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 (5.1). 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.

----- INDICATIONS AND USAGE ----- DEFINITY is an ultrasonic 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.

----- DOSAGE AND ADMINISTRATION ----- 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.

The recommended bolus dose for activated DEFINITY is 10 microliters (μL)/kg of the activated product by intravenous bolus injection within 30 to 60 seconds, followed by a 10 mL saline flush. Do not inject more than 10 mL saline flush at 4 mL/minute, but titrate as necessary to achieve optimal image enhancement, not to exceed 10 mL/minute.

----- DOSAGE FORMS AND STRENGTHS ----- DEFINITY 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.

----- CONTRAINDICATIONS ----- Do not administer DEFINITY to patients with known or suspected: Hypersensitivity to perflutren products.

----- WARNINGS AND PRECAUTIONS ----- Serious cardiopulmonary reactions, including fatalities, have occurred during or following perflutren-containing microsphere administration. Serious acute hypersensitivity reactions have occurred in patients with no prior exposure to perflutren-containing microsphere products (5.2, 6).

Always have cardiopulmonary resuscitation personnel and equipment readily available prior to DEFINITY administration and monitor all patients for acute reactions (5.1, 5.2).

----- ADVERSE REACTIONS ----- The most common adverse reactions (>0.5%) are headache, back/renal pain, flushing, nausea, chest pain, injection site reactions, and dizziness (5). 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. See 17 for Patient Counseling Information. Revised: 12/2018

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perflutren-containing microsphere administration. Serious reactions occur within 30 minutes of administration.

• Assess all patients for the presence of any condition that precludes DEFINITY administration.
• Always have resuscitation equipment and trained personnel readily available.

----- INDICATIONS AND USAGE ----- 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.

----- DOSAGE AND ADMINISTRATION ----- 2.1 Important Administration Instructions

• DEFINITY is intended for administration only after activation in combination or in sequence, has not been studied.

2.2 Dosage

• The maximum dose is either two bolus doses or one single intravenous infusion. The safety and efficacy of single intravenous infusions have not been established. The rate of infusion should be initiated at 4 mL/minute, but titrated as necessary to achieve optimal image enhancement, not to exceed 10 mL/minute.

2.3 Imaging Guidelines

Prior to activation, the headspace of each vial contains 6.52 mg/mL octafluoropropane and the clear liquid contains 0.75 mg/mL of perflutren liposomes. After activation, each vial contains a maximum of 2.2 mL octafluoropropane and 0.75 mg/mL perflutren liposomes, and about 150 microliter/mL (1.1 mg/mL) octafluoropropane [see Description (11)].

4 CONTRAINDICATIONS

Do not administer DEFINITY to patients with known or suspected:

• Hypersensitivity to perflutren products (4).

5 WARNINGS AND PRECAUTIONS

5.1 Serious Cardiopulmonary Reactions

Serious cardiopulmonary reactions including fatalities have occurred uncommonly during or shortly following perflutren-containing microsphere administration, typically within 30 minutes of administration. The risk for these reactions may be increased among patients with unstable cardiopulmonary conditions (acute coronary syndromes, hypotension or unstable congestive heart failure, or serious ventricular arrhythmias). Always have cardiopulmonary resuscitation personnel and equipment readily available prior to DEFINITY administration and monitor all patients for acute reactions.

The reported reactions include: fatal 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, loss of consciousness, and convulsions [see Adverse Reactions (6)].
5.2 Hypersensitivity Reactions

In postmarketing use, serious hypersensitivity reactions were observed during or shortly following perflutren-containing microsphere administration including:

Shock, bronchospasm, throat tightness, angioedema, edema (pharyngeal, palatal, mouth, peripheral, localized), swelling (face, eye, lip, tongue, upper airway), facial hypoaesthesia, rash, urticaria, pruritus, flushing, and erythema have occurred in patients with no prior exposure to perflutren-containing microsphere products [see Adverse Reactions (6)]. Always have cardiopulmonary resuscitation personnel and equipment readily available prior to DEFINITY administration and monitor all patients for hypersensitivity reactions.

5.3 Systemic Embolization

When administering DEFINITY to patients with a cardiac shunt, the microspheres can bypass filtering by the lung and enter the arterial circulation. Assess patients with shunts for embolic phenomena following DEFINITY administration. DEFINITY is only for intravenous administration; do not administer DEFINITY by intra-arterial injection [see Dosage and Administration (2.1)].

5.4 Ventricular Arrhythmia Related to High Mechanical Index

High ultrasound mechanical index values may cause microsphere cavitation or rupture and lead to ventricular arrhythmias. Additionally, end-systolic triggering with high mechanical indices has been reported to cause ventricular arrhythmias. DEFINITY is not recommended for use at mechanical indices greater than 0.8 [see Dosage and Administration (2)].

