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

Pediatric Postmarketing Pharmacovigilance Review

Date:	June 25, 2024
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Product Name:	Lumason (sulfur hexafluoride lipid-type A microspheres)
Pediatric Labeling Approval Date:	November 13, 2019
Application Type/Number:	NDA 203684
Applicant:	Bracco Diagnostics Inc.
TTT Record ID:	2024-9132

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Lumason (sulfur hexafluoride lipid-type A microspheres) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with Lumason in pediatric patients.

Lumason (sulfur hexafluoride lipid-type A microspheres) is an ultrasound contrast agent that was initially approved in the U.S. on October 10, 2014. Lumason is currently 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 with suboptimal echocardiograms
- Ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients
- Ultrasonography of the urinary tract for the evaluation of suspected or known vesicoureteral reflux in pediatric patients

This pediatric postmarketing safety review was stimulated by the Lumason pediatric labeling on November 13, 2019, for use in echocardiography to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border in pediatric patients 0 to 17 years of age with suboptimal echocardiograms.

DPV reviewed all U.S. serious FAERS reports with Lumason in pediatric patients less than 18 years of age from July 19, 2019, through April 8, 2024, and one report was identified; however, this report was excluded from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with Lumason in pediatric patients less than 18 years of age.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Lumason (sulfur hexafluoride lipid-type A microspheres) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with Lumason in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Lumason (sulfur hexafluoride lipid-type A microspheres) is an ultrasound contrast agent that was initially approved in the U.S. on October 10, 2014. Lumason is currently indicated for use in:[1]

- Echocardiography to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border in adult and pediatric patients with suboptimal echocardiograms
- Ultrasonography of the liver for characterization of focal liver lesions in adult and pediatric patients
- Ultrasonography of the urinary tract for the evaluation of suspected or known vesicoureteral reflux in pediatric patients

This pediatric postmarketing safety review was stimulated by the Lumason pediatric labeling on November 13, 2019, for use in echocardiography to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border in pediatric patients 0 to 17 years of age with suboptimal echocardiograms.[2]

On August 23, 2019, DPV completed a review of postmarketing adverse event reports with a serious outcome for Lumason in pediatric patients. DPV's evaluation did not identify any new safety concerns, and DPV recommended return to routine monitoring for adverse events with Lumason.[3] On July 13, 2020, DPV's evaluation was presented to the Pediatric Advisory Committee via webposting.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Lumason labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Lumason labeling information, please refer to the full prescribing information.[1]

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

See full prescribing information for complete boxed warning

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

- Assess all patients for the presence of any condition that precludes administration (4).
- Always have resuscitation equipment and trained personnel readily available (5.1).

----------**CONTRAINDICATIONS**----------

- Hypersensitivity to sulfur hexafluoride lipid microspheres or its components, such as polyethylene glycol (PEG) (4)

----------**WARNINGS AND PRECAUTIONS**----------

- Cardiopulmonary reactions, including fatalities. Always have resuscitation equipment and trained personnel readily available (5.1)
- Hypersensitivity reactions. Serious acute hypersensitivity reactions have occurred in patients with no prior exposure to sulfur hexafluoride lipid-containing microsphere products, including patients with prior hypersensitivity reaction(s) to PEG (5.2, 6)

----------**ADVERSE REACTIONS**----------

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

8.4 Pediatric Use

Echocardiography

Safety and effectiveness have been established for use in pediatric patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve delineation of the left endocardial border. Safety and effectiveness in pediatric patients are based on adequate and well-controlled studies in adults and are supported by a clinical study in 12 pediatric patients (mean age: 13.8 years) with extrapolation of efficacy to younger pediatric patients. No new adverse reactions were reported in the pediatric study [see Adverse Reactions (6.1) and Clinical Studies (14.1)]. Safety of intravenous use of Lumason was based on evaluation of published literature involving the use of Lumason in over 1400 pediatric patients (0 to 17 years).

Ultrasonography of the Liver

Safety and 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 1400 pediatric patients. Non-fatal anaphylaxis was reported in one pediatric patient.

Ultrasonography of the Urinary Tract

Safety and 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.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of search	April 9, 2024
Time period of search	July 19, 2019† – April 8, 2024
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Active moiety: sulfur hexafluoride
MedDRA search terms (Version 26.1)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † Data lock date of most recent pediatric postmarketing pharmacovigilance review Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from July 19, 2019, through April 8, 2024, with Lumason.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From July 19, 2019 through April 8, 2024, With Lumason			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18years)	771 (672)	580 (484)	43 (32)
Pediatrics (0 - < 18years)	5 (2)	4 (1)	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, or other serious important medical events.			

3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved one U.S. serious pediatric report from July 19, 2019, through April 8, 2024. We reviewed the U.S. FAERS pediatric report with a serious outcome and excluded it from further discussion because the age was miscoded (i.e., not a pediatric report).

3.1.3 Summary of U.S. Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.4 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=0)

There are no non-fatal pediatric adverse event cases for discussion.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with Lumason in pediatric patients less than 18 years of age from July 19, 2019, through April 8, 2024, and identified one report; however, the report was excluded from further discussion.

There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with Lumason in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for Lumason at this time and will continue routine pharmacovigilance monitoring for Lumason.

6 REFERENCES

1. Lumason® (sulfur hexafluoride lipid-type Amicrospheres) for injectable suspension, for intravenoususe or intravesical use [Prescribing Information]. Monroe Township, NJ: Bracco Diagnostics Inc; April 2021.
2. Coquia S. Medical Officer Clinical Review of Lumason® (sulfur hexafluoride lipid-type A microspheres). October 2019. https://www.fda.gov/media/133813/download?attachment.
3. Molnar D, Kim I, Gada N, Diak IL. FDA Office of Surveillance and Epidemiology - Pediatric Postmarketing Pharmacovigilance- Lumason (sulfur hexafluoride lipid-type A microspheres). 2019. https://www.fda.gov/media/140202/download.

7 APPENDICES

7.1 APPENDIX A. 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 terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

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 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.

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