Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	August 23, 2019
Safety Evaluator:	Danielle Molnar, PharmD, BCPS Division of Pharmacovigilance II (DPV II)
Medical Officer:	Ivone Kim, MD, FAAP DPV I
Team Leader:	Neha Gada, PharmD, BCPS DPV II
Deputy Division Director:	Ida-Lina Diak, PharmD, MS DPV II
Product Name:	Lumason (sulfur hexafluoride lipid-type A microspheres) injectable suspension
Pediatric Labeling Approval Date:	March 31, 2016 & December 22, 2016
Application Type/Number:	NDA 203684
Applicant/Sponsor:	Bracco Diagnostics, Inc.
OSE RCM #:	2019-985

We also acknowledge DPV cardiologist Daniel Woronow, MD, FACC, for his clinical assessment of select case reports.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Lumason (sulfur hexafluoride lipid-type A microspheres) in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on all serious adverse events associated with sulfur hexafluoride lipid-type A microspheres in pediatric patients.

The FDA approved Lumason on October 10, 2014 and it is currently indicated for use in echocardiography (adults), ultrasonography of the liver (adults and pediatrics), and ultrasonography of the urinary tract (pediatrics). The approved pediatric labeling is for use with ultrasound to characterize focal liver lesions and for use in ultrasonography of the urinary tract for the evaluation of suspected or unknown vesicoureteral reflux.

We reviewed all serious FAERS reports with sulfur hexafluoride lipid-type A microspheres in the pediatric population from the U.S. approval date through July 18, 2019. We identified three serious, non-fatal FAERS foreign cases with sulfur hexafluoride lipid-type A microspheres in the pediatric population. We identified no new safety signals or an increased severity or frequency of any labeled adverse events with sulfur hexafluoride lipid-type A microspheres. The three cases described adverse events with a compelling alternative etiology (history of recurrent UTIs and catheterization), were consistent with the known adverse reactions described in labeling (hypersensitivity reaction, cardiopulmonary reaction, and nausea), or had limited information which precluded a meaningful causality assessment.

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of sulfur hexafluoride lipid-type A microspheres.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Lumason (sulfur hexafluoride lipid-type A microspheres) in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious adverse events associated with sulfur hexafluoride lipid-type A microspheres in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Lumason (sulfur hexafluoride lipid-type A microspheres) is an ultrasound contrast agent for intravenous or intravesical use, supplied as a 3-part single-patient use kit for reconstitution of an injectable suspension. Lumason was initially approved by the FDA on October 10, 2014 for one indication in adults and subsequently gained approval for two additional indications, one in adults and pediatrics, and the other in pediatrics only (see Table 1).

Table 1. Lumason Approved Indications

Approval Date	Indications for Use	Population(s) for Use
October 10, 2014	• 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.	Adults
March 31, 2016	• in ultrasound of the liver to characterize focal liver lesions.	Adults and pediatrics
December 22, 2016	• in ultrasonography of the urinary tract for the evaluation of suspected or known vesicoureteral reflux.	Pediatrics

Bracco Diagnostics did not sponsor or conduct clinical pediatric studies to support either pediatric indication. Bracco has marketed Lumason in Europe since April 2001 under the trade name of SonoVue. At the time of both U.S. pediatric labeling approvals, SonoVue was marketed in 26 countries and had not received approval for use in the pediatric population in any of those countries. However, SonoVue had been used off-label in pediatric patients and documented in published literature.[1,2]

Data supporting efficacy and safety of Lumason for both pediatric indications were derived from published literature.

Effectiveness in pediatric patients for intravenous use in ultrasonography of the liver for characterization of focal liver lesions was extrapolated from trials in adult patients and a published clinical study of 44 pediatric patients aged 4 to 18 years. 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.[3]

The efficacy of intravesical use of Lumason for the evaluation of pediatric patients with suspected or known vesicoureteral reflux was established in two published studies comprising a total of 411 pediatric patients ranging in age from 2 days to 13 years. Safety was based on evaluation of published literature involving use of Lumason in over 6000 pediatric patients. No adverse reactions were reported.[3]

This review was prompted by the pediatric labeling approved on March 31, 2016 and December 22, 2016. DPV has not presented Lumason before the Pediatric Advisory Committee (PAC) in the past.