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:
- Serious Cardiopulmonary Reactions [see Warnings and Precautions (5.1)]
- Hypersensitivity Reactions [see Warnings and Precautions (5.2)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 1716 subjects were evaluated in pre-marketing clinical trials of activated DEFINITY. In this group, 1063 (61.9%) were male and 653 (38.1%) were female, 1329 (77.4%) were White, 258 (15.0%) were Black, 74 (4.3%) 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 1). There were 25 serious adverse events and 15 (0.9%) subjects discontinued because of an adverse event.

Serious Adverse Reactions

Among the 1716 study patients, 19 (1.1%) suffered serious cardiopulmonary adverse reactions.

For all adverse reactions, the overall incidence of adverse events was similar for bolus and infusion dosing. Table 1 summarizes the adverse reactions.

Table 1 New-Onset Adverse Reactions Occurring in ≥0.5% of All DEFINITY-Treated Subjects

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DEFINITY (N=1716)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Adverse Reactions</td>
<td>269</td>
</tr>
<tr>
<td>Total Number of Subjects with an Adverse Reaction</td>
<td>144 (8.4%)</td>
</tr>
</tbody>
</table>

Body System

<table>
<thead>
<tr>
<th>Body System</th>
<th>Preferred Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application Site Disorders</td>
<td>11 (0.6)</td>
</tr>
<tr>
<td>Injection Site Reactions</td>
<td>11 (0.6)</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>41 (2.4)</td>
</tr>
<tr>
<td>Back/renal pain</td>
<td>20 (1.2)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>13 (0.8)</td>
</tr>
<tr>
<td>Central and peripheral nervous system disorder</td>
<td>54 (3.1)</td>
</tr>
<tr>
<td>Headache</td>
<td>40 (2.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>41 (0.6)</td>
</tr>
<tr>
<td>Gastrointestinal system</td>
<td>31 (1.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>17 (1.0)</td>
</tr>
<tr>
<td>Vascular (extracardiac) disorders</td>
<td>19 (1.1)</td>
</tr>
<tr>
<td>Flushing</td>
<td>19 (1.1)</td>
</tr>
</tbody>
</table>

N=Sample size 1716 subjects who received activated DEFINITY
n=Number of subjects reporting at least one Adverse Reaction

Other adverse reactions that occurred in ≥0.5% of the activated DEFINITY-dosed subjects were:

- **Body as a Whole**: Fatigue, fever, hot flushes, pain, rigors, and syncope
- **Cardiovascular**: Abnormal ECGs, bradycardia, tachycardia, palpitation, hypertension and hypotension
- **Digestive**: Dyspepsia, dry mouth, tongue disorder, toothache, abdominal pain, diarrhoea and vomiting
- **Hematology**: Granulocytopenia, leucopenia, leucocytopenia, and eosinophilia
- **Musculoskeletal**: Arthralgia
- **Nervous System**: Leg cramps, hypotension, vertigo and paresthesia
- **Platelet, Bleeding, and Clotting**: Hematoma
- **Respiratory**: Coughing, hypoxia, pharyngitis, rhinitis and dysphonia
- **Special Senses**: Decreased hearing, conjunctivitis, abnormal vision and taste perversion
- **Skin**: Pruritus, rash, erythematous rash, urticaria, increased sweating, and dry skin
- **Urinary**: Albuminuria

6.2 Postmarketing Experience

In a prospective, multicenter, open-label registry of 1053 patients treated with DEFINITY 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 perflutren-containing microsphere products. 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.

Fatality cardiopulmonary and hypersensitivity reactions and other serious but non-fatal adverse reactions were uncommonly reported. These reactions typically occurred within 30 minutes of DEFINITY administration. These serious reactions may be increased among patients with unstable cardiopulmonary 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:

- **Cardiopulmonary**: Fatel cardiac or respiratory arrest, shock, syncope, symptomatic anaphylaxis DEFINITY administration, bradyarrhythmia, supraventricular tachycardia, ventricular fibrillation, ventricular tachycardia, hypotension, hypertension, dyspnea, hypoxia, chest pain, respiratory distress, stridor, wheezing.
- **Hypersensitivity**: Anaphylactic reaction, anaphylactic shock, bronchospasm, throat tightness, angioedema, edema (pharyngeal, palatal, mouth, peripheral, localized), swelling (face, eye, lip, tongue, upper airway), facial hypoaesthesia, rash, urticaria, pruritus, flushing, erythema.
- **Neurologic**: Coma, loss of consciousness, convulsion, seizure, transient ischemic attack, agitation, tremor, vision blurred, dizziness, headache, fatigue.
- **8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from case reports with DEFINITY use in pregnant rats and rabbits during organogenesis at doses up to 10 and 16 times, respectively, the maximum human dose based on body surface area (see Data). All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in
After activating the contents of the vial in a VIALMIX, each mL of the milky white suspension contains a maximum of 1.2 x 10^8 perfluor lipid microspheres, and about 150 microL/mL (1.1 mg/mL) of octafluoropropane. The microsphere particle size parameters are listed in Table 2 below:

