Office of Clinical Pharmacology Review

NDA or BLA Number	203-684
Submission Date	January 30, 2019, SDN 180
Submission Type	New Indication (b) (4)
Brand Name	Lumason®
Generic Name	Sulfur hexafluoride (SF_6) lipid-type A microspheres for injectable suspension, for intravenous use
Dosage Form and Strength	For injectable suspension: 25 mg of lipid-type A lyophilized powder with headspace fill of 60.7 mg sulfur hexafluoride in a single-patient use vial for reconstitution. Following reconstitution, Lumason is a homogeneous, milky white suspension containing1.5 to 5.6 $x10^8$ microspheres/mL with 45 mcg/mL of sulfur hexafluoride.
Route of Administration	For intravesical administration in pediatric patients. Avoid intra-arterial injection.
Proposed <u>New</u> Indication **New Indications: In Bold**	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 **and pediatric** patients (b) (4) with suboptimal echocardiograms • In ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients • In ultrasonography of the urinary tract for the evaluation of suspected or known vesicoureteral reflux in pediatric patients
Dosage <u>New</u> Regimen **New Indications: in Bold**	<u>For intravenous injection:</u> • Echocardiography **in adults**: After reconstitution, administer 2 mL as an intravenous injection (b) (4). • **Echocardiography in pediatric patients (b) (4): After reconstitution, administer 0.03 mL per kg as an intravenous injection up to a maximum of 2 mL per injection**

	• 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 <u>For intravesical administration in pediatric patients:</u> • Ultrasonography of the urinary tract: After reconstitution, administer 1 mL via sterile 6-8F urinary catheter. Bladder should be first emptied and then partially filled with saline before injection of Lumason After Lumason administration, 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
Applicant	Bracco Diagnostics, Inc.
Associated IND	46,958 (first submitted December 23, 1994)
OCP Review Team	Sam Habet, R.Ph., Ph.D., Christy S. John, Ph.D.

Executive Summary

Lumason was approved by FDA under NDA 203684 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. The applicant is seeking an extension of the indication for use of Lumason in patients (b) (4) years of age who are suspected of having cardiac disease or are undergoing evaluation of cardiac anatomy with suboptimal echocardiogram.

The applicant conducted Study BR1-140 in 12 patients ages 9-17 to assess the safety and efficacy of Lumason (0.03 mL/kg) in resting echocardiography. The dose was selected based on approved adult dose of 2 mL. A weight adjusted dose of 0.03 mL/kg based on 2 mL dose for 70 kg adult was used. A dose of 0.03 mL/kg is also approved dose for characterization of liver lesion in pediatric patients.

This dose showed substantial increase in change in left ventricular endocardial border delineation (LV EBD) score between unenhanced ultrasound (UEUS) and contrast-enhanced ultrasound (CEUS). All patients (100%) showed adequate left ventricle opacification. The dose of 0.03 mL/kg in this patient population was determined to be efficacious based on all patients showing adequate left ventricle opacification and safe.

Recommendations
The Office of Clinical Pharmacology (OCP) has reviewed the information contained in NDA 203684. This application is approvable from a clinical pharmacology perspective.

Summary of Clinical Pharmacology Assessment
The Applicant submitted a multicenter safety and efficacy study (BRI-140) in pediatric patients from 9-17 years of age using Lumason as a contrast agent in pediatric echocardiography. The trial was expected to include in the application pharmacokinetic assessment from 12 patients in this PREA required pediatric trial. Because of the difficulty in recruiting patients (953 screen failures and 12 enrolled subjects) and the absence of any apparent safety concern with the intravenous use of Lumason in children, FDA agreed to accept termination of the PMR study 2803-1 (BR1-140 study).

The Applicant at the request of the FDA agreed to submit an 505(b)(2) supplemental new drug application (sNDA) with safety and efficacy data to include results of Study BR1-140 and a summary of relevant literature supporting the use of Lumason for pediatric echocardiography. There were no subjects enrolled with plasma sampling for PK assessment and, therefore, no PK analysis was performed.

Pharmacology and Clinical Pharmacokinetics
No new clinical pharmacology studies were conducted by the sponsor.

General Dosing and Therapeutic Individualization

Pediatric Patients
The recommended dose of Lumason after reconstitution in pediatric patients (b) (4) is 0.03 mL per kg administered as an intravenous injection during echocardiography. The dose was selected based on approved adult dose of 2 mL. A weight adjusted dose of 0.03 mL/kg based on 2 mL dose for 70 kg adult was used. During a single examination, a second injection of 0.03 mL per kg may be administered, if needed. Do not exceed 2.0 mL per injection. Follow Lumason injection with an intravenous flush using 5 mL of 0.9% Sodium Chloride Injection.

Outstanding Issues
There are no outstanding issues.

Signatures
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