1.2 RELEVANT LABELED SAFETY INFORMATION[3]

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)].***

CONTRAINDICATIONS
History of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in Lumason.

WARNINGS AND PRECAUTIONS
5.1 Serious 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.

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

USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use
Ultrasonography of the Liver
(See section 1.1 of this review.)

Ultrasonography of the Urinary Tract
(See section 1.1 of this review.)

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

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 2.

Table 2. FAERS Search Strategy*	
Date of Search	July 19, 2019
Time Period of Search	October 10, 2014† - July 18, 2019
Search Type	FBIS Quick Query, Product-Manufacturer Reporting Summary
Product Terms	Active moiety: sulfur hexafluoride
MedDRA Search Terms (Version 22.0)	All Preferred Terms (PT)
* See Appendix A for a description of the FAERS database. † U.S. approval date of Lumason (NDA 203684)	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 3 presents the number of adult and pediatric FAERS reports from October 10, 2014 through July 18, 2019 with sulfur hexafluoride lipid-type A microspheres.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA from October 10, 2014 – July 18, 2019 with Lumason			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	149 (117)	132 (77)	16 (9)
Pediatrics (0 - <18 years)	4 (0)	**4 (0)**	0 (0)
* May include duplicates and transplacental exposures, and have not been assessed for causality † For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.			

3.1.2 Selection of Serious Pediatric Cases in FAERS

After excluding one duplicate, our FAERS search identified three serious pediatric cases from October 10, 2014 through July 18, 2019. We reviewed all FAERS pediatric cases with a serious outcome. We did not identify any fatal pediatric AE reports.

We summarize the three cases in the sections below. See Appendix B for a line listing of the case series.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event cases.

3.1.4 Summary of Non-Fatal Pediatric Serious Cases (N=3)

We identified three serious FAERS cases with sulfur hexafluoride lipid-type A microspheres in the pediatric population reporting a non-fatal serious outcome. All three cases, summarized below, are foreign cases from countries where the product is marketed as SonoVue. We identified no compelling cases in the pediatric population with sulfur hexafluoride lipid-type A

microspheres that are serious and unlabeled. No clear patterns or trends suggested a new safety signal associated with the reported serious unlabeled adverse events in our pediatric cases.

Ultrasonography of the Urinary Tract (N=1)
Case 10584753, Greece, Expedited, FDA Received Date November 14, 2014

A literature case[4] with follow-up information gathered by Bracco reported a 6-month-old male with a history of urinary tract infections (UTIs) who underwent a contrast enhanced voiding urosonography to rule out vesicoureteral reflux. SonoVue 0.5ml/bladder filling was administered intravesically through transurethral bladder catheterization. Five days after the ultrasound with SonoVue, he developed a fever to 39°C (102.2°F) and was diagnosed two days later with a urinary tract infection supported by positive urinalysis and urine culture. He was treated with unspecified antibiotic(s) on an outpatient basis and recovered. The report included one concomitant medication, trimethoprim sulfate, for UTI prophylaxis.

Reviewer's comments: In this patient with UTIs and catheter placement prior to Lumason use, alternate clinically compelling etiologies of fever and UTI, such as catherization, cannot be ruled out. Similarly, the authors of the source literature case concluded the adverse events they observed could not be directly related to the ultrasound contrast agent and were most likely related to the catheterization process.[4]

Ultrasonography of the Liver (N=1)
Case 12319605, Italy, Expedited, FDA Received Date April 11, 2016

A 15-year-old female experienced arterial hypotension to 60/30 mmHg, visual impairment, abdominal pain, diarrhea, and nausea on the same day as, but unspecified time after, receiving SonoVue for liver lesion characterization. After treatment with methylprednisolone sodium succinate and intravenous (IV) fluids, her blood pressure improved to 120/70 mmHg, and she recovered on the same day. The patient's medical history included acute lymphocytic leukemia, cachexia, lung abscess attributed to Aspergillus, and pyogenic liver abscess attributed to Candida. The case did not report concomitant medication(s). This was the patient's second exposure to SonoVue. The first time was approximately two weeks earlier and no adverse events were reported.

