PRODUCT MONOGRAPH

Pr DEFINITY®
(Perflutren Injectable Suspension)

(Injectable Lipid-Encapsulated Perfluoropropane Microbubbles)

Contrast Enhancing Imaging Agent

Manufacturer:
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Distributor:
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Control No.: 142757

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PRODUCT MONOGRAPH

DEFINITY®
(perflutren)
(Lipid-Encapsulated Perfluoropropane Microbubbles, Injectable)
Injectable Suspension

THERAPEUTIC CLASSIFICATION

Contrast Enhancing Imaging Agent
for Echocardiography and Diagnostic Ultrasound of Liver and Kidney

ACTION AND CLINICAL PHARMACOLOGY

DEFINITY® (perflutren injectable suspension) is an ultrasound contrast imaging agent that is designed to improve echocardiographic and radiologic ultrasound image quality by enhancing the echogenicity of the organs/tissues of interest. DEFINITY is a sterile, non-pyrogenic suspension of phospholipid-encapsulated perfluoropropane microbubbles that is activated by shaking with the aid of the Vialmix™, and is used for contrast enhancement during cardiac and abdominal ultrasound imaging procedures.

DEFINITY microbubbles exhibit lower acoustic impedance than blood. Ultrasound waves are scattered and reflected at the microbubble-blood interface and are ultimately visualized in the ultrasound image. At the frequencies used in diagnostic ultrasound (1-7.5 MHz), the microbubbles resonate, further increasing the extent of ultrasound scattering and reflection.

Pharmacokinetics

The pharmacokinetics of the perfluoropropane (PFP) component of activated DEFINITY was studied in 12 normal and 12 chronic obstructive pulmonary disease (COPD) patients following a 50 µL/kg dose. PFP was rapidly cleared from the systemic circulation (via the lungs). PFP was not detectable after 10 minutes in most subjects, either in the blood or expired air. In all subjects, maximal concentrations of PFP were achieved at approximately 1.0 to 2.0 minutes after the start of injection.

Doppler ultrasound measurements were performed with DEFINITY in conjunction with the pharmacokinetic evaluation of PFP. Doppler signal intensity corresponded well with measured and extrapolated PFP concentrations in blood. The time to maximum Doppler signal intensity t_{max} was shown to be similar to the PFP blood t_{max} (1.13 versus 1.77 minutes). The observed 99% drop in Doppler signal intensity within 10 minutes ($t_{½}$ approximately 5 minutes) was in agreement with the decline in measurable blood levels of PFP. Human pharmacokinetic data on the fate of intact or degassed microbubbles is not available.

Metabolism

PFP is a stable gas that is not metabolized. The three lipid components of DEFINITY (DPPA, DPPC and DPPE) are naturally occurring in man as blood lipids. The amount of these lipids in a dose of DEFINITY represent ~1% (DPPE), ~0.02% (DPPC) and ~0.002% (DPPA) of the naturally occurring levels in plasma and are expected to follow similar metabolic pathways as reported for endogenous phospholipids.

INDICATIONS AND CLINICAL USE

Echocardiography

DEFINITY (perflutren injectable suspension) is indicated for contrast-enhanced ultrasound imaging of cardiac structures (ventricular chambers and endocardial borders) and function (regional wall motion) in adult patients with suboptimal echocardiograms.

Abdominal Ultrasound

DEFINITY is also indicated for contrast-enhanced ultrasound imaging of the liver and kidneys in adult patients to improve the evaluation of pathology.

CONTRAINDICATIONS

Do not administer DEFINITY (perflutren injectable suspension) to patients with known:

- Hypersensitivity to DEFINITY or its components (See PHARMACEUTICAL INFORMATION – Composition, WARNINGS - Hypersensitivity Reactions and ADVERSE REACTIONS - Post Market Adverse Drug Reactions).
- Right-to-left, bi-directional, or transient right-to-left cardiac shunts (see WARNINGS-Systemic Embolization).

DEFINITY should not be injected by direct intra-arterial injection (see WARNINGS-Systemic Embolization).

Gas contrast agents, for use in diagnostic ultrasound examinations, should not be administered within 24 hours prior to extracorporeal shock wave lithotripsy.

WARNINGS

WARNING: Serious Cardiopulmonary Reactions

Serious cardiopulmonary reactions, including fatalities, have occurred during or following DEFINITY® administration.

- Assess all patients for the presence of any condition that precludes DEFINITY administration (see CONTRAINDICATIONS).
- Observe patients with unstable cardiopulmonary conditions for at least 30 minutes after DEFINITY administration (see WARNINGS).
- Always have cardiopulmonary resuscitation equipment and trained personnel readily available.

Serious Cardiopulmonary Reactions:

Serious cardiopulmonary reactions, including fatalities, have occurred during or following DEFINITY 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, serious ventricular arrhythmias or respiratory failure, including patients receiving mechanical ventilation). In these patients, observe closely for at least 30 minutes after DEFINITY administration.

