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331 Treble Cove Road
N. Billerica, Massachusetts 01862
USA

DEFINITY®

VIAL FOR (Perflutren Lipid Microsphere)

INJECTABLE SUSPENSION

FOR INTRAVENOUS USE

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all of the information needed to use DEFINITY® safely and effectively. See full prescribing information for DEFINITY®.

DEFINITY® (Perflutren Lipid Microsphere) Injectable Suspension

Initial U.S. Approval: 2001

WARNING: SERIOUS CARDIOPULMONARY REACTIONS	
<i>See full prescribing information for complete boxed warning</i>	
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.	
<ul style="list-style-type: none"> Assess all patients for the presence of any condition that precludes DEFINITY® administration (4). Always have resuscitation equipment and trained personnel readily available. 	

RECENT MAJOR CHANGES

BOXED WARNING	OCTOBER/2011
INDICATIONS AND USAGE (1)	OCTOBER/2011
WARNINGS AND PRECAUTIONS (5)	OCTOBER/2011

INDICATIONS AND USAGE

DEFINITY® is an ultrasound 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 (microL)/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 (microL)/kg 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 4.0 mL/minute, but titrated 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. Each package contains four (4) single-use vials.

CONTRAINDICATIONS

Do not administer DEFINITY® to patients with known or suspected:

- Right-to-left, bi-directional, or transient right-to-left cardiac shunts,
- Hypersensitivity to perflutren.

Do not administer DEFINITY® by intra-arterial injection.

WARNINGS AND PRECAUTIONS

- Serious cardiopulmonary reactions, including fatalities, have occurred during or following perflutren-containing microsphere administration.
- Serious acute anaphylactoid reactions have occurred in patients with no prior exposure to perflutren-containing microsphere products (5, 6).

Assess all patients for the presence of any condition that precludes DEFINITY® administration (4). 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 (6).

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.

DRUG INTERACTIONS

Specific drug-drug interactions have not been studied.

USE IN SPECIFIC POPULATIONS

Pediatric use: Safety and effectiveness not established (8.4).

See 17 for Patient Counseling Information.

FULL PRESCRIBING INFORMATION: CONTENTS*

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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 [See WARNINGS AND PRECAUTIONS (5.1)]. Most serious reactions occur within 30 minutes of administration.	
<ul style="list-style-type: none"> 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. 	

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

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 ordered 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. The maximum dose is either two bolus doses or one single intravenous infusion. The safety of bolus and infusion dosing in combination or in sequence, has not been studied.

2.1 Bolus

The recommended bolus dose for activated DEFINITY® is 10 microliters (microL)/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 (microL)/kg dose followed by a second 10 mL saline flush may be administered 30 minutes after the first injection to prolong contrast enhancement.

2.2 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 4.0 mL/minute, but titrated as necessary to achieve optimal image enhancement, not to exceed 10 mL/minute.

2.3 Imaging

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/min.

2.4 DEFINITY® Activation, Preparation and Handling Instructions

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

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

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

Do not use this drug unless it has completed a full 45 second activation cycle in the VIALMIX®. DEFINITY® will not be properly activated unless the full 45 second activation cycle is completed. Do not reactivate the vial if VIALMIX® did not complete a full 45 second cycle. Do not reactivate 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.

- Immediately after activation in the VIALMIX®, activated DEFINITY® appears as a milky white suspension and may be used immediately after activation. If the product is not used within 5 minutes of VIALMIX® activation, the microspheres should be resuspended by 10 seconds of hand agitation by inverting the vial before the product is withdrawn in a syringe. The activated DEFINITY® may be used for up to 12 hours from the time of VIALMIX®, but only after the microspheres are resuspended by hand agitation. Store the activated DEFINITY® at room temperature in the original product vial.

- Invert the vial and withdraw the activated milky white suspension using the Intellipin™ (Dispensing Pin) or 18 to 20 gauge syringe needle. Withdraw the material from the middle of the liquid in the inverted vial. Do not inject air into the DEFINITY® VIAL.

- Use the product immediately after its withdrawal from the vial; do not allow the product to stand in the syringe.

For single use only: DEFINITY® 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 DEFINITY® carefully and to adhere to strict aseptic procedures during preparation.

3. DOSAGE FORMS AND STRENGTHS

DEFINITY® is supplied as a single use 2-mL clear glass vial containing a clear liquid. Each package contains four (4) single-use vials.

Prior to activation, the headspace of each vial contains 6.52 mg/mL octafluoropropane and the clear liquid contains 0.75mg/mL of a lipid blend. After activation, each vial contains a maximum of 1.2 X 10¹⁵ perflutren lipid microspheres, and about 150 microL/mL (1.1 mg/mL) octafluoropropane [see DESCRIPTION (11)].

4. CONTRAINDICATIONS

Do not administer DEFINITY® to patients with known or suspected:

- Right-to-left, bi-directional, or transient right-to-left cardiac shunts,
- Hypersensitivity to perflutren [see WARNINGS AND PRECAUTIONS (5)].