Reviewer's comments: Given symptoms on the same day as the patient's second exposure to the drug, hypotension with gastrointestinal symptoms and visual impairment suggests a hypersensitivity reaction that responded to glucocorticoid treatment and IV fluids. Lumason is labeled for hypersensitivity reactions including anaphylactic shock. Her profound hypotension alone could be a serious cardiopulmonary reaction, also labeled for Lumason; however, a causal association cannot be established without a time to onset.

DPV cardiologist's comments: The Boxed Warning of "serious cardiopulmonary reactions" is not construed by this reviewer as defining a pathophysiologic mechanism for these reactions, and instead is a brief description of the reported adverse reaction. The Warnings and Precautions section 5.1 also delineates additional subtypes of cardiopulmonary reactions, including "shock...hypotension." Therefore, it is possible for a reaction to concurrently be both

a cardiopulmonary reaction and have an anaphylactoid reaction as the pathophysiologic mechanism. In addition to anaphylactoid and similar hypersensitivity reactions (e.g., Complement Activation Related Pseudo Allergy, CARPA),[5] other pathophysiologic mechanisms have also been hypothesized for serious cardiopulmonary reactions associated with ultrasound contrast agents (e.g., microsphere rupture facilitated by high mechanical index interacting with vascular endothelium).[6,7,8] Therefore, the mechanism for the serious cardiopulmonary reaction in this 15-year-old female is felt to be a hypersensitivity reaction, which is supported by factors cited in the above reviewer's comments and also supported by the patient's clinical improvement with glucocorticoids and intravenous fluids. Although less likely, we cannot exclude the possibility that the ultrasonographer applied excessive pressure with the ultrasound transducer, causing compression of the hepatic abscess resulting in a transient septicemia.

Off-label Use, Ultrasonography of the Kidney (N=1)
Case 15710236, Spain, Expedited, FDA Received Date 12/11/2018

A 4-year-old female patient received SonoVue for a kidney ultrasound for renal trauma imaging. Fifteen seconds after the 2.4ml intravenous bolus of SonoVue, she experienced coughing, vomiting, and livedo reticularis. She also developed dyspnea and rash at an unspecified time after contrast administration. The patient was hospitalized, including 5 hours in the intensive care unit, and was treated with high respiratory tract aspiration and oxygen support. She recovered from the adverse events the same day. An unspecified skin test was negative. She received SonoVue without incident one week earlier. Her medical history included catheter placement and nephrostomy. The report did not include concomitant medication(s).

Reviewer's comments: The time-to-onset and reported symptoms described in this case are suggestive of labeled events for Lumason (hypersensitivity reaction, nausea).

4 DISCUSSION

We reviewed all serious FAERS reports with sulfur hexafluoride lipid-type A microspheres in the pediatric population through age 17 years from the U.S. approval date (October 10, 2014) through July 18, 2019.

We included three cases in our case series, all foreign reports. Our review focused on serious adverse events, labeled and unlabeled, associated with sulfur hexafluoride lipid-type A microspheres in pediatric patients. We did not identify any deaths associated with sulfur hexafluoride lipid-type A microspheres. The cases described adverse events with a compelling alternative etiology (history of recurrent UTIs and catheterization), were consistent with the known adverse reactions described in labeling (hypersensitivity reaction, cardiopulmonary reaction, and nausea), or had limited information which precluded a meaningful causality assessment.

We did not identify any new safety signals, increased severity, or increased frequency of adverse events associated with sulfur hexafluoride lipid-type A microspheres.

