Leading Societal Standards and Guidelines for the Appropriate Use of Ultrasound Contrast in Echocardiography

DEFINITY®
The #1 prescribed ultrasound contrast agent in the US.¹
Setting the standard for diagnostic quality, safety and commitment.

Please see Indications and Important Safety Information on page 7 and full Prescribing Information on pages 9-11, including boxed WARNING regarding serious cardiopulmonary reactions.
American Society of Echocardiography (ASE) Consensus Statement on the Clinical Applications of Ultrasound Contrast in Echocardiography

Excerpts of Suggested Applications

• In difficult-to-image patients presenting for rest echocardiography with reduced image quality
  o To enable improved endocardial visualization and assessment of left ventricular (LV) structure and function when ≥2 contiguous segments are not seen on noncontrast images
  o To reduce variability and increase accuracy in LV volume and LV ejection fraction (LVEF) measurements by 2-dimensional (2D) echocardiography
  o To increase the confidence of the interpreting physician in LV functional, structure, and volume assessments

• In all patients presenting for rest echocardiographic assessment of LV systolic function (not solely difficult-to-image patients)
  o To reduce variability in LV volume measurements through 2D echocardiography
  o To increase the confidence of the interpreting physician in LV volume measurement

• To confirm or exclude the echocardiographic diagnosis of the following LV structural abnormalities, when nonenhanced images are suboptimal for definitive diagnosis
  o Apical variant of hypertrophic cardiomyopathy
  o Ventricular noncompaction
  o Apical thrombus
  o Complications of myocardial infarction, such as LV aneurysm, pseudoaneurysm, and myocardial rupture

• To assist in the detection and correct classification of intracardiac masses, including tumors and thrombi
• For echocardiographic imaging in the intensive care unit (ICU) when standard tissue harmonic imaging does not provide adequate cardiac structural definition
  o For accurate assessment of LV volumes and LVEF
  o For exclusion of complications of myocardial infarction, such as LV aneurysm, pseudoaneurysm, and myocardial rupture

ASE Recommendations for Quality Echocardiography Laboratory Operations

Excerpts of Recommendations

To establish a high level of quality in echo, laboratories should:

• Obtain accreditation
• Have sufficient equipment for echo procedures including contrast
• Maintain appropriate personnel training/credentialing
• Have quality assurance policies to minimize uninterpretable or nondiagnostic studies
• Have written policies for the use of contrast
• Implement quality assessment and improvement programs

When contrast is used appropriately, <5% of transthoracic echocardiographic studies should be identified as nondiagnostic

Please see Indications and Important Safety Information on page 7 and full Prescribing Information on pages 9-11, including boxed WARNING regarding serious cardiopulmonary reactions.
ASE Guidelines for the Cardiac Sonographer in the Performance of Contrast Echocardiography

Guidelines to help Sonographers Overcome Technical and Administrative Barriers to Contrast Utilization

- Understand microbubble physics and ultrasound instrumentation
- Recognize when and how to perform contrast echo
- Obtain intravenous (IV) access privileges
- Develop written policies and procedures for contrast administration

Initiatives to ensure appropriate use:

- Increase awareness of the value of contrast in various clinical settings
- Increase the number of sonographers who are trained in starting IV lines and administering contrast

Scope of Practice and Clinical Standards for the Diagnostic Medical Sonographer

Representative of leading societal organizations

Contrast administration and IV insertion is within the sonographer scope of practice

- With appropriate education and training, Sonographer uses proper technique for intravenous line insertion and administers intravenous contrast according to facility protocol
- Sonographer initiates additional scanning techniques or procedures (e.g., administering contrast agents) when indicated
Intersocietal Accreditation Commission Echocardiography Laboratories (IAC Echo)\(^6\)

Use of Contrast for Suboptimal Image Quality - Contrast is indicated for use when 2 contiguous segments are not visualized in any 3 of the apical views (poor endocardial border definition) as it provides greater accuracy in determining left ventricular function

