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.

The following (indented) is excerpted from the preNDA meeting minutes of September 25, 2015. The NDA should include justification for the dose and imaging parameters (window and acquisition parameters) for the new indication. Body weight or BSA-based dosing is the starting point for consideration of pediatric dosing; size-based dosing often results in less variable exposure than occurs with age-based dosing. Integration of the literature data should be performed with the intent of giving prescribers a single or narrow (after adjustment for size or age) optimal dose rather than a wide range.

### **3.2 General Pharmacology and Pharmacokinetic Characteristics**

No pharmacokinetics data have been collected following intravesical administration. The following information (indented), acquired after intravenous administration, is excerpted from the approved package insert.

#### **12.3 Pharmacokinetics**

The pharmacokinetic of the SF<sub>6</sub> gas component of Lumason was evaluated in 12 healthy adult subjects (b) (4). After intravenous bolus injections of 0.03 mL/kg and 0.3 mL/kg of Lumason, corresponding to approximately 1 and 10 times the recommended doses, concentrations of SF<sub>6</sub> in blood peaked within 1 to 2 minutes for both doses. The terminal half-life of SF<sub>6</sub> in blood was approximately 10 minutes for the 0.3 mL/kg dose. (b) (4) The area-under-the-curve of SF<sub>6</sub> was dose-proportional over the dose range studied.

#### Distribution

In a study of healthy subjects, the mean values for the apparent steady-state volume of distribution of SF<sub>6</sub> were 341 mL and 710 mL 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 SF<sub>6</sub> component of Lumason is eliminated via the lungs. In a clinical study that examined SF<sub>6</sub> elimination twenty minutes following Lumason injection, the mean cumulative recovery of SF<sub>6</sub> in expired air was 82 ± 20% (SD) at the 0.03 mL/kg dose and 88 ± 26% (SD) at the 0.3 mL/kg dose.

SF<sub>6</sub> undergoes first pass elimination within the pulmonary circulation; approximately 40% to 50% of the SF<sub>6</sub> content was eliminated in the expired air during the first minute following Lumason injection.

#### Metabolism

SF<sub>6</sub> undergoes little or no biotransformation; 88% of an administered dose is recovered unchanged in expired air.

#### Pharmacokinetics in <sup>(b) (4)</sup> Populations

##### *Pulmonary Impairment:*

In a study of patients with pulmonary impairment, blood concentrations of SF<sub>6</sub> peaked at 1 to 4 minutes following Lumason administration. The cumulative recovery of SF<sub>6</sub> in expired air was 102 ± 18% (mean ± standard deviation), and the terminal half-life of SF<sub>6</sub> in blood was similar to that measured in healthy subjects.

For the proposed indication of use of Lumason during VUS, the contrast agent is administered through a catheter into the bladder and ultrasound imaging is acquired during filling of the bladder and voiding. Voiding is a substantial part of the VUS procedure, and is necessary for completion of an adequate exam. The literature studies that support approval consisted of adequate exams.

Studies have demonstrated that post-voiding residual volume is limited in children. In one study assessing the safety of intravesical administration of Lumason during VUS in 1,010 children, it was reported that 965 patients were able to void directly at the end of the ultrasound procedure and 45 (4.4%) patients were not. In the same study, significant post-void residual urine volume (defined as a residual volume >10% of the actual bladder volume) was present in 148 (14.6%) patients. No adverse events related to the administration of Lumason were reported.

In addition to the limited residual volume, the anatomical characteristics of the urinary bladder make it unlikely that Lumason would be absorbed to have a systemic effect following its intravesical administration. The bladder wall is lined by the urothelium which creates a barrier. The barrier function of the urothelium is effective despite large variations in urine volume during bladder filling and voiding. The anatomical characteristics of the bladder inhibit drug absorption, as evidenced by intravesical administration of cytotoxic agents successfully reducing systemic exposure in patients treated for superficial bladder cancer.