DEFINITY should only be administered to such patients after a careful risk/benefit assessment. Assess all patients for the presence of any condition that precludes DEFINITY administration (see CONTRAINDICATIONS).

In the absence of these underlying conditions, observe patients closely during and following DEFINITY administration for at least 30 minutes for potential serious reactions.

In postmarketing use, rare but serious reactions observed during or shortly following DEFINITY administration included fatal cardiac or respiratory arrest, hypotension, hypertension, chest pain, myocardial infarction, cardiac ischemia, syncope, symptomatic arrhythmias (bradycardia, atrial fibrillation, supraventricular tachycardia, ventricular tachycardia or fibrillation), hypoxia, respiratory distress or decreased oxygenation and loss of consciousness or convulsions (see ADVERSE REACTIONS).

Always have cardiopulmonary resuscitation equipment and trained personnel readily available prior to DEFINITY administration and observe all patients for acute reactions. Diagnostic procedures that involve the use of DEFINITY should be carried out under the direction of a physician with appropriate training and a thorough knowledge of the procedure to be performed

The safety of DEFINITY (perflutren injectable suspension) in humans with compromised pulmonary vascular beds or with small cross-sectional vascular area has not been studied

and it should be administered with caution to patients with chronic pulmonary disorders (e.g. severe emphysema, pulmonary vasculitis, or other causes of reduced pulmonary vascular cross-sectional area). In a special trial with a small sample size and a higher (50 μL/kg) than recommended dose of DEFINITY, the incidence of adverse experiences was considerably higher in patients with COPD than in healthy volunteers; dyspnea, dizziness and chest pain occurred in COPD patients but not in healthy subjects. In pooled trials, the overall incidence of adverse experiences was similar in patients with or without a history of COPD.

DEFINITY should also be administered with caution to patients with congestive heart failure (CHF) or arrhythmia. In clinical trials with DEFINITY the incidence of adverse experiences was higher in patients with a history of CHF. Rhythm disorders were only observed among patients with a history of CHF.

In dogs, DEFINITY given at a dose of 1mL/kg (13.5 x maximum human dose based on body surface area) increased the respiratory rate and pulmonary pressure (300% and 188% respectively). One dog died displaying signs consistent with cardiopulmonary collapse. In dogs with artifically induced acute pulmonary hypertension, DEFINITY (tested up to 200 μL/kg) did not alter hemodynamics (includes pulmonary arterial pressure).

Systemic Embolization of DEFINITY in Patients with Cardiac Shunts:
The safety of DEFINITY in patients with right-to-left, bi-directional or transient right-to-left cardiac shunts has not been studied. In these patients, encapsulated microbubbles can bypass the pulmonary particle-filtering mechanisms and directly enter the arterial circulation. In an animal study utilizing intra-arterial administration of DEFINITY, microbubble trapping was seen in small arterioles < 15 μm, especially at branch points and in capillaries at all doses tested (1-6x the maximal human dose based on body surface area). An animal study utilizing an intravenous administration did not result in microvascular obstruction because of presumed filtering by the lungs. Do not administer DEFINITY by intra-arterial injection (see CONTRAINDICATIONS).

Hypersensitivity Reactions
Serious immediate hypersensitivity reactions which could be life threatening have been reported following the administration of DEFINITY, including in patients with prior allergic reaction(s) to polyethylene glycol (see PHARMACEUTICAL INFORMATION - Composition). Therefore, patients should be closely monitored. These reactions include anaphylactoid/anaphylactic reactions, angioedema, shock, bronchospasm, respiratory distress, swelling of the tongue, eyes, face, upper airway and throat, decreased O_2 saturation, and loss of consciousness.

Diagnostic procedures using DEFINITY should be carried out under the direction of a physician experienced in the management of hypersensitivity reactions including severe allergic reactions, which might require resuscitation. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

PRECAUTIONS

General Precaution

Diagnostic procedures that involve the use of intravenous contrast-enhancing agents containing microbubbles of gas should be carried out under the direction of a physician with a prerequisite training and a thorough knowledge of the procedure to be performed in appropriate facilities for conducting diagnostic imaging (see WARNINGS – Serious Cardiopulmonary and Hypersensitivity Reactions).

The recommended dose and mode of administration and procedures for activation of DEFINITY (perflutren injectable suspension) should be strictly adhered to.

DEFINITY should be administered with caution in patients with a history of drug allergies, asthma or hay fever, and multiple allergies.

A specific analysis correlating the mechanical index values (0.3 to 1.9) used in clinical trials with DEFINITY with the observed cardiac disturbances is not available. The safety of DEFINITY at mechanical indices greater than 0.8 has not been established. Users of diagnostic ultrasound devices should employ exposures, in any relevant mode, which are As Low As Reasonably Achievable (ALARA).