• Contrast should be used in the presence of poor endocardial border definition:
  o For quantification of chamber dimensions, volumes, ejection fraction
  o For assessment of regional wall motion
  o To assess conditions such as hypertrophic cardiomyopathy
  o When left ventricular thrombus is suspected

American College of Cardiology Foundation Appropriate Use Criteria for Echocardiography\(^7\)

• Appropriate use of contrast: when 2 or more contiguous segments of the left ventricular endocardial border cannot be visualized

*Activated DEFINITY® (Perflutren Lipid Microsphere) Injectable Suspension

Please see Indications and Important Safety Information on page 7 and full Prescribing Information on pages 9-11, including boxed WARNING regarding serious cardiopulmonary reactions.
Use of contrast for suboptimal image quality - contrast is indicated when 2 contiguous segments are not visualized in any 3 of the apical views (poor endocardial border definition) as it provides greater accuracy in determining left ventricular function

• Contrast should be used in the presence of poor endocardial border definition for quantification of chamber dimensions, volumes, ejection fraction, and assessment of regional wall motion

• Contrast should be used to assess conditions such as hypertrophic cardiomyopathy or when left ventricular thrombus is suspected

• If contrast is used, there must be a written policy for the use of contrast. If contrast is not able to be used, there must be a policy for alternative imaging
INDICATIONS
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.

CONTRAINDICATIONS
Do not administer DEFINITY® to patients with known or suspected right-to-left, bi-directional or transient right-to-left cardiac shunts, by intra-arterial injection, or to patients with known hypersensitivity to perflutren.

IMPORTANT SAFETY INFORMATION

WARNING: Serious Cardiopulmonary Reactions
Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perflutren-containing microsphere administration [See WARNINGS AND PRECAUTIONS (5.1)]. Most serious reactions occur within 30 minutes of administration.

- Assess all patients for the presence of any condition that precludes DEFINITY® administration [See CONTRAINDICATIONS (4)].
- Always have resuscitation equipment and trained personnel readily available.

In postmarketing use, rare but serious cardiopulmonary or anaphylactoid reactions have been reported during or shortly following perflutren-containing microsphere administration [See ADVERSE REACTIONS (6)]. The risk for these reactions may be increased among patients with unstable cardiopulmonary conditions [See Postmarketing Experience (6.2)]. It is not always possible to reliably establish a causal relationship to drug exposure due to the presence of underlying cardiopulmonary disease.

Please see full Prescribing Information on pages 9-11, including boxed WARNING regarding serious cardiopulmonary reactions.
DEFINITY® Most Used¹, Most Studied¹⁰, Most Trusted¹¹

• DEFINITY® is the #1 prescribed ultrasound contrast agent in the US, with use in more than 5.6 million patients¹

• DEFINITY® is engineered to produce small and consistently sized durable microbubbles to fully evaluate the left ventricle¹²

• DEFINITY® has extensive safety experience and a consistent safety profile across broad patient populations in multiple care settings⁹,¹¹,¹²

• DEFINITY® has a proven diagnostic advantage that optimizes outcomes, patient management, and cost-effectiveness⁹

Lantheus Medical Imaging
Setting the standard for diagnostic quality, safety and commitment with the largest dedicated sales force in the field of contrast-enhanced ultrasound and comprehensive programs to support customers


Please see Indications and Important Safety Information on page 7 and full Prescribing Information on pages 9-11, including boxed WARNING regarding serious cardiopulmonary reactions.
Specific drug-drug interactions have not been studied. Do not use this drug unless it has a full 45 second activation cycle. Activated DEFINITY® may be properly activated unless the full 45 second activation cycle is completed. Do not re-activate the vial if VIALMIX® did not complete a full 45 second cycle. Do not re-activate a successfully activated DEFINITY® vial (see step 3). Do not use a VIALMIX® that is not functioning properly. Refer to the “VIALMIX® User’s Guide” for the “VIALMIX® calibration and replacement procedures” to ensure that a properly functioning VIALMIX® is used.

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 microL/kg bolus and was approximately 7.1 minutes during continuous infusion of 1.3 mL activated DEFINITY® in 50 mL saline at a rate of 4 mL/min.

