Cross-Discipline Team Leader Review

Date	12/10/16
From	Ira Krefting, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	203-684 2
Applicant	Bracco Diagnostics
Date of Submission	6/29/2016
PDUFA Goal Date	12/29/2016
Proprietary Name / **Established (USAN) names**	Lumason Sulfur hexafluoride lipid-type A microspheres
Dosage forms	Kit for preparation of injectable suspension • vial: (b) (4) SF_6 / 25 mg lipid-type A • diluent prefilled syringe: 5ml 0.9%NaCl
Strength	Reconstituted product: 45 mcg/ml SF_6 equivalent to 1.5-5.6x10^8 microspheres/ mL
Patient dose	0.1 mL intravesical (instilled into the urinary bladder) The bladder may be refilled with normal saline for a second cycle of voiding and imaging, without the need of a second Lumason administration.
Proposed **Indication(s)**	Lumason is an ultrasound contrast agent indicated for use **1. evaluation of suspected or known vesicoureteral reflux in pediatric patients** Previously approved indications 2. 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 3. in ultrasonography of the urinary tract for evaluation of suspected or known vesicoureteral reflux in pediatric patients
Recommended:	Approval

Glossary of Terms

VCUG	Fluoroscopic voiding cysto-urethrography
UTI	Urinary tract infection
VUR	Vesicoureteral reflux
VUS	Voiding urosonography

1. Introduction

Supplemental NDA 203-684 provided data in the form of published studies to support the use of Lumason, an ultrasound contrast agent, as a diagnostic imaging modality in the evaluation of vesicular ureteral reflux (VUR) in children. Vesicular reflux (retrograde urine flow from the bladder back to the ureter, see figure 1) in children is a condition which can lead to chronic renal failure if untreated. Currently approved imaging modalities for the evaluation of this suspected condition are radiologic and nuclear scanning techniques that expose children to significant amounts of radiation; Lumason ultrasonography provides a diagnostic modality without the risk exposure to ionizing radiation. Dr. Kress, the clinical reviewer, provided further information on the clinical context of use in his review.

This supplemental NDA was submitted as a 505(b)(2) application because the efficacy data presented are exclusively from published literature; the safety data are literature based and from sporadic reports in Bracco post- marketing surveillance database. The public health goal of reducing radiation exposure in children, an unmet medical need, led to the designation for this sNDA as a priority review.

The prospective published studies selected by the sponsor all compare the performance of Lumason ultrasonography (VUS) to fluoroscopic voiding cysto-urethrography in a representative pediatric population. Bracco has not conducted clinical trials for this indication, nor does Bracco have right of reference to the raw data that is reported in the published literature used in support of this application. Bracco was only able to provide patient level data from the Kljucevsek[1] study, one of the prospective studies submitted in support of this indication. The strength of the provided data to support the efficacy and safety of Lumason ultrasonography of the pediatric urinary tract and the appropriateness of the sponsor's recommended dose constitute the major review issues. Product labeling for this proposed indication relies on information from peer-reviewed literature and guidelines published by internationally recognized medical societies.

2. Background

Lumason is composed of microbubbles with a lipid shell and containing sulfur hexafluoride gas (SF6) that resonates and reflects ultrasound waves from an ultrasound generator device. The reflection contrasts with the existing anatomic milieu and may improve the delineation of anatomic structures as compared to non-contrast ultrasound or other available imaging modalities. Current approved indications are for intravenous use: improved delineation of the left ventricle of the heart and for the detection of liver lesions. For vesicular ureteral reflux evaluation Lumason is instilled into the urinary bladder; the echogenicity of the Lumason ultrasound bubbles to externally applied ultrasound indicate when saline previously instilled into the bladder through a urinary catheter (as a surrogate for urine) inappropriately passes back into the ureters (figure 1). This procedure may help evaluate a defect in the sphincter

[1] Kljucevsek, et.al. Acta Paediatr. 2012

between the bladder and ureter which is potentially repairable. Lumason is not absorbed into the body beyond the bladder and is removed as the bladder is emptied.

Lumason's regulatory history has been detailed in other recent reviews. This review did not raise any new regulatory issues.

3. CMC/Device

Lumason is an approved product and has been the subject of two previous reviews for use in cardiac and liver imaging; there are no new CMC issues.