### **3.3 Clinical Pharmacology Review Questions**

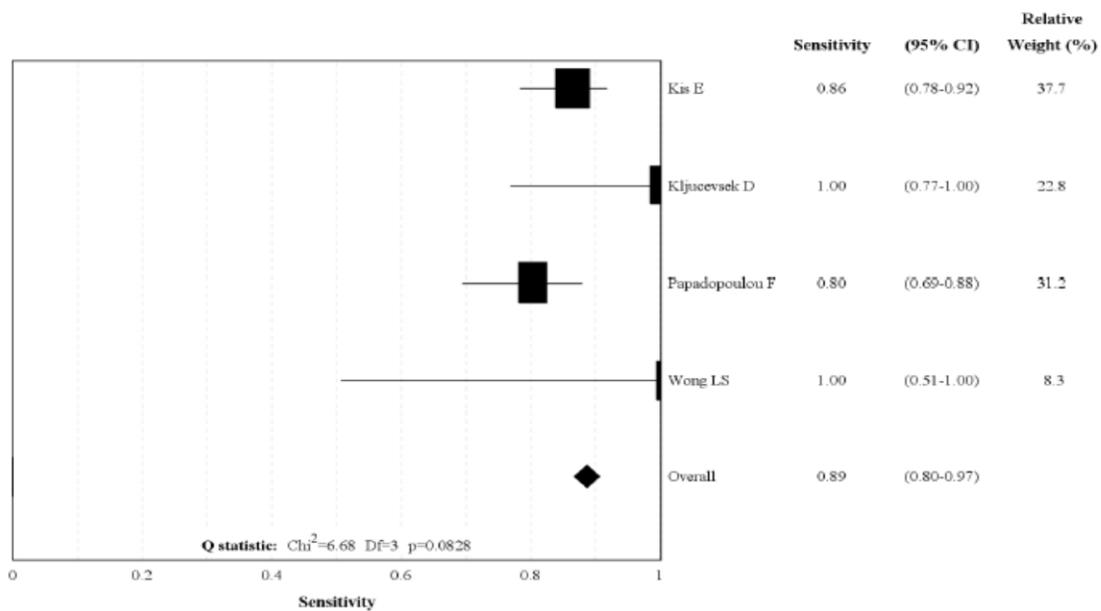
#### ***3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?***

No pharmacokinetics data have been collected following intravesical administration. No dose exploration was conducted: all studies of intravesical administration used a 1 mL dose. Clinical pharmacology information is not available to provide pivotal or supportive evidence of effectiveness.

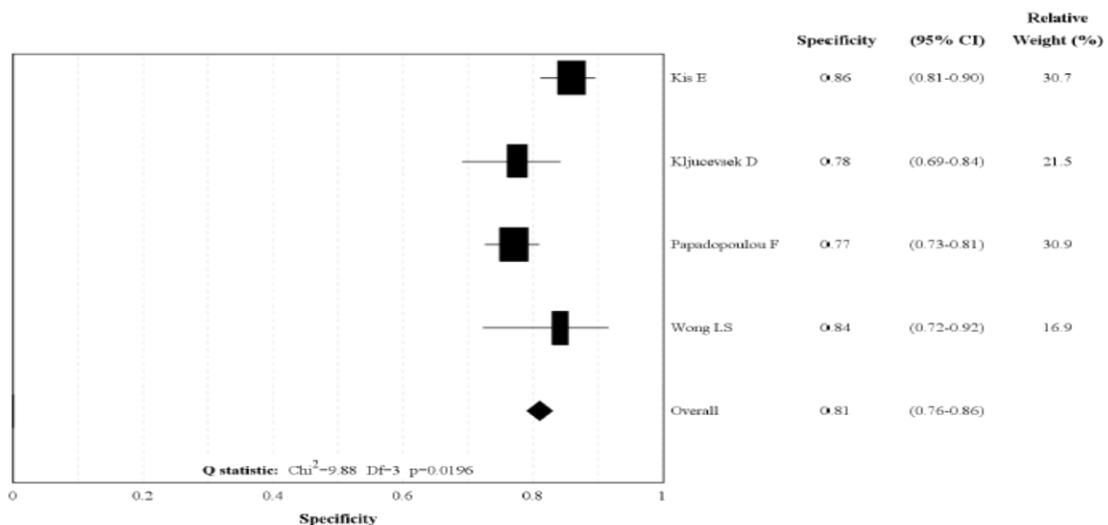
### 3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Across four published studies, 508 pediatric patients referred for assessment of vesicoureteral reflux (275 males, 233 female, age range: 2 days to 13 years) were evaluated after intravesical administration of 1.0 mL of Lumason. Voiding cystourethrography was the truth standard. A meta-analysis resulted in a pooled sensitivity of 89% (95% CI: 80% to 97%) and pooled specificity of 81% (95% CI: 76% to 86%) (applicant's analyses). **Figure 1** shows the sensitivity data by study, and **Figure 2** shows the specificity data by study.

**Figure 1.** Forest Plot for Sensitivity



**Figure 2** Forest Plot for Specificity



No reports of ineffective imaging or technical artifacts were reported in any of the studies, even though the same 1.0 mL dose was used in newborns, infants and older children.

A lack of reporting of ineffective imaging provides support that the flat 1.0 mL dose is sufficient, but leaves open the question of whether lower doses might be equi-effective, especially for small children. No AEs were observed with the 1.0 mL dose and it is unlikely that intravesical administration will result in significant systemic absorption of SF<sub>6</sub> (see **3.2 General Pharmacology and Pharmacokinetic Characteristics**). We conclude that an exploration of lower doses is not needed.

### ***3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?***

No adverse events, or reports of ineffective imaging or technical artifacts, were reported in the four literature articles that are the basis for approval. Thus, there is no evidence of a subpopulation that would benefit from an alternative dosing regimen and/or management strategy.

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

/s/  
-----

SAM HABET  
11/30/2016

GENE M WILLIAMS  
11/30/2016  
I concur with the recommendations

NAM ATIQUR RAHMAN  
11/30/2016  
I agree with the Team's recommendation.