Office of Clinical Pharmacology Supplement Review

NDA or BLA Number	21064/S033
Link to EDR	\\CDSESUB1\evsprod\NDA21064\0145
Submission Date	5/1/2023
Submission Type	Efficacy Supplement-33
Brand Name	DEFINITY (Perflutren Lipid Microsphere) Injectable Suspension, for intravenous use
Generic Name	Perflutren Lipid Microsphere
Dosage Form and Strength	DEFINITY is supplied as a single patient use 2 mL clear glass vial or RFID-tagged vial containing clear liquid in packages of four (4) and sixteen (16) single patient use vials.
Route of Administration	Intravenous bolus or infusion
Proposed Indication	Activated Definity (Perflutren Lipid Microsphere) Injectable Suspension is indicated for use **in adult and pediatric patients** with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.
Proposed Dosing Regimen	The proposed dose of activated Definity in pediatric patients is 3 microliters (µL)/kg, administered via an IV bolus injection over 30 to 60 seconds.
Applicant	Lantheus Medical Imaging Inc
Associated INDs	48626
OCP Reviewer	Runyan Jin, Ph.D.
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1. EXECUTIVE SUMMARY

Definity (perflutren lipid microsphere) is an ultrasound contrast agent that was approved by the FDA in 2001 for use in adults with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. Definity is activated by mechanical shaking prior to its administration to a patient. Mechanical activation results in the consistent formation of homogeneous, opaque, milky white injectable suspension of perflutren lipid microspheres. The approved bolus dose in adult patient for activated Definity is 10 µL/kg of the activated product by intravenous (IV) bolus injection within 30 to 60 seconds, followed by a 10 mL saline flush. The approved infusion dose for activated Definity is via an IV infusion of 1.3 mL added to 50 mL of preservative-free saline. The proposed dosage of active Definity in pediatric patiens is 3 µL/kg administered via an IV bolus injection over 30 to 60 seconds. The maximum dose is two bolus doses 30 minute apart.

The applicant proposes to modify the labeling indication to include pediatric patients based on the clinical efficacy data from the completed pediatric clinical study DMP115-419 (Golding Study) in 2003 and safety data from the Golding Study and two identified published trials of Definity conducted among pediatric patients (2016 Kutty Study and 2021 Fine Study). Of note, no PK assessment of perflutren lipid microsphere was conducted in pediatric patients. Therefore, no labeling changes are proposed in the clinical pharmacology section 12.

Overal, the review team deems that the applicant's proposed dosage of perflutren lipid microsphere for pediatric patients appears acceptable based on the dose response relationship for image contrast opacification and duration of imaging across 4 age groups and 3 dose levels in the Golding Study and the overall safety profile in the clinical study and literature reports in pediatric patients.

1.1 Recommendations

The Office of Clinical Pharmacology Division of Cancer Pharmacology I has reviewed the information contained in NDA 21064 efficacy supplement 33. This NDA supplement is approvable from a clinical pharmacology perspective.

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

There is no new PK data submitted in this efficacy supplement.

2.2 Dosing and Therapeutic Individualization

The proposed dosage of Perflutren Lipid Microsphere is accptable for the proposed pediatric population aged < 18 years based on the effcicacy and safety data from the Golding Study and the two published trials (2016 Kutty study and 2021 Fine study).

2.3 Outstanding Issues

None

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Definity was approved by the FDA in 2001 for use in adults with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. In the NDA approval letter, FDA required the applicant to conduct a study of Definity dosing and echocardiographic usage among pediatric patients.

3.2 General Pharmacological and Pharmacokinetic Characteristics

Refer to the labeling of Definity (Perflutren Lipid Microsphere) Injectable Suspension, for intravenous use.

3.3 Clinical Pharmacology Questions

3.3.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

Yes, the effectiveness of Definity in the proposed pediatric indication is supported from the Golding Study.