Lumason for all indications is supplied as a 3 part kit for single patient use. The kit consists of: a glass vial containing Lumason (25 mg of lipid type A sterile lyophilized powder with headspace filled with 60.7 mg of sulfur hexafluoride gas; a prefilled syringe containing 5 ml of saline and a mini-spike (containing a syringe tip). Saline is injected into the vial by the syringe linked to the mini-spike. The vial is shaken to form a homogenous white milky liquid which indicates formation of the sulfur hexafluoride lipid microspheres. For ultrasonography of the urinary tract 1 mL is withdrawn.

There are no product quality issues and no facilities inspections were necessary.

4. Nonclinical Pharmacology/Toxicology

I agree with Dr. Awe that the submitted data indicates that Lumason is well tolerated during a single- and a repeat-dose bladder administration in the rat.
The studies of were required of the sponsor because the bladder route of administration had not been previously evaluated in animal studies. Based on the studies, Dr. Awe estimated that the safety margin for the proposed 0 month to 17 years old pediatric patient = 52.5 - 260.4 X Maximum Human Dose (MHD). Dr. Awe did not envisage any safety concerns following the intravesical administration of 1ml proposed human dose.

5. Clinical Pharmacology/Biopharmaceutics

The potential for systemic absorption of Lumason and the appropriate dose were the major concerns addressed by Drs. Habet and Williams of clinical pharmacology. I agree with their findings that due to the nature of the uroepithelium (the tissue lining the bladder) no systemic absorption occurs. I also agree that a uniform dose of 1 ml is acceptable; a requirement to calculate a weight based dose particularly in infants potentially could lead to dosage measurement inaccuracies due to the small volumes involved. Some of the publications presented in the sNDA for safety used higher and lower doses; the review team concluded that overall the uniform 1 ml dose appears safe in all age and weight groups and was used in all the

prospective studies presented for efficacy. Accordingly the label recommends no dosage adjustments.

From the clinical pharmacology review:

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_6.

6. Clinical Microbiology

No microbiology reviews were necessary

7. Clinical/Statistical- Efficacy

I concur with Dr. Misra that the efficacy of Lumason for the evaluation of pediatric patients with suspected or known vesicoureteral reflux (VUR) was established through review of four published prospective studies. These four studies selected by the sponsor met the predetermined criteria of: indication; blinding; inclusive of the pediatric population and use of a uniform 1 mL dose. Notably the sponsor could only supply patient level data for the Kljucevsek study, despite requests by FDA for data from all of the studies. Across these studies, the efficacy endpoint was diagnostic performance, sensitivity and specificity, for the detection or exclusion of VUR, measured against cystourethrography (VCUG) as the standard of truth. The unit of analysis was termed either the pelvis-ureter unit or kidney ureter unit, the anatomic junction where the ureter meets the bladder (see figure 1). The sponsor additionally provided a meta-analysis which was further analyzed through fixed and random effects modeling by Dr. Satish of statistics.

In these four selected studies 508 pediatric patients (275 males, 233 females, age range 2 days to 13 years) received 1 mL of Lumason instilled into the bladder filled with saline and underwent voiding urosonography (VUS). Patients were then evaluated with voiding cystourethrography (VCUG), a radiologic imaging procedure, as the reference standard.
At the ureter level (generally each patient had 2 ureters, except for 3 patients with additional ureters see figure 1), the sensitivity of Lumason ultrasonography for the detection of vesicoureteral reflux ranged from 80% to 100% while the specificity ranged from 77% to 86%.