Do not administer DEFINITY® by intra-arterial injection.

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 myocardial infarction, acute coronary artery syndromes, worsening 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 Anaphylactoid Reactions:

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

Shock, hypersensitivity, bronchospasm, throat tightness, angioedema, edema (pharyngeal, palatal, mouth, peripheral, localized), swelling (face, eye, lip, tongue, upper airway), facial hypoesthesia, rash, urticaria, pruritus, flushing, and erythema have occurred in patients with no prior exposure to perflutren-containing microsphere products [see ADVERSE REACTIONS (6)].

5.3 Systemic Embolization of DEFINITY® in Patients with Cardiac Shunts:

In patients with right-to-left, bi-directional, or transient right-to-left cardiac shunts phospholipid-encapsulated microspheres can bypass the pulmonary particle-filtering mechanisms and directly enter the arterial circulation resulting in microvascular occlusion and ischemia. In an animal study utilizing intra-arterial administration of activated DEFINITY®, microsphere trapping was seen in small arterioles <15 µm, especially at branch points and in capillaries at all doses tested, including doses directly applicable to those used in humans. An animal study utilizing intravenous administration did not result in arterial microvascular obstruction presumably because of filtering by the lungs. Do not administer DEFINITY® by intra-arterial injection [see CONTRAINDICATIONS (4)].

5.4 High Ultrasound 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. The safety of activated DEFINITY® at mechanical indices greater than 0.8 has not been evaluated [see DOSAGE AND ADMINISTRATION (2)]. The safety of activated DEFINITY® with the use of end-systolic triggering has not been evaluated.

5.5 QTc Prolongation:

ECG parameters for doses up to 10 microL/kg 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 64 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 activated DEFINITY®. In this group, 1063 (61.9%) were male and 653 (38.1%) were female, 1328 (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 6.1). There were 26 serious adverse events and 15 (0.9%) subjects discontinued because of an adverse event.

Deaths and Serious Adverse Events

Among the 1716 activated DEFINITY® patients, 19 (1.1%) suffered serious cardiopulmonary adverse events including eight deaths. The deaths occurred several days after activated DEFINITY® administration and appeared to be related to the course of underlying disease. Of the 11 other serious adverse events, which appeared within 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, dyspnea 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 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 6.1 summarizes the most common adverse reactions.

Table 6.1. New-Onset Adverse Reactions Occurring in ≥0.5% of All Activated DEFINITY®-Treated Subjects		
	All activated DEFINITY® (N=1716)	
Total Number of Adverse Reactions	269	
Total Number of Subjects with an Adverse Reaction	144	(8.4%)
Body system		
Preferred term	n	(%)
Application Site Disorders	11	(0.6)
Injection Site Reactions	11	(0.6)
Body as a Whole		
Back/renal pain	41	(2.4)
Chest pain	20	(1.2)
	13	(0.8)
Central and peripheral nervous system disorder		
Headache	54	(3.1)
Dizziness	40	(2.3)
	11	(0.6)
Gastrointestinal system		
Nausea	31	(1.8)
	17	(1.0)
Vascular (extracardiac) disorders		
Flushing	19	(1.1)
	19	(1.1)
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, diarrhea and vomiting

Hematology: Granulocytosis, leukocytosis, leukopenia, and eosinophilia

Musculoskeletal: Arthralgia

Nervous System: Leg cramps, hypertonia, 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: 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 receiving 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.

Fatal cardiopulmonary and anaphylactoid events and other serious but non-fatal adverse reactions were uncommonly reported. These events typically occurred within 30 minutes of DEFINITY® administration. These serious events 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

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.

Anaphylactoid

Anaphylactic/anaphylactoid reaction, anaphylactic shock, hypersensitivity, bronchospasm, throat tightness, angioedema, edema (pharyngeal, palatal, mouth, peripheral, localized), swelling (face, eye, lip, tongue, upper airway), facial hypoesthesia, rash, urticaria, pruritus, flushing, erythema.

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.

8.3 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 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between 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) and WARNINGS AND PRECAUTIONS (5)].

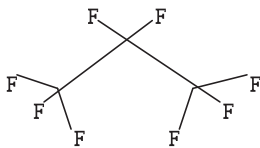
11 DESCRIPTION

DEFINITY® (Perflutren Lipid Microsphere) Injectable Suspension is an ultrasound contrast agent. The DEFINITY® vial contains components that upon activation yield perflutren 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, non-pyrogenic, hypertonic liquid, which upon activation with the aid of a VIALMIX®, provides a homogeneous, opaque, milky white injectable suspension of perflutren lipid microspheres. The suspension of activated DEFINITY® is administered by intravenous injection.