2.4 DEFINITY® Activation, Preparation and Handling Instructions

1. Allow the vial to warm to room temperature before starting the activation procedure.

2. Activate DEFINITY® by shaking the vial for 45 seconds using a VIALMIX®

Note: Illustrations of this procedure are contained in the VIALMIX® Users Guide.

To report SUSPECTED ADVERSE REACTIONS, contact Lantheus Medical Imaging, Inc. at 1-800-362-2668 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

See full prescribing information for complete boxed warning. Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perflutren-containing microsphere administration (5, 11). Most serious reactions occur within 30 minutes of administration. • Assess all patients for the presence of any condition that precludes DEFINITY® administration (4).

Always have resuscitation equipment and trained personnel readily available.

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perflutren-containing microsphere administration (5, 11). Most serious reactions occur within 30 minutes of administration. • Assess all patients for the presence of any condition that precludes DEFINITY® administration (4).

Always have resuscitation equipment and trained personnel readily available.

ASYMPTOMATIC TIME TO ViALMIX®. After activation, each vial contains a maximum of 1.2 X 10

DEFINITY® is supplied as a single use 2-mL clear glass vial containing a clear liquid in packages of four (4) and sixteen (16) single-use vials.

Asymptomatic time to ViALMIX® change was estimated to be approximately 20 minutes for a single bolus dose, followed by a 10 mL saline flush. If necessary, a second 10 microL/mL dose may be administered within 10 minutes after the first injection to prolong contrast enhancement.

Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perflutren-containing microsphere administration (5, 11). Most serious reactions occur within 30 minutes of administration. • Assess all patients for the presence of any condition that precludes DEFINITY® administration (4).

Activated DEFINITY® has been shown to produce echocardiographic images within 10 seconds of injection, compared to 30-60 seconds for unactivated DEFINITY®.

Always have resuscitation equipment and trained personnel readily available.
5.5 QTc Prolongation:
EGM parameters for doses up to 10 micro-L were monitored in 221 subjects at multiple time points from 1 hour to 72 hours after the first bolus injection. In the 221 subjects, QTc prolongations of >30 msec were noted in 64 (29%) subjects. Forty-six out of 84 subjects with QTc prolongations were further evaluated and 39% (18/46) showed associated cardiac rhythm changes. The effects of concomitant drugs were not studied.

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience
A total of 1716 subjects were evaluated in pre-market clinical trials of DEFINITY®. In this group, 1063 (61.9%) were male and 653 (38.1%) were female, 1282 (74%) were White, 25 (15.0%) were Black, 47 (2.4%) were Hispanic, and 56 (3.3%) were classified as other racial or ethnic groups. The mean age was 56.1 years (range 18 to 93). Of these, 144 (8.4%) had at least one adverse reaction (Table 6.1). There were 28 serious adverse events and 15 (9.0%) subjects discontinued because of an adverse event.

Deaths and Serious Adverse Events
Among the 1716 DEFINITY® patients, 19 (1.1%) suffered serious cardiovasculard adverse events including eight deaths. The deaths occurred several days after administration of DEFINITY® and appeared to be related to the course of underlying disease. Of the 11 other serious adverse events, which occurred during the days of the drug administration (2-15 days), all appeared to be a progression underlying cardiac and non-cardiac disease. However, a role for DEFINITY® in the initiation or course of these adverse events cannot be ruled out.

Discontinuations
There were 15 discontinuations reported with a mean age of 41.5 years. Nine of these patients were discontinued after the first injection. One patient experienced a hypersensitivity reaction with urticaria and pruritus and all the other patients experienced dizziness, chest pain, drowsiness, or back pain. These adverse reactions appeared within minutes (1–15 min) of the drug administration and were of moderate intensity resolving usually without treatment within minutes or hours after onset.

For all adverse reactions, the overall incidence of adverse reactions was similar between the <65 year age group and the >65 year age group, similar in males and in females, similar among all racial or ethnic groups, and similar for the <65 year age group and the > 65 year age group, similar in males and females. As with other contrast agents, monitoring of vital signs and other parameters for at least 15 minutes after the completion of the injection is recommended to ensure that patients are not adversely affected by the contrast agent.