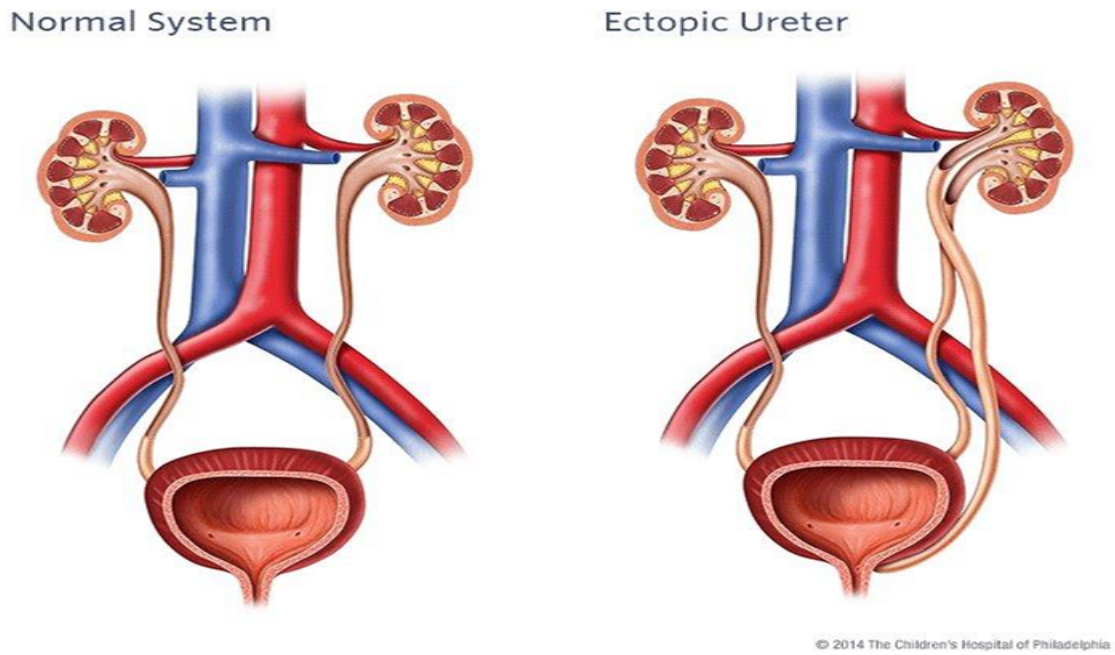

Figure 1: The Urinary tract and blood vessels: The blue vessel is the vena cava; the red the aorta. In the normal system each kidney has a ureter which conducts urine to the bladder. As an anatomic variant some patients have an (additional) ectopic ureter as was detected in the prospective studies. VUR takes place at the junction of the ureter and the bladder. Image accessed from Google Images

Table 1: Performance results at the ureter level for the 4 prospective studies

Study[2]		Age Range	N (Gender)		N (ureter units)*	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
#	Authors		Males	Females			
1	Wong et al.	2-48 Months	23	8	62	100 (55-100)	84 (73-92)
2	Ključevšek et al.	5 days – 1 year	35	31	132	100 (79-100)	78 (69-85)
3	Kis et al.	2 days–44 months	94	89	366	86 (78-92)	86 (81, 90)
4	Papadopoulou et al.	6 days to 13 years	123	105	463	80 (69-89)	77 (73-81)

Table 2: Diagnostic Performance Results at the Ureter and Patient Level in the Study By Ključevšek et al.

Unit of Analysis	Total Number	With VUR	Without VUR	Sensitivity	Specificity	True Positive	False Negative	True Negative	False Positive
Ureter	132	16	116	100.0	77.59	16	0	90	26
Patient	66	13	53	100.0	69.81	13	0	37	16

Sensitivity = TP/(TP+FN) Specificity =TN/(TN+FP)

[2] Detailed reference information is available in the clinical review

For the Kljucevsek study where Bracco provided patient level data, patient level efficacy data could be derived which did not differ significantly from the sensitivity and specificity calculated at the ureter level as presented in Table 2. A patient was considered to have VUR if one ureter had reflux. However the patient level data reveals that 3 patients had VUR in both their right and left ureters (16 ureter segments with VUR; 13 patients with VUR).

Dr. Misra performed further analyses using both a fixed and random effects model; however the fixed effect model is preferable for this situation. The results of analyzes showed almost the same estimates of sensitivity and specificity which in retrospective is apparent since there is no significant variability in the 4 studies.

The lack of patient level data in the other three studies was discussed within the review team, with DPMH, and at the PeRC meeting (see section 10 Pediatrics). The overall conclusion was to accept the data as provided and the findings from Dr. Misra's analysis to support the efficacy of Lumason in the evaluation of VUR. We based this conclusion on the totality of the evidence; all four studies showed a uniform high level of sensitivity and specificity which was also present in the available patient level data. We were also cognizant that there is already significant clinical use of ultrasound contrast agents in VUS studies (based on the multiple additional supportive publications presented by the sponsor) throughout the world with the provision of useful patient care data. I concur with the other review team members in accepting this approach: the four studies even without the uniform availability of patient level data support approval of the vesicoureteral reflux indication in pediatric patients.

