DEFINITY is a 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.

-------- DOSEAGE AND ADMINISTRATION --------
DEFINITY may be injected by either an intravenous (IV) bolus or infusion. The maximum dose is either two bolus doses or single intravenous infusion.

The recommended bolus dose for activated DEFINITY is 10 microL/kg of the activated product by intravenous bolus injection within 30 to 60 seconds, followed by a 10 mL saline flush. If necessary, a second 10 microL/kg of dose followed by a second 10 mL saline flush may be administered 30 minutes after the first injection to prolong contrast enhancement. The recommended infusion 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 mL/minute, but titrated as necessary to achieve optimal image enhancement, not to exceed 10 mL/minute.

-------- DOSEAGE FORMS AND STRENGTHS --------
DEFINITY is supplied as a single use 2 mL clear glass vial or RFID-tagged 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 lipid microsphere or its components.

-------- WARNINGS AND PRECAUTIONS --------
Serious cardioluminary 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 contraindicates DEFINITY administration (4).
- Always have resuscitation equipment and trained personnel readily available.

Full Prescribing Information

--- INDICATIONS AND USAGE ---
Activated DEFINITY (Perflutren Lipid Microsphere) Injectable Suspension, for intravenous use

1 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.

2 DOSAGE AND ADMINISTRATION
2.1 Important Administration Instructions
DEFINITY is intended for administration only after activation in the VIALMIX apparatus. Before injection, this product must be activated and prepared according to the instructions outlined below. The VIALMIX apparatus should be obtained from Lantheus Medical Imaging, 331 Treble Cove Road, North Billerica, MA, 01862. For customer orders call 1-800-299-3431. DEFINITY may be injected by either an intravenous (IV) bolus or infusion. Do not administer DEFINITY by intra-arterial injection (See Warnings and Precautions (5.8)).

2.2 Dosage

Bolus
The recommended bolus dose for activated DEFINITY is 10 microL/kg of the activated product by intravenous bolus injection within 30 to 60 seconds, followed by a 10 mL saline flush. If necessary, a second 10 microL/kg dose followed by a second 10 mL saline flush may be administered 30 minutes after the first injection to prolong contrast enhancement.

Infusion
The recommended infusion 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 mL/minute, but titrated as necessary to achieve optimal image enhancement, not to exceed 10 mL/minute.

2.3 Imaging Guidelines
After baseline non-contrast echocardiography is completed, set the mechanical index for the ultrasound device at 0.8 or below (see Warnings and Precautions (5.4)). Then inject activated DEFINITY (as described above) and begin ultrasound imaging immediately. Evaluate the activated DEFINITY echocardiogram images in combination with the non-contrast echocardiogram images.

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 the continuous infusion of 1.3 mL activated DEFINITY in 50 mL saline at a rate of 4 mL/minute.

2.4 DEFINITY Activation, Preparation and Handling Instructions
Follow directions for activation of DEFINITY carefully and adhere to strict aseptic procedures during preparation.

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 DEFINITY RFID device.
3. Immediately after activation in the VIALMIX or VIALMIX RFID, activated DEFINITY appears as a milky white suspension.
4. Invert the vial and withdraw the activated DEF
5. Use the product immediately after its withdrawal from the vial; do not allow the product to stand in the syringe.

Special instructions for the DEFINITY Radio Frequency Identification (RFID)-Tagged Vial
This information is for vials containing DEFINITY that have been labeled with a Radio Frequency Identification (RFID) tag. Full instructions for use of VIALMIX RFID are provided on the VIALMIX RFID screen and User's Guide.

- The RFID tag allows for the exchange of product information such as activation time and activation rate.
- VIALMIX RFID will only activate DEFINITY RFID-tagged vials. Function of the RFID technology is not dependent on vial orientation as it is placed in the VIALMIX RFID. If the RFID tag is damaged or otherwise non-functional, the VIALMIX RFID will notify the user and the vial with DEFINITY will not activate. Only use a functioning DEFINITY vial with VIALMIX RFID. Discard the non-functional RFID-tagged DEFINITY vial.
- Follow all manufacturers’ guidelines and do not operate any part of the VIALMIX RFID and DEFINITY RFID-tagged vials within 6 inches (15 cm) of a pacemaker and/or defibrillator.

