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APPLICATION NUMBER:

203684Orig1s000

OFFICE DIRECTOR MEMO

Office Director Action Memo

Date	October 7, 2014
From	Charles J. Ganley, MD
Subject	Office Director Action Memo
NDA/BLA #	NDA: 203-684
Applicant Name	Bracco Diagnostics, Inc.
Date of Submission	April 11, 2014 submission to a complete response letter dated November 27, 2014
PDUFA Goal Date	October 10, 2014
Proprietary Name / Established (USAN) Name	Lumason (accepted by FDA November 4, 2013) sulfur hexafluoride lipid-type A microspheres
Dosage Forms / Strength	The drug is supplied as a kit that is composed of: a glass vial containing 25 mg powdered sulfur hexafluoride lipid microspheres; a prefilled syringe containing 5 mL saline (diluent); and a transfer device for attaching the syringe to the vial. per vial: (b) (4) SF6 / 25 mg lipid-type A; for reconstituted product: 45 mcg SF6/mL equivalent to 1.5-5.6 x108 microspheres/ mL
Indication(s)	Lumason is an ultrasound contrast agent indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.
Action/Recommended Action	Approval

Regulatory History

- 1/29/2001: NDA #21-315 submitted
- (b) (4)
- 7/1/2003: NDA #21-315 resubmitted
- (b) (4)
- 12/26/2007: NDA #21-315 withdrawn
- 12/21/2011: submitted NDA 203-684
- 10/19/2012: Complete response letter
- 5/31/2013: resubmitted NDA 203-684
- 11/27/2013: Complete response letter
- 4/11/2014: resubmitted NDA 203-684

Introduction

The regulatory history of this application is quite extensive and is outlined in the division director's memo. Please refer to the division director's memo for a brief summary. A complete response letter signed by Dr. Shaw Chen was sent to the sponsor on November 27, 2013. The deficiencies cited in the letter primarily involved chemistry, manufacturing and controls issues. Labeling revisions and the need for a safety update on resubmission were also requested in the letter.

Disciplines with no New Data

In the current submission, there is no new non-clinical pharmacology/toxicology, clinical pharmacology, statistical, efficacy and clinical microbiology data. The device review was completed on March 7, 2014 and found to be acceptable.

Safety

The sponsor submitted an update of post-marketing safety reports and safety data from ongoing clinical studies with the cut-off date being September 13, 2013. In the studies, two serious adverse events are included that were not included in the original NDA submission. Both events occurred in studies that evaluated the use of Lumason in focal liver lesions. Neither event was related to Lumason.

Lumason is marketed in 39 countries (marketed as SonoVue). There were 98 new serious adverse events included in the submission (estimated exposure 859,854) following the original NDA submission in 2011. Sixty-two of the cases were related to allergy-like or anaphylactic reactions. Forty-three were cardiac related (not mutually exclusive from allergy type reaction). Four deaths were reported which gives a total of thirteen deaths reported for the NDA. Eight of the deaths are deemed related to Lumason. Since 2001, it is estimated that over (b) (4) doses of Lumason has been administered to patients. The risk of death and anaphylactic reaction is quite rare. Even though it is rare, it is significant enough to include a boxed warning describing the risk of serious cardiac events shortly after infusion. Section 5.2 of the package insert describes the risk of Anaphylactoid Reactions. These events are similar to those reported with similar drugs (Optison, Definity: perflutren in lipid microsphere).

The Division of Medication Error Prevention and Risk Management found the name Lumason acceptable (10/31/2013 Memo). The Division of Risk Management found that a Risk Evaluation and Mitigation Strategy not to be necessary.

Chemistry and Manufacturing

The primary deficiency in the 2013 complete response letter involved the incorporation of critical process and control parameters into the NDA and completion of another facility inspection of Bracco Suisse SA. The sponsor incorporated the process controls which were found acceptable by Dr. Salazar (chemistry reviewer). One of the primary issues involved the control of (b) (4) A facility inspection of Bracco Suisse SA was completed and found acceptable (10/1/2013 email from R. Wittorf to M. Salazar and F. Lutterodt).

Pediatric

The sponsor agreed to conduct a study in pediatric patients 9 to 17 years of age. A deferral was requested for children less than 9 years of age. The Pediatric Research Committee granted this request on 10/16/2013.

Labeling

The package insert should state that the drug vial is sterile. In Section 17 of the package insert, delete the word (b) (4) in the first sentence.

Conclusion and Recommendation

The sponsor responded adequately to the November 27, 2013 complete response letter. I agree with the recommendation of the division to approve the application. See labeling comments.

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/s/

CHARLES J GANLEY
10/07/2014