8. Safety

I concur with Dr. Kress, the clinical reviewer, that an extensive peer reviewed database supports the safety of Lumason administration for the intravesical administration. The sponsor identified 12 references containing safety data for intravesical administration in approximately 6000 pediatric patients. Eleven of these peer-reviewed clinical publications with varying Lumason doses reported on 2,153 patients, with Papadopoulou[3] reporting on a study of 1010 patients receiving 0.5 mL. The Papadopoulou publication reported adverse events in 37 patients. Most events were non-serious and self-limited. There was one report each of: increased frequency of micturition; perineal irritation and urinary tract infection 10 days after VUS.

A multicenter retrospective survey conducted by the Uroradiology Task Force of the European Society of Paediatric Radiology (ESPR) and the Paediatric Work Group of the European Society of Urogenital Radiology (ESUR). The safety survey reviewed 45 European sites and 5079 administrations of Lumason both intravascular and intravesical[4]. The authors estimate that 4131 intravesical administrations were performed with Lumason (there was also a small number of other agents used) at 29 centers. There were no adverse events attributed to the contrast agent; there were a few complaints reported related to the catheterization.

[3] Papadopoulou et.al. Pediatr Radiol. 2014
[4] Riccabona. Pediatr Radiol. 2012

OSE Report

A recent 915 summary (mandatory FDA review after 18 months) focused on the intravascular route of Lumason administration. The OSE reviewer queried the FAERS data base for reports related to urinary tract imaging. The only entry was the urinary tract infection report noted in the Papadopoulou publication.

9. Advisory Committee Meeting

Since Lumason is not a NME and no efficacy or safety issues requiring external discussion were identified, no advisory committee meeting was held.

10. Pediatrics

Dr. Hausman provided the pediatric review document in which he concurred that contrast ultrasonography in the pediatric age group fulfills an unmet medical need and spare the pediatric patient from exposure to ionizing radiation. He did not identify any concerns with the imaging procedure or dose. Dr. Hauseman provide editorial changes to the label which addressed revisions to the indications (section1); Dosing and Administration (section 2); Pediatric Use (section 8.4); Pharmacodynamics (section 12.2) and Clinical Studies (section 14.4). These editorial suggestions were considered at labeling meetings and incorporated in revised form into the sponsor's provided label.

PeRC Review

This sNDA was presented to the PeRC on 11/16/2016. The issue of approval based on medical literature was discussed and the PeRC provided the following recommendation (from the meeting minutes):

The PeRC noted again that literature based approvals have been acceptable as long as the division is confident that there is sufficient patient level efficacy and safety data to support the finding of substantial evidence of safety and effectiveness.

11. Other Relevant Regulatory Issues

Office of Prescription Drug Promotion: Dr. Patel, the reviewer, in a pre-decisional agency memo stated OPDP had no comments.

12. Labeling

Dr. Fedowitz, the Associate Director for Labeling, oversaw the updating of the Lumason to reflect the new indication, the instructions for use and the presentation of the data supporting the new indication. I concur with her recommendations which have also been accepted by the sponsor.

Most notable are sections 8.4 Pediatric Use and Section 14 Clinical Studies

Section 8.4 Pediatric Use briefly outlines Lumason use for ultrasonography of the urinary tract. The two largest studies (studies 3 & 4 in table 1 and listed as study A & B in the label) comprising 411 patients (from the 4 submitted by the sponsor) are referenced for effectiveness and safety is supported by published literature involving Lumason use in over 600 patients.

Section 14 Clinical Studies details the two largest studies: Each study (A & B) is individually described indicating the number of ureter segments with the presence or absence of reflux that were appropriately identified when compared to a radiologic reference standard. The clinical and statistic teams felt that presentation of the actual findings was more instructive of Lumason's performance characteristics (b) (4)

13. Recommendations/Risk Benefit Assessment

Recommendation

This reviewer recommends approval of this supplemental NDA. The sponsor provided acceptable publically available data to support the efficacy and safety of Lumason ultrasonograpy as an imaging modality for the evaluation of VUR.

Risk Benefit Assessment

Lumason ultrasonography provides an imaging modality not requiring radiation exposure to aide in the diagnosis of VUR, an important childhood condition which must be treated to avoid long term consequences of kidney dysfunction. The few adverse events that have been reported in a 6000 patient publication database are not serious and usually self-limited. The risk benefit assessment is very much in favor of the approval of Lumason for the evaluation of VUR.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

I have no recommendations for REMS or PMRs.

Recommended Comments to Applicant

No deficiencies need to be addressed.

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

/s/

IRA P KREFTING
12/19/2016