The Golding Study was a single center, prospective, open label study in 4 age subgroups of patients (aged 1 month - < 1 year; ≥ 1- 5 years; 6 -10 years; 11 - 18 years) undergoing routine echocardiography. The primary objective was establishing the optimum dosage of Definity for left ventricular opacification and endocardial border delineation. Overall, 40 patients received up to 3 sequential doses of Definity, which was administered via IV bolus injection at doses of 2 µL/kg, 3 µL/kg and 5 µL/kg. Instead of the traditional exposure-response analysis for efficacy, the relationship between the dose levels of Definity a diagnostic acoustic image was assessed to support the dose selection in pediatric population. In this case, the formation of left ventricular opacification image is considered as a measurement for effectiveness and is assessed using a scale range from Grade 0 to Grade 4 as following whereby the "adequate contrast" summary score refers to a Grade 2 or 3.

- Grade 0=No contrast effect
- Grade 1=Weak or minimal contrast effect
- Grade 2=Adequate contrast effect
- Grade 3=Full contrast effect
- Grade 4=Excessive contrast effect

The applicant stated that dose of 3 µL/kg appeared to produce optimal contrast effect while the highest dose (5 µL/kg) produced excessive contrast that obscured visualization of cardiac structures as shown in Table 1 below. When the opacification grade is broken down by age groups in Table 2, the similar trend was observed that dose of 3 µL/kg appeared to produce more adequate contrast across all age groups than the highes dose of 5 µL/kg, particularly in A4C views.

Table 1: Golding Study-Left Ventricular Opacification by Dose (n = 40)

Opacification Grade	Baseline No contrast agent	Dose 1 2 µL/kg	Dose 2 3 µL/kg	Dose 3 5 µL/kg
Total (N=40) A4C Views				
Grade 0	33 (82.5%)	0	0	0
Grade 1	1 (2.5%)	3 (7.5%)	0	0
Grade 2	0	4 (10%)	3 (7.5%)	1 (2.5%)
Grade 3	1 (2.5%)	33 (82.5%)	35 (87.5%)	34 (85%)
Grade 4	0	0	2 (5%)	4 (10%)
Adequate contrast	1 (2.5%)	37 (92.5%)	38 (95%)	35 (87.5%)
A2C Views				
Grade 0	31 (77.5%)	0	0	0
Grade 1	0	3 (7.5%)	0	0
Grade 2	0	3 (7.5%)	2 (5%)	2 (5%)
Grade 3	1 (2.5%)	26 (65%)	30 (75%)	32 (80%)
Grade 4	0	0	0	2 (5%)
Adequate contrast	1 (2.5%)	29 (72.5%)	32 (80%)	34 (85%)

Note: A4C refers to the apical four chamber view and A2C refers to the apical two chamber view.

(Data Source: Table 3 on page 10 in Summary of Clinical Pharmacology)

Table 2: Adequate Contrast Opacification by Dose Group for Each Age Group

Adequate Contrast Opacification by Age Group	Baseline No contrast agent	Dose 1 2 µL/kg	Dose 2 3 µL/kg	Dose 3 5 µL/kg
A4C Views				
1m-<1 year (N=10)	0	9 (90.0%)	9 (90.0%)	9 (90.0%)
1-5 years (N=9)	0	8 (88.9%)	9 (100.0%)	9 (100.0%)
6-10 years (N=10)	0	10 (100.0%)	9 (90.0%)	10 (100.0%)
11-18 years (N=11)	1 (9.1%)	10 (90.9%)	11 (100.0%)	7 (63.6%)

A2C Views				
1m-<1 year (N 10)	0	5 (50.0%)	5 (50.0%)	7 (70.0%)
1-5 years (N=9)	0	7 (77.8%)	7 (77.8%)	8 (88.9%)
6-10 years (N=10)	0	8 (80.0%)	9 (90.0%)	10 (100.0%)
11-18 years (N 11)	1 (9.1%)	9 (81.8%)	11 (100.0%)	9 (81.8%)

Note: A4C refers to the apical four chamber view and A2C refers to the apical two chamber view.

