515987-0221

Lantheus Medical Imaging®

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 the information needed to use DEFINITY safely and effectively. See full prescribing information for DEFINITY.

DEFINITY (Perflutren Lipid Microsphere) Injectable Suspension, for intravenous use

Initial U.S. Approval: 2001

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 (5.1).

- **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----------

Dosage and Administration (2.4)	7/2020
Contraindications (4)	4/2021
Warnings and Precautions (5.2)	4/2021

----------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 (1).

----------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 (2.1).

The recommended bolus dose for activated DEFINITY is 10 microliters (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 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).

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 (2.2).

----------DOSAGE FORMS AND STRENGTHS----------

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

----------CONTRAINDICATIONS----------

Do not administer DEFINITY to patients with known or suspected:

Hypersensitivity to perflutren lipid microsphere or its components, such as polyethylene glycol (PEG) (4).

----------WARNINGS AND PRECAUTIONS----------

Serious cardiopulmonary reactions, including fatalities, have occurred during or following perflutren-containing microsphere administration (5.1).

Serious acute hypersensitivity reactions have occurred in patients with no prior exposure to perflutren-containing microsphere products, including patients with prior hypersensitivity reaction(s) to PEG (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 (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*.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 4/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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.

- **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

2.1 Important Administration Instructions

- DEFINITY is intended for administration only after activation in the VIALMIX RFID apparatus. Before injection, this product must be activated and prepared according to the instructions outlined below. The VIALMIX RFID 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. Do not administer DEFINITY by intra-arterial injection *[see Warnings and Precautions (5.3)]*.
- 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.

2.2 Dosage

Bolus

The recommended bolus dose for activated DEFINITY is 10 microliters (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 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.

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/min.

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 VIALMIX device or VIALMIX RFID device.

   Note: illustrations of this procedure are contained in the VIALMIX or VIALMIX RFID User’s Guide.

   Do not use this drug unless it has completed a full 45 second activation cycle in the VIALMIX or VIALMIX RFID. DEFINITY will not be properly activated unless the full 45 second activation cycle is completed. Error messages will display if the vial is not properly activated. Do not reactivate the vial if VIALMIX or VIALMIX RFID did not properly activate the vial. Never reactivate a successfully activated DEFINITY vial (see step 3). A VIALMIX or VIALMIX RFID that is not functioning properly must never be used. Only use a vial activated from a properly functioning VIALMIX or VIALMIX RFID. Refer to the VIALMIX or VIALMIX RFID User’s Guide to ensure that a properly functioning VIALMIX or VIALMIX RFID is used.
3. Immediately after activation in the VIALMIX or VIALMIX RFID, 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 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 activation, but only after the microspheres are resuspended by hand agitation. Store the activated DEFINITY at room temperature in the original product vial.
4. Invert the vial and withdraw the activated milky white suspension using the Intellipin (Dispensing Pin), the PINSYNC (Vented Vial Adapter 13mm), 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.
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 the nonfunctional RFID tag cannot be used to activate DEFINITY with VIALMIX RFID. Discard the nonfunctional RFID-tagged DEFINITY vial.
- Follow all manufacturers’ guidelines and do not operate any part of the VIALMIX RFID with 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 patient use 2 mL clear glass vial or RFID-tagged vial containing a clear liquid in packages of four (4) and sixteen (16) single patient 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 10^{10} 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:

- Hypersensitivity to perflutren lipid microsphere or its components, such as polyethylene glycol (PEG) *[see Warnings and Precautions (5.2) and Description (11)]*.

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 Hypersensitivity Reactions

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

Anaphylaxis, with manifestations that may include death, shock, 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.

These reactions have occurred in patients with no prior exposure to perflutren-containing microsphere products. DEFINITY contains PEG. There may be increased risk of serious reactions including death in patients with prior hypersensitivity reaction(s) to PEG *[see Adverse Reactions (6.2) and Description (11)]*. Clinically assess patients for prior hypersensitivity reactions to products containing PEG, such as certain colonoscopy bowel preparations and laxatives. 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-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 1). There were 26 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 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 1 New-Onset Adverse Reactions Occurring in ≥0.5% of All DEFINITY-Treated Subjects

	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	41	(2.4)
Back/renal pain	20	(1.2)
Chest pain	13	(0.8)
Central and peripheral nervous system disorder	54	(3.1)
Headache	40	(2.3)
Dizziness	11	(0.6)
Gastrointestinal system	31	(1.8)
Nausea	17	(1.0)
Vascular (extracardiac) disorders	19	(1.1)
Flushing	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 and PEG-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 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 pre-existing PEG hypersensitivity and/or 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.