Tachyarrhythmias were reported in some patients. However, no evidence of impaired ventricular function or harm to the fetus due to DEFINITY® was observed. Cardiac arrhythmia studies are not predictive of human response, this drug should be used during pregnancy only if clearly needed.

6.2 Postmarketing Experience

6.2.1 Introduction
In routine clinical practice, heart rate, respiratory rate, and pulse oximetry were monitored for 30 minutes after DEFINITY® administration. No deaths or serious adverse reactions were reported, suggesting that these reactions are unlikely to occur at a rate of more than 0.3% when DEFINITY® is used according to recommendations.

The following adverse reactions have been identified during the post-marketing use of perfluorocarbon microspheres. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Fetal cardiodysrhythmia and anaphylactoid events and other serious but non-fatal adverse reactions were uncommonly reported. These events typically occurred within 24 hours of DEFINITY® administration. These serious events may be increased among patients with unstable cardiodysrhythmia conditions (acute myocardial infarction, acute coronary artery syndromes, worsening or unstable congestive heart failure, or serious ventricular arrhythmias) [see WARNINGS AND PRECAUTIONS (5.1, 5.2)].

Reported reactions included:
- Cardiodysrhythmia
- Cardiac or respiratory arrest, shock, syncope, symptomatic arrhythmias (atrial fibrillation, tachycardia, bradycardia, supraventricular tachycardia, ventricular fibrillation, ventricular tachycardia), hypertension, hypotension, dyspnea, hypoxia, chest pain, respiratory distress, stridor, wheezing.
- Anaphylactoid

Anaphylactic/anaphylactoid reaction, anaphylactic shock, hypereosinophilia, hypotension, hypotension, hypertension, dyspnea, hypoxia, chest pain, respiratory distress, stridor, wheezing.

Neurologic

Coma, loss of consciousness, convulsion, seizure, transient ischemic attack, agitation, tremor, vision blurred, dizziness, headache, fatigue.

7 DRUG INTERACTIONS

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B
There are no adequate and well-controlled studies of DEFINITY® in pregnant women. Reproduction studies performed in rats and rabbits at doses up to 24 and 15 times the human dose based on body surface area (in rats and rabbits, respectively) revealed no evidence of impaired fertility or harm to the fetus due to DEFINITY®. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.2 Nursing Mothers

It is not known whether DEFINITY® is excreted in human milk. Based on the rapid clearance of this drug, advise nursing mothers to pump and discard breast milk once after treatment [see CLINICAL PHARMACOLOGY (12)]. Because many drugs are excreted in human milk, caution should be exercised when DEFINITY® is administered to a nursing mother.

8.4 Pediatric Use

The safety and effectiveness of activated DEFINITY® have not been established in the pediatric population.

The safety of injecting activated DEFINITY® in neonates and infants with immature pulmonary vasculature has not been studied.

The pharmacokinetics of activated DEFINITY® in pediatric subjects has not been studied.

8.5 Geriatric Use

In clinical trials, the overall incidence of adverse reactions was similar for the <65 year age group and the >65 year age group. Of the total number of subjects in clinical trials of DEFINITY®, 144 (33%) were > 65 years old. No overall differences in safety or effectiveness were observed between these subjects and the older subjects, and other reported clinical experience has not identified idiosyncratic reactions in the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Gender

The overall incidence of adverse reactions was similar between males and females.

8.7 Race

The overall incidence of adverse reactions was similar among all racial and ethnic groups.

