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RESEARCH**

APPLICATION NUMBER:

021064Orig1s011

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA	21-064 SDN 203 Supplement-11 (Efficacy)
Submission Date	September 29, 2010
Category	1S
Brand Name	DEFINITY® Vial for (Perflutren Lipid Microsphere) Injectable Suspension
Formulation:	Injectable Suspension
Route of Administration	Intravenous
Dosing Regimen	<p>DEFINITY® may be injected by either an intravenous (IV) bolus or infusion. The maximum dose is either two bolus doses or one single intravenous infusion.</p> <p>The recommended dose for activated DEFINITY® is 10 microliters (µL)/kg of the activated product by intravenous bolus injection within 30-60 seconds, followed by a 10 mL saline flush. If necessary, a second 10 microliters (µL)/kg dose followed by a second 10 mL saline flush may be administered 30 minutes after the first injection to prolong contrast enhancement.</p> <p>The recommended dose for activated DEFINITY® is via an IV infusion of 1.3 mL added to 50 mL of preservative-free saline. The rate of infusion should be initiated at 4.0 mL/minute, but titrated as necessary to achieve optimal image enhancement, not to exceed 10 mL/minute.</p>
Indication	<p>DEFINITY® is an ultrasound contrast-enhancing 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.</p>
Sponsor	Lantheus Medical Imaging
Type of Submission	Efficacy supplement

Reviewer Christy S. John, Ph.D.
Acting Team Leader Gene Williams, Ph.D.

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1. EXECUTIVE SUMMARY

Lantheus Medical Imaging (LMI) has submitted this efficacy supplement New Drug Application. The application contains clinical trial results for the use of Definity in stress echocardiography. LMI does not seek an indication for stress echocardiography, (b) (4)

In addition to content changes in the Boxed Warning, Warnings, Adverse Reactions and Use in Specific Populations sections of the package insert, the application has changed the format of the package insert to comply with the requirements on content and format of labeling under CFR 201.56 and 201.57.

There are no new clinical pharmacology data in the submission.

1.1 Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology V has reviewed the submission NDA 21-064. The submission is acceptable from a clinical pharmacology perspective.

1.2 Post-marketing Requirements and Commitments

We have no recommendations for post-marketing requirements or commitments.

1.3 Summary of Clinical Pharmacology Findings

There are no clinical pharmacology findings.

2. QUESTION-BASED REVIEW

2.1. General Attributes of Drug

DEFINITY® (DEFINITY® Vial for [Perflutren Lipid Microsphere] Injectable Suspension), is a second-generation microbubble contrast agent. The phospholipid-encapsulated perfluoropropane (PFP, also known as perflutren) filled microsphere suspension is designed for intravenous (IV) administration. The product enhances echocardiographic ultrasound images. Following IV administration, DEFINITY® acts as an echogenic contrast agent in blood during ultrasound imaging.

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

Lantheus Medical Imaging (LMI) has submitted this supplemental New Drug Application. This application includes clinical trial results for the use of Definity in stress echocardiography. LMI does not seek an indication for stress echocardiography, (b) (4)

This application also includes revisions to the Boxed Warning, Warnings, Adverse Reactions and Use in Specific Populations sections of the package insert. The application proposes changes to prescription drug labeling to comply with the requirements on content and format of labeling under CFR 201.56 and 201.57 (Physician's Labeling Rule, PLR). However, there are no new clinical pharmacology data in the submission.

2.1.2 What are the highlights of the chemistry and physicochemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology of the drug?

There are no changes in formulation in the current submission.

2.2. General Clinical Pharmacology

The clinical pharmacology section of the most recently approved proposed package insert (PI) is reproduced (indented).

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

After activation of DEFINITY[®] and intravenous injection, the physical acoustic properties of activated DEFINITY[®] (see DESCRIPTION) provide contrast enhancement of the endocardial borders during echocardiography. The perflutren lipid microspheres exhibit lower acoustic impedance than blood and enhance the intrinsic backscatter of blood.

In animal models the acoustic properties of activated DEFINITY[®] were established at or below a mechanical index of 0.7 (1.8 MHz frequency). In clinical trials, the majority of the patients were imaged at or below a mechanical index of 0.8.

In a crossover trial of 64 patients randomized to both bolus and infusion, the duration of clinically useful contrast enhancement for fundamental imaging was approximately 3.4 minutes after a 10 $\mu\text{L}/\text{kg}$ bolus and was approximately 7.1 minutes during the continuous infusion of 1.3 mL activated DEFINITY[®] in 50 mL saline at a rate of 4 mL/min.