3 DOSAGE FORMS AND STRENGTHS
DEFINITY is supplied as a single use 2 mL clear glass vial or RFID-tagged vial containing clear liquid in packages of four (4) and sixteen (16) single-use vials.

Prior to activation, the headspace of each vial contains 6.52 mg/octafluoropropane and the clear liquid contains 0.75mg/mL of perflutren lipid microspheres, and about 150 microL/mL of water. After activation, each vial contains a maximum of 1.2 X 10^10 perflutren lipid microspheres, and about 150 microL/mL of octafluoropropane [see Description (11)].

4 CONTRAINDICATIONS
Do not administer DEFINITY to patients with known or suspected: Hypersensitivity to perflutren lipid microsphere or its components [see Warnings and Precautions (5) and Description (11)].
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 myocardial infarction, acute coronary artery syndromes, worsening or unstable congestive heart failure, or severe 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 (5)).

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 hypertonia, rash, urticaria, pruritus, flushing, and erythema have occurred in patients with no prior exposure to perflutren-containing microsphere products, in particular, patients with an allergic reaction(s) to polyethylene glycol [see Adverse Reactions (8) and Description (1)]. 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 syndromes, worsening or unstable congestive heart failure, or serious ventricular arrhythmias. 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-market clinical trials. DEFINITY was administered intravenously to rabbits at doses of 0.1, 0.3, and 1.0 mL/kg (approximately 0.8, 2.4, and 8 times the recommended maximum human dose based on body surface area); DEFINITY was administered intravenously to rats from day 6 to day 17 of gestation. DEFINITY was administered intravenously to rabbits at doses of 0.1, 0.3, and 1.0 mL/kg (approximately, 1.6, 4.8, and 16 times the recommended maximum human dose based on body surface area); DEFINITY doses were administered daily from the 7th to 17th day of gestation. No significant findings on the fetuses were observed.

6.2 Postmarketing Experience

In a prospective, multicenter, open-label registry of 1053 patients receiving DEFINITY in routine clinical practice, heart rate, respiratory rate, and pulse were observed after administration of DEFINITY. 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 under 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.

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 experiences was similar for 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 bolus and infusion dosing. Table 1 summarizes the most common adverse reactions.

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

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

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>n (%)</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>Bodily 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>11 (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, and diarrhea
- Hematologic: Granulocytosis, leukocytosis, leukaemia, and eosinophilia
- Musculoskeletal: Arthralgia
- Nervous System: Leg cramps, hypnnesia, vertigo and paresthesia
- Platelet, Bleeding, and Clotting: Hematoma
- Respiratory: Coughing, hypoxia, pharyngitis, rhinitis and dyspnea
- Special Senses: Decreased hearing, conjunctivitis, abnormal vision and taste perversion
- Skin: Pruritis, rash, erythematous rash, urticaria, increased sweating, and dry skin
- Urinary: Albuminuria

6.3 Laboratory Tests

Serious laboratory abnormalities that were uncommon during the clinical trials and postmarketing experience include:

- Hematologic:
  - Anemia
  - Leukocytosis
  - Leukopenia
  - Lymphopenia
- Hematology:
  - Decreased hematocrit
  - Decreased hemoglobin
  - Increased platelet count
  - Increased white blood cell count

6.4 Other Adverse Reactions

Other adverse reactions that occurred in ≤0.5% of the activated DEFINITY have not been classified as other racial or ethnic groups. The mean age of patients was 65 years. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experiences has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

11 DESCRIPTION

DEFINITY (Perflutren Lipid Microsphere) Injectable Suspension is an ultrasonic contrast agent. The DEFINITY vial contains components that upon activation yield perflutren lipid microspheres. The vial contains a clear, colorless, sterile, non-pyrogenic, hyperosmotic solution that contains perflutren lipid microspheres. 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 use, 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 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experiences has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

11 DESCRIPTION

DEFINITY (Perflutren Lipid Microsphere) Injectable Suspension is an ultrasonic contrast agent. The DEFINITY vial contains components that upon activation yield perflutren lipid microspheres. The vial contains a clear, colorless, sterile, non-pyrogenic, hyperosmotic solution that contains perflutren lipid microspheres. The safety and effectiveness of activated DEFINITY have been established by intravenous injection.