Hypersensitivity

Anaphylaxis, with manifestations that may include death, shock, 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.

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 women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. DEFINITY has a very short half-life; therefore, administration of DEFINITY to a pregnant woman is not expected to result in clinically relevant fetal exposure. No adverse developmental outcomes were observed in animal reproduction studies with administration of activated DEFINITY in pregnant rats and rabbits during organogenesis at doses up to 8 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 clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

DEFINITY was administered intravenously to rats 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 doses were administered daily 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 day 7 to day 19 of gestation. No significant findings on the fetus were observed.

8.2 Lactation

Risk Summary

There are no data on the presence of DEFINITY in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for DEFINITY and any potential adverse effects on the breastfed infant from DEFINITY or from the underlying maternal condition.

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

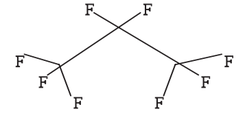
In clinical trials, the overall incidence of adverse reactions was similar for the <65 year age group and the ≥65 year age group. Of the total number of subjects in clinical trials of DEFINITY, 144 (33%) were 65 and over. No overall differences in safety or effectiveness were observed between these subjects 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.

11 DESCRIPTION

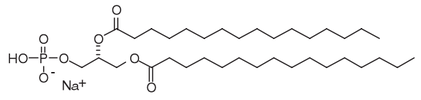
DEFINITY (**P**erflutren Lipid Microsphere**)** Injectable Suspension is an ultrasound contrast agent. The DEFINITY vial contains components that upon activation yield perflutren lipid microspheres. The vial contains a clear, colorless, sterile, non-pyrogenic, hypertonic liquid, which upon activation with the aid of a VIALMIX or VIALMIX RFID, 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-trioxa-4-phosphapentacosan-1-aminium, 4-oxide, inner salt (abbreviated DPPC); and (R)-ω-[6-hydroxy-6-oxido-9-[(1-oxohexadecyl)oxy]-5,7,11-trioxa-2-aza-6-phosphahexacos-1-yl]-ω-methoxypoly(ox-1,2-ethanediyl), monosodium salt; commonly called N-(**m**ethoxy**p**oly**e**thylene **g**lycol **5000** carbamoyl)-1,2-**di**palmitoyl-sn-glycero-3- **p**hosphatidyl**e**thanolamine, monosodium salt (abbreviated MPEG5000 DPPE).

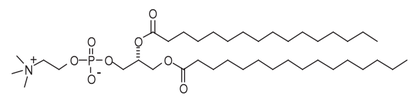
Octafluoropropane is chemically characterized as 1,1,1,2,2,3,3,3-octafluoropropane. It has a molecular weight of 188, empirical formula of C_3F_8 and has the following structural formula:



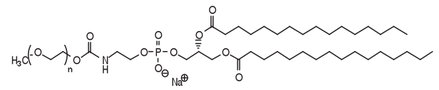
DPPA has a molecular weight of 670, empirical formula of $C_{35}H_{68}O_8PNa$, and following structural formula:



DPPC has a molecular weight of 734, empirical formula of $C_{40}H_{80}NO_8P$, and following structural formula:



MPEG5000 DPPE has an approximate molecular weight of 5750 represented by empirical formula $C_{289}H_{527}NO_{123}PNa$, contains <100ppm Ca+2 and Mg+2 and the following structural formula:



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 10^{10} perflutren lipid microspheres, and about 150 microL/mL (1.1 mg/mL) octafluoropropane. The microsphere particle size parameters are listed in Table 2 below:

Table 2 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.

12.3 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 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).

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 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

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.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DEFINITY is supplied as a single patient use 2 mL clear glass vial or a single patient use 2 mL clear glass Radio Frequency Identification (RFID)-tagged vial containing clear liquid in packages of four (4) and sixteen (16) single patient use vials.

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

16.2 Storage and Handling

Store between 2° to 8°C (36° to 46°F).

Regarding interference with medical devices, the RFID tag and VIALMIX RFID unit meets the IEC 60601-1-2 requirements for emission and immunity standards for medical devices.

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.

Distributed By
Lantheus Medical Imaging
331 Treble Cove Road
N. Billerica, Massachusetts 01862 USA

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