CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021064Orig1s011

SUMMARY REVIEW

Summary Review for Regulatory Action
Second Cycle

Date	October 21, 2011
From	Dwaine Rieves, MD
Subject	Division Director Summary Review
NDA/BLA #	021-064/efficacy supplement under 505b2
Applicant Name	Lantheus Medical Imaging
Date of Submission	September 29, 2010 CR letter issued 7/28/2011 and sponsor supplied a complete response/resubmission on 8/24/2011
PDUFA Goal Date	October 24, 2011
Proprietary Name / Established (USAN) Name	DEFINITY/Vial for Perflutren Lipid Microsphere Injectable Suspension
Dosage Forms / Strength	No new dosage proposed; current dosage is 10 mcL/kg bolus injection with option for second dose; may also be administered as an infusion as described in current labeling
Proposed Indication(s)	"Activated DEFINITY (Perflutren Lipid Microsphere) Injectable Suspension is 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 (b) (4) [redacted]
Action/Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Ross Filice, MD & Louis Marzella, MD, PhD (CDTL)
Statistical Review	Janelle Charles, PhD & LaRee Tracy, PhD (TL)
Pharmacology Toxicology Review	Not applicable/no data
CMC Review/OBP Review	Not applicable/no data
Microbiology Review	Not applicable/no data
Clinical Pharmacology Review	Christy John, PhD & Y. Gene Williams, PhD (TL)
DDMAC	James Dvorsky
DSI	Not applicable/no inspections
CDTL Review	Louis Marzella, MD, PhD
OSE/DMEPA	Not applicable
OSE/DDRE	Not applicable
Pediatric and Maternal Health	Upasana Bhatnager, MD, Jeanine Best & Karen

	Feibus, MD (TL)
Consultative Reviewer	Suchitra Balakrishnan/CardioRenal Drugs
Project Manager	Frank Lutterodt

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader
TL = Team Leader
CMC = chemistry, manufacturing and controls

1. Introduction:

This supplement was originally submitted in 201 (b) (4) . The review was completed in the first review cycle and a Complete Response letter was issued on July 28, 2011 (b) (4) The sponsor responded with a labeling proposal that (b) (4) included the previously agreed upon safety labeling information. (b) (4) , so the sponsor's response was deemed acceptable during the second review cycle.

During this second review cycle, the Office of Regulatory Policy requested the medical staff to examine the supplement for user fee determination. Based upon the available guidance, the medical staff initially thought one user fee was appropriate (as the sponsor had paid) although the staff noted that user fee review does not appear a component of the 21st review expectations and this expertise appears beyond the division's insight. Ultimately, the Officer of Regulatory Policy determined that the supplement was bundled inappropriately and user fees applied inappropriate such that 3 user fees were necessary (b) (4) and the sponsor requested that the safety information be regarded as the supplement for review. (b) (4)

Definity is a "microbubble" contrast agent used in echocardiography to enhance visualization among patients with suboptimal echocardiograms. Importantly, most patients have adequate echocardiographic visualization without the use of a contrast agent. This is an important consideration because both approved echocardiographic contrast agents (Definity and Optison) have been associated with uncommon but serious cardiovascular reactions. These reactions prompted the addition of a boxed warning to the labeling (of both drugs) in 2007 along with new contraindications and other safety information. Subsequently, accumulating information led to a revision of the labeling to remove some of the contraindications (2008) for both drugs; this labeling approval was

accompanied with a commitment for Lantheus to complete at least three clinical studies (the other sponsor similarly was required to complete certain safety studies):

a) a study of pulmonary hemodynamics;

b) a retrospective/observational study of the use of Definity among critically ill patients;

c) complete a previously requested post-marketing "registry" study of Definity "in actual clinical use."

The current submission included the three requested clinical study results plus:

(b) (4)

The safety data were discussed at a May 2, 2011 meeting of the Cardiovascular and Renal Drugs Advisory committee. The most notable advice from the Committee was the citation of many limitations within the observational study conducted among critically ill patients. The advisors expressed opinions that generally indicated these study results were not useful and potentially misleading due to uncontrolled bias as well as other limitations associated with the retrospective design. These observations helped to refine the types of safety information to be included in labeling.

2. Background:

The initial development of Definity occurred among patients who had few underlying co-morbidities. This consideration prompted the FDA to request (and the sponsor agreed to) a post-marketing commitment to study Definity "as it is actually used in clinical practice." (from 2001 approval letter). However, this commitment was not fulfilled by the time post-marketing reports had begun to show serious (and sometimes fatal) reactions shortly following Definity administration (reports that culminated in the 2007 label revision). The reports of the serious reactions generally involved patients with fairly severe underlying comorbidities (ie., the types of conditions that would have generally excluded patients from premarketing studies). The FDA was also concerned in 2007 by the reports of pulmonary hypertension in animal models ((b) (4)

Ultimately, the FDA worked with the sponsor to develop a plan to obtain clinical data that helped to better characterize the safety of Definity. This supplement contained this

safety data [redacted] (b) (4)

3. Chemistry, Manufacturing and Controls:

No new information.

4. Nonclinical Pharmacology/Toxicology:

No nonclinical data were submitted.

5. Clinical Pharmacology/Biopharmaceutics:

I concur with the conclusions reached by Drs. Christy John and Gene Williams regarding the necessary text for the PLR format.

No new clinical pharmacology data were provided.

6. Clinical Microbiology:

No new data.

7. Clinical/Statistical-Efficacy:

Dr. Ross Filice provided the first cycle main clinical review and Dr. Louis Marzella provided the Cross Discipline Review.

Dr. Janelle Charles provided the first cycle main statistical review and Dr. Laree Tracy provided the supervisory review.

The application included the following main data sources:

Study	Features
DMP 115-415	Phase IV registry study of Definity in clinical practice
DMP 115-416	Pulmonary hemodynamics
DMP 115-418	Retrospective, observational database study of critically ill patients

[redacted] (b) (4)

The data contained multiple deficiencies as summarized in the first cycle review memorandum.

8. Safety:

The first cycle supplied safety data provide useful information regarding the potential for adverse reactions to Definity. The data importantly detected no signal for pulmonary hemodynamic alterations (among relatively "stable" patients). Together, the review team concluded that modification of the prescribing information was appropriate to include some of the supplied safety data. The team did not concur with the sponsor's proposal to remove the boxed warning.

Post-marketing Requirements (PMR): none

Post-marketing Commitments: none

9. Advisory Committee Meeting:

Safety was discussed at a May 2, 2011 advisory committee, as noted above.

10. Pediatrics:

(b) (4)

11. Other Relevant Regulatory Issues:

No inspections were performed. Consultation was provided by the CardioRenal Drug Products review division during the first review cycle.

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/s/

RAFEL D RIEVES
10/21/2011