(Data Source: Table 4 on page 11 in Summary of Clinical Pharmacology)

In addition, the duration of contrast effects based on left ventricular opacification were summarized by dose cohorts and age groups as shown in Table 3. The applicant stated that the duration of contrast imaging was the shortest at dose of 2 µL/kg (mean duration of 1.9 minutes) and the longest at dose of 5 µL/kg (mean duration of 3.9 minutes) across all age groups.

Table 3: Dose-response in Imaging Duration (minutes) by Age Group

Dose	Statistic	Value By Age Group				
		1 m – <1 yr (Group 1) (N=10)	1-5 yrs (Group 2) (N=9)	6 – 10 yrs (Group 3) (N=10)	11 – 18 yrs (Group 4) (N=11)	Total (N=40)
Dose 1	N	7	8	10	10	35
	Mean (SD)	1.3 (0.60)	1.9 (0.68)	2.1 (0.69)	2.2 (1.33)	1.9 (0.93)
2 µL/kg	Median	1.5	1.9	2.0	2.2	2.0
	Min Max	0.2 2.0	1.0 3.3	1.0 3.0	0.6 4.6	0.2 4.6
Dose 2	N	10	8	10	10	38
	Mean (SD)	1.8 (1.01)	3.2 (2.28)	2.8 (1.22)	3.1 (1.68)	2.7 (1.61)
3 µL/kg	Median	2.0	2.5	3.0	2.7	2.4
	Min – Max	0.2 – 3.1	1.0 – 7.9	1.0 – 4.3	1.6 – 7.3	0.2 – 7.9
Dose 3	N	9	9	10	11	39
	Mean (SD)	2.7 (1.36)	3.8 (1.60)	4.7 (2.13)	4.4 (2.29)	3.9 (1.99)
5 µL/kg	Median	3.4	3.5	4.3	4.8	3.9
	Min Max	0.0 4.1	2.0 7.4	1.0 8.3	1.0 8.3	0.0 8.3

(Data Source: Table 5 on page 12 in Summary of Clinical Pharmacology)

Overall, the review team agrees with the applicant's assessment that dose of 3 µL/kg produced better adequate contrast opacification images than the other two dose levels across the 4 age groups in Golding Study based on the supportive evidence from the dose response relationship for image contrast opacification and duration of contrast imaging.

3.3.2 Is the proposed general dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed initial dose of 3 µL/kg administered via an IV bolus injection followed by a second bolus dose of 3-5 µL/kg if necessary appears appropriate for the proposed pediatric patient population. The maximum dose is two bolus doses 30 minute apart.

A total of 189 pediatric patiens who ranged in age from one month to 21 years from the Golding Study and the two literature trials (2016 Kutty study and 2021 Fine study) are included for the safety assessment. The Golding Study reported no adverse events (AEs), serious adverse events (SAEs), or deaths during the usage of Definity in 40 pediatric patients, which was administered as a series of up to 3 bolus injections (2 µL/kg, 3 µL/kg and 5 µL/kg) to each patient (a cumulative dose of 10 µL/kg).

The 2021 Fine study included 36 patients with a mean age of 13.5 years (10-21 years), who had previously undergone a heart transplant and underwent Definity enhanced echocardiography. For the pediatric patients (≤60 kg), a cumulative dose of 20 µL/kg was administered, which was two-fold higher than the dose used in the Golding study. It was reported that 33% (12/36) patients experienced mild AEs during the dobutamine stress testing. AEs consisted of palpitations, headache, nausea, and dyspnea, which were considered to be attributed to the stress test procedure and not as effects of Definity administration.
The 2016 Kutty study included 113 patients with a mean age of 17.8 years (5 – 21 years) and a cumulative bolus dose of approximately 20 µL/kg was administered to each patient. Symptoms such as pain (chest, back, neck pain), headache, fatigue, dizziness, and shortness of breath were reported very brief and in all cases and resolved without intervention.
Taken together, the effcicacy and safety data from the Golding Study and the two published trials (2016 Kutty study and 2021 Fine study) demonstrated that the proposed dosage of Definity is appropriate for the proposed pediatric population aged < 18 years, which includes both younger and older pediatric patients.

APPEARS THIS WAY ON ORIGINAL

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/s/

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