### Table 2 Microsphere Size Distribution

<table>
<thead>
<tr>
<th>Mean diameter range</th>
<th>Microsphere particle size parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 µm – 3.5 µm</td>
<td>1.1 µm – 3.5 µm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percent less than 10 µm</th>
<th>98%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum diameter</td>
<td>20 µm</td>
</tr>
</tbody>
</table>

### 12 CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

Perfluor lipid microspheres exhibit lower acoustic impedance than blood and enhance the intrinsic backscatter of blood. These physical acoustic properties of activated DEFINITY provide contrast enhancement of the left ventricular chamber and aid delineation of the left ventricular endocardial border during echocardiography.

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.

#### 12.3 Pharmacokinetics

Human pharmacokinetics information is not available for the intact or degassed lipid microspheres. The pharmacokinetics of octafluoropropane gas (OFP) was evaluated in healthy subjects (n=8) after the IV administration of activated DEFINITY at a 50 microL/kg dose.

**Distribution**

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) was 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.

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

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Studies with activated DEFINITY have not been performed to evaluate carcinogenic potential. Evidence of genotoxicity was not found in the following studies with activated DEFINITY: 1) bacterial mutagenesis assay (Ames assay), 2) in vitro mammalian mutagenesis assay, 3) in vivo human lymphocyte chromosome aberration assay, and 4) in vivo rat micronucleus assay.

Impairment of male or female fertility was not observed in rats and rabbits treated with activated DEFINITY at doses up to 24 and 15 microL/kg, respectively.

#### 14 CLINICAL STUDIES

#### 14.1 Echocardiography

A total of 249 subjects were evaluated in clinical trials (208 received activated DEFINITY and 41 placebo). In this group, 154 (61.8%) were male and 95 (38.2%) were female; 183 (73.5%) were aged at or below a mechanical index of 0.8.

Activated DEFINITY was evaluated in four controlled clinical trials. Two open-label baseline controlled, unpaired blinded image evaluation studies and two identical placebo-controlled, unpaired blinded image evaluation studies. Subjects were eligible for these studies if they had two or more (of six) non-evaluable segments in the apical 2- or 4-chamber view in 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 activated DEFINITY. 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 1:2 ratio to receive two IV bolus doses of either saline (placebo) or activated DEFINITY 10 microL/kg (17 placebo vs. 56 activated DEFINITY patients, respectively). The outcome measure for assessing the effect of activated DEFINITY was the blinded assessment of improvement in ventricular chamber enhancement (measured by videodensitometry at end-diastole and end-systole).

**Endocardial Border Length**

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

**Ventricular Chamber Enhancement**

Left ventricular chamber enhancement after an activated DEFINITY dose of 10 microL/kg was significantly increased from baseline compared 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.

**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 DEFINITY 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 to 37% of the patients, depending on the reader, activated DEFINITY was found to obscure the wall motion rendering the image non-evaluable.

**Ejection Fraction**

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

### Table 3 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>Study A: N = 67</th>
<th>Study B: N = 59</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apical 2-chamber</td>
<td>Baseline</td>
<td>Post-DEFINITY</td>
</tr>
<tr>
<td>Mean(SD) at End-Diastole</td>
<td>8.0(3.4)</td>
<td>4.7(2.8)</td>
</tr>
<tr>
<td>Mean(SD) at End-Systole</td>
<td>6.8(3.3)</td>
<td>4.5(2.7)</td>
</tr>
<tr>
<td>Apical 4-chamber</td>
<td>Baseline</td>
<td>Post-DEFINITY</td>
</tr>
<tr>
<td>Mean(SD) at End-Diastole</td>
<td>13.5(2.5)</td>
<td>6.8(3.1)</td>
</tr>
<tr>
<td>Mean(SD) at End-Systole</td>
<td>11.5(4.6)</td>
<td>4.3(2.6)</td>
</tr>
</tbody>
</table>

**Notes:**
- Significant change from baseline (paired t-test, p<0.05)
- Activated DEFINITY Bolus Dose = 10 µL/kg

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

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

### 14.2 Pulmonary Hemodynamic Effects

The impact of DEFINITY 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 this 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 DEFINITY on visualization of cardiac or pulmonary structures.

### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 16.1 How Supplied

DEFINITY 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.

- One (1) 2mL vial - NDC (11994-011-01)
- Four (4) 2mL vials per kit - NDC (11994-011-04)
- Sixteen (16) 2mL vials per kit - NDC (11994-011-16)

**Storage and Handling**

Store between 2-8°C (36°-46°F).

### 17 PATIENT COUNSELING INFORMATION

Advise patients to inform their healthcare provider if they develop any symptoms of hypersensitivity after DEFINITY administration, including rash, wheezing, or shortness of breath.