The perflutren lipid microspheres are composed of octafluoropropane encapsulated in an outer lipid shell consisting of (R) – hexadecanoyl acid, 1-[(phosphonyloxy)methyl]-1,2-ethanediyl ester, monosodium salt (abbreviated DPPA); (R) – 4-hydroxy-N,N,N-trimethyl-10-oxo-7-[1-[(oxo-1-oxo-4-oxa-5-panoencapsulated] 1-aminooxy, 4-oxime, inner salt (abbreviated DPPP); and (R)-[(4-hydroxy-6-oxo-9-[1-[(oxo-1-oxo-4-oxa-5-panoencapsulated] 2-oxo-4-oxime, inner salt, sodium salt, common from D(50)-N-(methoxypolyethylene glycol) 5000 carboxamido-1,2-dipalmitylsn-glyco-3-phosphatidylethanolamine, monosodium salt (abbreviated MPEG5000 DPPE).
Octafluoropropane is chemically characterized as 1,1,1,2,2,3,3,3-octafluoropropane. It has a molecular weight of 188, empirical formula of C₈F₂₀ and has the following structural formula:

\[ \text{C}_8\text{F}_{20} \]

DPPA has a molecular weight of 670, empirical formula of C₉H₈NO₃P, and has the following structural formula:

\[ \text{C}_9\text{H}_8\text{NO}_3\text{P} \]

DPPC has a molecular weight of 734, empirical formula of C₁₁H₁₀NO₄P, and has the following structural formula:

\[ \text{C}_{11}\text{H}_{10}\text{NO}_4\text{P} \]

MPEG5000 DPPE has an approximate molecular weight of 5750 represented by empirical formula C₉H₁₀NO₃P, contains <100ppm Ca²⁺ and Mg²⁺ and has the following structural formula:

\[ \text{C}_9\text{H}_{10}\text{NO}_3\text{P} \]

Prior to activation, the DEFINITY vial contains 6.52 mg/mL octafluoropropane in the headspace which was required to be confirmed by positive IR spectroscopic testing in every vial. Each mL of the clear liquid contains 0.75 mg lipid blend (consisting of 0.045 mg DPPA, 0.401 mg DPPC, and 0.304 mg MPEG5000 DPPE), 103.5 mg propylene glycol, 126.2 mg glycerin, 2.34 mg sodium phosphate monobasic monohydrate, 2.16 mg sodium phosphate dibasic heptahydrate, and 4.87 mg sodium chloride in Water for Injection. The pH is 6.2-6.8. DEFINITY does not contain bacterial preservative.

After activating the contents of the DEFINITY vial, each mL of the milky white suspension contains a maximum of 1.2 X 10¹⁰ perfluorooctyl butyrate, with the exception of the 4-chamber view.

The microsphere particle size parameters are listed in Table 2 below:

<table>
<thead>
<tr>
<th>Microsphere Size Distribution</th>
<th>Mean diameter range</th>
<th>Percent less than 10 µm</th>
<th>Maximum diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.1 µm - 3.3 µm</td>
<td>96%</td>
<td>20 µm</td>
</tr>
</tbody>
</table>

### 12 CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

Perflutren 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 echocardiographic studies. 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.

#### 12.2 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 µmol/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 mutagenicity assay (Ames assay), 2) in vitro mammalian mutagenicity assay, 3) in vitro 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 13 times the human dose based on body surface area (in rats and rabbits 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 White, 38 (15.3%) were Black, 21 (8.4%) were Hispanic, and 7 (2.8%) were classified as other racial or ethnic groups. The mean age was 53.8 years (range 18 to 67).

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 either 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 µmol/kg activated DEFINITY. In these studies, the outcome measures 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 µmol/kg (17 placebo vs. 33 activated DEFINITY patients and 24 placebo vs. 49 activated DEFINITY patients, respectively). The outcome measure for determination of the effectiveness 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 µmol/kg of activated DEFINITY 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-systole was statistically significant for all readers in the apical 4-chamber view and for 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 in 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 µmol/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, 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 in 58 to 99% 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, 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.