5 CONCLUSION

DPV did not identify any pediatric safety concerns for sulfur hexafluoride lipid-type A microspheres at this time.

6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of sulfur hexafluoride lipid-type A microspheres.

7 REFERENCES

1 Kress, S, Clinical Review: Characterization of Focal Liver Lesions (NDA 203684 supplement), 2016, accessed July 25, 2019, https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2012-present.

2 Kress, S, Clinical Review: Lumason for Ultrasonography of Urinary Tract I Pediatric Patients to Evaluate Vesicoureteral Reflux (NDA203684 supplement), 2016, accessed July 25, 2019, https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2012-present.

3 Lumason (sulfur hexafluoride lipid-type A microspheres) injectable suspension for intravenous or intravesical use [package insert], 2016, Monroe Township, NJ: Bracco Diagnostics Inc, accessed July 25, 2019, http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=203684.

4 Papadopoulou F, A Ntoulia, E Siomou, K Darge, Contrast-enhanced voiding urosonography with intravesical administration of a second-generation ultrasound contrast agent for diagnosis of vesicoureteral reflux: prospective evaluation of contrast safety in 1,010 children, Pediatr Radiol, 2014, 44(6): 719-728, accessed July 31, 2019, https://doi.org/10.1007/s00247-013-2832-9.

5 Muskula PR, ML Main, 2017, Safety with Echocardiographic Contrast Agents, Circ Cardiovasc Imaging. 2017, 10(4), accessed August 7, 2019, https://doi.org/10.1161/CIRCIMAGING.116.005459.

6 Porter T, S Mulvagh, S Abdelmoneim, H Becher, J Belcik, M Bierig, J Choy, N Gaibazzi, L Gillam, R Janardhanan, S Kutty, H Leong-Poi, J Lindner, M Main, W Mathias, M Park, R Senior, F Villanueva, Clinical Applications of Ultrasonic Enhancing Agents in Echocardiography: 2018 American Society of Echocardiography Guidelines Update, J Am Soc Echocardiogr. 2018, 31(3): 241-274, doi: 10.1016/j.echo.2017.11.013.

7 Shim CY, YN Liu, T Atkinson, A Xie, T Foster, B Davidson, M Treible, Y Qi, J Lopez, A Munday, Z Ruggeri, J Lindner, Molecular imaging of platelet-endothelial interactions and endothelial von Willebrand factor in early and mid-stage atherosclerosis. Circ Cardiovasc Imaging, 2015, 8(7), accessed August 7, 2019, https://doi.org/10.1161/CIRCIMAGING.114.002765.

8 Xie A, T Belcik, Y Qi, T Morgan, S Champaneri, S Taylor, B Davidson, Y Zhao, A Klibanov, M Kuliszewski, H Leong-Poi, A Ammi, J Lindner, Ultrasound-mediated vascular gene transfection by cavitation of endothelial-targeted cationic microbubbles, J Am Coll Cardiol Img, 2012, 5(12): 1253-1262, accessed August 7, 2019, https://doi.org/10.1016/j.jcmg.2012.05.017.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=3)

	Initial FDA Received Date [Duplicate]	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	11/14/2014	10584753	2	GR-BRACCO-000041	Expedited	0.5	Male	Greece	OT
2	4/29/2016	12319605	1	IT-BRACCO-005390	Expedited	15	Female	Italy	HO
3	[4/29/2016]	[12341207]†	[1]	[IT-005390]	[Non-expedited]	[15]	[Female]	[Italy]	[HO]
4	12/11/2018	15710236	2	ES-BRACCO-2018ES06314	Expedited	4	Male	Spain	OT

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case may have more than one serious outcome.
Abbreviations: HO=Hospitalization, OT=Other medically significant
† Represents a duplicate of case ID 12319605

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DANIELLE M MOLNAR
09/24/2019 11:29:02 AM

IVONE E KIM
09/24/2019 12:19:59 PM

NEHA GADA
09/24/2019 12:48:39 PM

IDA-LINA DIAK
09/24/2019 12:54:16 PM