10 OVERDOSAGE

The clinical consequences of overdosing with activated DEFINITY® are not known. Treatment of an overdose should be directed toward the support of all vital functions and prompt institution of symptomatic therapy [see CONTRAINDICATIONS (4), WARNINGS AND PRECAUTIONS (5)]

11 DESCRIPTION

DEFINITY® (Perfluor Liquefied Microspheres) Injectable Suspension is an ultrasonic contrast agent. The DEFINITY® vial contains components that upon activation yield perfluor lipid microspheres, a diagnostic drug that is intended to be used for contrast enhancement during the indicated echocardiographic procedures. The vial contains a clear, colorless, sterile, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, isotonic, iso...
14 CLINICAL STUDIES

14.1 Echocardiography

A total of 249 subjects were evaluated in clinical trials (208 received activated DEFINTY® and 41 placebo). In this group, 154 (61.8%) were male and 95 (38.2%) were female; 183 (73.5%) were White, 38 (15.2%) were Black, 21 (8.4%) were Hispanic, and 7 (2.8%) were classified as other racial or ethnic groups. The mean age was 53.9 years (range 18 to 87).

Activated DEFINTY® was evaluated in four controlled clinical trials: Two open-label baseline controlled, unpaired blinded imaging evaluation studies and two identical placebo-controlled, unpaired blinded imaging evaluation studies. Subjects were eligible for these studies if they had two or more (6/6) non-evaluable images in either the apical 2- or 4-chamber view in non-contrast fundamental echocardiography.

In the baseline controlled studies, a total of 126 (67 in study A and 59 in study B) subjects received a bolus dose of 10 microL/kg of activated DEFINTY®. The outcome measures in these studies included the blinded assessment of ejection fraction (EF), endocardial border length (EBL) obtained by direct measurement, and qualitative assessment of wall motion.

In the two placebo-controlled studies a total of 123 subjects were randomized in a 1:2 ratio to receive two IV bolus doses of either saline (placebo) or activated DEFINTY® 10 microL/kg (17 placebo vs. 33 activated DEFINTY® patients and 24 placebo vs. 49 activated DEFINTY® patients, respectively). The outcome measure for assessing the effectiveness of activated DEFINTY® was the blinded assessment of improvement in ventricular chamber enhancement (measured by videosdensitometry at end-diastole and end-systole).

14.1.1 Endocardial Border Length

As shown in Table 14.1, compared to baseline, a single bolus dose of 10 microL/kg of activated DEFINTY® increased the length of endocardial border that could be measured at both end-systole and end-diastole. The mean change in border length from baseline to end-diastole was statistically significant for all readers in the apical 4-chamber view and for 3 out of 4 readers for the apical 2-chamber view. The mean change in border length from baseline at end-systole was statistically significant for 3 out of 4 readers for the apical 4-chamber view and for 2 out 4 readers for the apical 2-chamber view.

14.1.2 Ventricular Chamber Enhancement

Left ventricular chamber enhancement after an activated DEFINTY® dose of 10 microL/kg was significantly increased from baseline to placebo in both views at the mid-ventricular and apical levels at end-diastole. Similar results were noted at end-systole, with the exception of the 4-chamber view.

14.1.3 Wall Motion

In a retrospective analysis, in a subset of subjects (n=12 to 47, depending on reader) having at least 2 adjacent segments non-evaluable on non-contrast imaging, activated DEFINTY® converted a baseline non-evaluable image to an evaluable image in 58 to 91% of the patients, depending on the reader. In the converted images, the accuracy of wall motion (i.e., normal versus abnormal) improved in 42 to 71% of the patients, depending on the reader, however, improvement in the specific diagnostic accuracy (e.g., hypokinetic, akinetic etc.) was not established. Also, in 13 of 37% of the patients, depending on the reader, activated DEFINTY® was found to obscure the wall motion rendering the image non-evaluable.

14.1.4 Ejection Fraction

In the 2 baseline controlled studies, ejection fraction results were evaluated in comparison to MLI. The results were evaluated by 3 blinded, independent radiologists. In these studies, although there was a statistically significant increase in ventricular chamber enhancement, activated DEFINTY® did not significantly improve the assessment of ejection fraction compared to the baseline images.