PHARMACOKINETICS

Human pharmacokinetics information is not available for the intact or degassed lipid microspheres. The pharmacokinetics of octafluoropropane gas (OFP) were evaluated in healthy subjects (n=8) after the IV administration of activated DEFINITY[®] at a 50 $\mu\text{L}/\text{kg}$ dose.

Octafluoropropane (OFP) Protein Binding

OFP gas binding to plasma proteins or partitioning into blood cells has not been studied. However, OFP protein binding is expected to be minimal due to its low partition coefficient into whole blood.

Metabolism

OFP is a stable gas that is not metabolized. The phospholipid components of the microspheres are thought to be metabolized to free fatty acids.

Elimination

OFP was not detectable after 10 minutes in most subjects either in the blood or in expired air. OFP concentrations in blood were shown to decline in a mono-exponential fashion with a mean half-life of 1.3 minutes in healthy subjects.

SPECIAL POPULATIONS

The pharmacokinetics of octafluoropropane gas (OFP) were evaluated in subjects (n=11) with chronic obstructive pulmonary disease (COPD). The mean half-life of OFP in blood was 1.9 minutes. The total lung clearance of OFP was similar to that in healthy subjects.

Microspheres may obstruct the vasculature of some patients. See WARNINGS for use in subjects with cardiac shunts and pulmonary hypertension.

The pharmacokinetics of activated DEFINITY[®] has not been studied in subjects with hepatic diseases or congestive heart failure.

Gender:

The effects of activated DEFINITY[®] appeared to be similar in men and women.

Age/Race:

The effects of age and race on the pharmacokinetics of activated DEFINITY[®] have not been studied.

Pediatrics:

The pharmacokinetics of activated DEFINITY[®] in pediatric subjects has not been studied. The safety of injecting activated DEFINITY[®] in neonates and infants with immature pulmonary vasculature has not been studied (see WARNINGS).

Elderly:

The pharmacokinetics of activated DEFINITY[®] in the elderly has not been studied.

DRUG-DRUG INTERACTIONS

Drug-drug interactions for activated DEFINITY[®] have not been studied.

3. DETAILED LABELING RECOMMENDATIONS

The sponsor has proposed changes to package insert section **5.1.5 QTc Prolongation**. These changes were reviewed and rejected by Dr. Suchitra Balakrishnan of the Interdisciplinary Review Team for QT assessment (the IRT, review dated May 17, 2011).

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4. APPENDICES

- 4.1 Proposed Package Insert (Annotated)
- 4.2 Most Recent FDA-approved Package Insert
- 4.3 Cover Sheet and OCP Filing/Review Form

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APPENDIX 4.3 COVER SHEET AND OCP FILING/REVIEW FORM

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA or IND Number	N 21-064 (S-11)	Brand Name	Definity
OCPB Division	DCP-5	Generic Name	Perflutren Lipid Microspheres
Medical Division	DMIP	Drug Class	Diagnostic agent
OCPB Reviewer	Christy John	Indication(s)	For use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of left ventricular endocardial border (b) (4)
OCPB Team Leader	Young Moon Choi	Dosage Form	A single use 2-ml vial containing clear liquid
		Dosing Regimen	Intra-venous bolus of 10 microliter/kg
Date of Submission	9/29/2011	Route of Administration	IV
Estimated Due Date of OCPB Review	5/29/2011	Sponsor	Lantheus Medical Imaging
PDUFA Due Date	7/29/2011	Priority Classification	S

Clin. Pharmaco. and Biopharm. Information

	“X” if included at filing	Number of study submitted	Number of study reviewed	Comments
STUDY TYPE				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, prove of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS study				
III. Other				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Filability and QBR comments				
	“X” if yes	Comments		
Application filable ?	x			
Comments sent to firm ?				
QBR questions (key issues to be considered)				
Other comments or information not included above	The submission includes data from PMR clinical trials and proposed labeling with PLR format. There is no data needed for specific analysis from clinical pharmacology perspectives. The clinical pharmacology review will focus on the labeling format in accordance with the 21CFR201.56 (d) and the appropriateness of the labeling language.			
Primary reviewer Signature	Christy S. John, Ph.D.			
Secondary reviewer Signature	Young Moon Choi, Ph.D.			

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/s/

CHRISTY S JOHN
12/01/2010

YOUNG M CHOI
12/01/2010
I concur.

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/s/

CHRISTY S JOHN
06/29/2011

GENE M WILLIAMS
06/29/2011
I concur