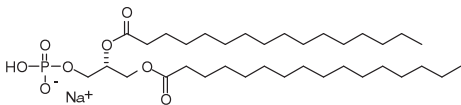
The perflutren lipid microspheres are composed of octafluoropropane encapsulated in an outer lipid shell consisting of (R) – hexadecanoic acid, 1-[[[phosphonoxy]methyl]-1,2-ethanediyl] ester, monosodium salt (abbreviated DPPA); (R) – 4-hydroxy-N,N,N-trimethyl-10-oxo-7-[[1-(oxohexadecyl)oxy]-3,4,9-trioxo-4-phosphapentacosan-1-aminium, 4-oxide, inner salt (abbreviated DPPE); and (R) – α -[6-hydroxy-6-oxido-9-[[1-(oxohexadecyl)oxy]-5,7,11-trioxo-2-aza-6-phosphahexacos-1-yl]- ω -methoxypropyl(ox-1,2-ethanediyl), monosodium salt (abbreviated MPEG5000 DPPE).

Revised: October, 2011

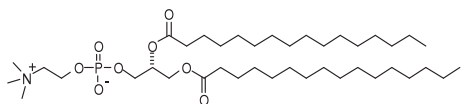
Octafluoropropane is chemically characterized as 1,1,1,2,2,3,3,3-octafluoropropane. It has a molecular weight of 188, empirical formula of C₃F₈ and has the following structural formula:



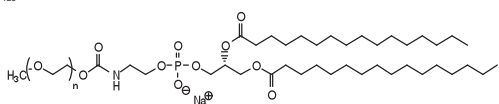
DPPA has a molecular weight of 670, empirical formula of C₃₅H₅₈O₈PNa, and following structural formula:



DPPC has a molecular weight of 734, empirical formula of C₄₀H₈₀NO₈P, and following structural formula:



MPEG5000 DPPE has an approximate molecular weight of 5750 represented by empirical formula C₂₆₅H₅₂₇NO₁₂₃PNa, and the following structural formula:



Prior to VIALMIX[®] activation, the DEFINITY[®] vial contains 6.52 mg/mL octafluoropropane in the headspace. 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.

After activating the contents of the vial in a VIALMIX[®], each mL of the milky white suspension contains a maximum of 1.2 X 10¹⁰ perflutren lipid microspheres, and about 150 microL/mL (1.1 mg/mL) octafluoropropane. The microsphere particle size parameters are listed in Table 11.1 below:

Table 11.1. Microsphere Size Distribution

	Microsphere particle size parameters
Mean diameter range	1.1 µm – 3.3 µm
Percent less than 10 µm	98%
Maximum diameter	20 µm

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 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.

12.2 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 microL/kg dose.

12.2.1 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.

12.2.2 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.

12.2.3 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.

12.2.4 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 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 15 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 53.9 years (range 18 to 87).

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 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 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. 33 activated DEFINITY[®] patients and 24 placebo vs. 49 activated DEFINITY[®] patients, respectively). The outcome measure for assessing the effectiveness of activated DEFINITY[®] was the blinded assessment of improvement in ventricular chamber enhancement (measured by videodensitometry 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 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 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 4 readers for the apical 2-chamber view.

14.1.2 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.

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 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.

14.1.4 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 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

Study/View	Endocardial Border Length – Blinded Read			
	Mean(SD) at End-Diastole		Mean(SD) at End-Systole	
	Reader 1	Reader 2	Reader 1	Reader 2
Study A: (N = 67)				
Apical 2-chamber				
Baseline	8.0(3.4)	4.7(2.8)	7.1(3.3)	4.3(2.6)
Post-DEFINITY [®]	12.8(5.2)*	5.8(2.6)*	10.6(5.0)*	4.4(2.3)
Apical 4-chamber				
Baseline	8.1(3.3)	4.5(2.6)	7.6(3.2)	4.5(2.7)
Post-DEFINITY [®]	13.5(5.2)*	6.8(3.3)*	11.5(4.4)*	5.3(3.1)
Study B: (N = 59)				
Apical 2-chamber				
Baseline	4.3(2.6)	7.8(5.3)	4.1(2.4)	6.5(5.1)
Post-DEFINITY [®]	5.7(4.7)*	8.2(6.5)	5.5(4.4)*	6.9(6.3)
Apical 4-chamber				
Baseline	4.0(2.7)	9.2(5.9)	3.8(2.6)	7.3(5.6)
Post-DEFINITY [®]	7.1(5.5)*	11.5(7.5)*	5.9(5.3)*	8.7(6.3)*
Activated DEFINITY [®] 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 DEFINITY[®] in 50 mL saline at the rate of 4 mL/min)

dosing 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.

15 REFERENCES

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. Each package (clear plastic clamshell) contains four (4) single-use vials.

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

16.2 Storage and Handling

Store between 2-8°C (36°-46°F).

FOR SINGLE USE ONLY: DEFINITY[®] 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 DEFINITY[®] carefully and to adhere to strict aseptic procedures during preparation.

17 PATIENT COUNSELING INFORMATION

Patients receiving activated DEFINITY[®] 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 DEFINITY[®] [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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