Table 14.1 MEAN (SD) ENDOCARDIAL BORDER LENGTH (CM) BY BOTH APICAL 2- AND 4-CHAMBER VIEWS AT END-SYSTOLE AND END-DIASTOLE BY STUDY, EVALUABLE SUBJECTS

<table>
<thead>
<tr>
<th>Study/View</th>
<th>Endocardial Border Length – Blinded Read</th>
<th>Endocardial Border Length – Blinded Read</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean(SD) at End-Diastole</td>
<td>Mean(SD) at End-Systole</td>
</tr>
<tr>
<td></td>
<td>Reader 1</td>
<td>Reader 2</td>
</tr>
<tr>
<td>Study A: (N = 67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apical 2-chamber</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.0(3.4)</td>
<td>4.7(2.9)</td>
</tr>
<tr>
<td>Post-DEFINTY®</td>
<td>12.8(3.2)*</td>
<td>5.8(2.6)*</td>
</tr>
<tr>
<td>Apical 4-chamber</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.1(3.3)</td>
<td>4.5(2.6)</td>
</tr>
<tr>
<td>Post-DEFINTY®</td>
<td>13.5(5.2)*</td>
<td>6.8(3.3)*</td>
</tr>
<tr>
<td>Study B: (N = 59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apical 2-chamber</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.3(2.6)</td>
<td>7.6(5.3)</td>
</tr>
<tr>
<td>Post-DEFINTY®</td>
<td>5.7(4.7)*</td>
<td>8.2(6.5)</td>
</tr>
<tr>
<td>Apical 4-chamber</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.0(2.7)</td>
<td>9.2(5.9)</td>
</tr>
<tr>
<td>Post-DEFINTY®</td>
<td>7.1(5.5)*</td>
<td>11.5(7.5)*</td>
</tr>
</tbody>
</table>

Activated DEFINTY® Bolus Dose = 10 µL/kg

* Significant change from baseline (paired t-test, p<0.05)

In an open administration, crossover trial, 64 patients were randomized to receive both bolus (10 microL/kg) and infusion (1.3 mL, activated DEFINTY® in 50 mL saline at the rate of 4 mL/min) dosing of activated DEFINTY®. Outcome measures for this study included clinically useful ventricular cavity enhancement and endocardial border length. Similar results were seen as described above.

Optimal activated DEFINTY® doses and device settings for harmonic imaging have not been established.

14.2 Pulmonary Hemodynamic Effects

The impact of DEFINTY® on pulmonary hemodynamics was explored in a prospective, open-label study of patients with normal (< 35 mmHg, 16 patients) and elevated (> 35 mmHg, < 75 mmHg, 16 patients) pulmonary artery systolic pressure undergoing right heart catheterization. Patients with pulmonary artery systolic pressure greater than 75 mmHg were excluded from the study. Systemic hemodynamic parameters and ECGs were also evaluated. No clinically important pulmonary hemodynamic, systemic hemodynamic, or ECG changes were observed. This study did not assess the effect of DEFINTY® on visualization of cardiac or pulmonary structures.

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DEFINTY® is supplied as a single use 2-mL clear glass vial containing clear liquid in packages of four (4) and sixteen (16) single-use vials.

- NDC (11994-011-01), vial
- NDC (11994-011-04), 4 vial kit
- NDC (11994-011-16), 16 vial kit

16.2 Storage and Handling

Store between 2-8°C (36°-46°F).

FOR SINGLE USE ONLY: DEFINTY® does not contain bacterial preservative. Bacterial contamination with the risk of post-administration septicemia can occur following the puncture of the elastomeric septum. It is essential to follow directions for activation of DEFINTY® carefully and to adhere to strict aseptic procedures during preparation.

17 PATIENT COUNSELING INFORMATION

Patients receiving activated DEFINTY® should be instructed to inform their healthcare provider if they:

1. have a congenital heart defect, or recent worsening of heart or lung conditions (see CONTRAINDICATIONS (4) and WARNINGS AND PRECAUTIONS (5.1))
2. have had prior reactions to DEFINTY® (see CONTRAINDICATIONS (4))
3. may be pregnant, are trying to become pregnant, or are nursing (see USE IN SPECIFIC POPULATIONS (8)).

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