Electrocardiographic (ECG) Changes: High Mechanical Index (MI) values may cause microbubble cavitation or rupture and in combination with end systolic triggering may induce premature ventricular contractions (PVC). In addition, end-systolic triggering with high MI has been reported to cause ventricular arrhythmias following administration of a microsphere product. In clinical trials with DEFINITY, the majority of patients were imaged at or below a mechanical index of 0.8. The safety of DEFINITY at MI values greater than 0.8 or with the use of high mechanical index end-systolic triggering has not been established.

A total of 1716 patients received DEFINITY in clinical trials. The incidence of treatment-related cardiovascular events was < 0.5% and included: abnormal ECGs, bradycardia, tachycardia, palpitation, hypertension, and hypotension. Two patients had treatment-related cardiac adverse events and associated QTc changes (1 increase and 1 decrease) of ≥ 30 msec from baseline.

QTc Interval Prolongation: In 610 subjects (568 received DEFINITY and 42 received placebo) during rest echocardiography, ECG parameters after doses up to 40 μL/kg were recorded for up to 72 hours after the first bolus injection. QTc prolongation of =30 msec was noted in 70 (12.3%) DEFINITY treated subjects and in 12 (28.6%) placebo treated subjects. QTc prolongation of >60 msec was noted in 20 (3.5%) DEFINITY treated subjects and 2 (4.8%) placebo treated subjects.

ECG parameters for doses up to 10 μL/kg were monitored in 509 patients in five

placebo-controlled efficacy trials using stress echocardiography (exercise treadmill and pharmacologic stress [dobutamine and dipyridamole]). ECG parameters were assessed at Baseline, 0 to 60 minutes, and 24 hours post-dose. Across all ECG parameters, comparisons of patients in the placebo and DEFINITY groups find only minor differences between the treatment groups except for what would be anticipated by undergoing a treadmill or pharmacologic stress test. There were no significant DEFINITY - related ECG changes in PR, QRS, and QTc intervals. The statistically significant increase of 7.3 (12.55) bpm in RR during the first 60 minutes post-dose is expected during stress testing. In the placebo group, 48.5% of patients had no post-Baseline QTc change ≥30 msec, compared to 50.3% in the DEFINITY group.

Although no serious cardiac symptomatology or mortality attributable to QTc prolongation occurred with DEFINITY treatment in clinical trials, certain predisposing conditions may increase the risk for ventricular arrhythmias.

The effect of DEFINITY on patients with congenital prolongation of the QT interval or on concomitant medications known to cause prolongation of the QT interval has not been studied.

Because of limited clinical experience, DEFINITY should be used with extreme caution and only after careful risk/benefit assessment in patients with ongoing proarrhythmic conditions, previous history of symptomatic arrhythmias, family history of congenital long QT syndrome and on concomitant medications known to cause QTc prolongation. An ECG examination before use of DEFINITY may be appropriate to exclude these conditions.

Use in Pregnancy and Lactation: Results of reproduction toxicity studies in rats and rabbits revealed that DEFINITY in doses up to 1.0 mL/kg (24x and 15x maximal human dose based on body surface area for rats and rabbits, respectively) did not adversely affect fetal growth, survival or morphological development. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, DEFINITY should be used in pregnancy only if potential benefit to the mother justifies the potential risk to the fetus.

It is not known whether DEFINITY is excreted in human milk; therefore, caution should be exercised when DEFINITY is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in the pediatric population below the age of 16 have not been established.

Drug Interactions: Drug-drug interactions with DEFINITY have not been studied.

To assure safe and effective use of DEFINITY, patients should be advised of the following information and instructions when appropriate:

- to inform their physician if they have a congenital heart defect, recent worsening of heart or lung condition, or a prior history of allergic reaction to DEFINITY or other echocardiographic contrast agents
- that DEFINITY may produce changes in the electrocardiogram (QTc interval prolongation)
- that DEFINITY may add to the QTc prolonging effects of other drugs such as cisapride, erythromycin, some antipsychotics, and tricyclic antidepressants
- to inform their physician if they are currently receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents
- to inform their physician of any family history of QTc prolongation or proarrhythmic conditions such as recent hypokalemia, significant bradycardia, acute myocardial ischemia, clinically relevant heart failure with reduced left-ventricular ejection fraction or previous history of symptomatic arrhythmias
- to inform their physician if they are or may be pregnant or nursing
- to inform their physician of any medications they take
- to contact their physician if they experience palpitations or fainting spells after injection of DEFINITY.

ADVERSE REACTIONS

Clinical Trials Experience During Rest

A total of 1716 patients were evaluated in clinical trials of activated DEFINITY (perflutren injectable suspension). 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 (range 18 to 93). Of these, 144 (8.4%) patients had at least one treatment-related adverse reaction (Table 1).

Deaths and serious adverse events: Among the 1716 DEFINITY patients studied, serious adverse events were reported in 30 patients, which included 8 deaths. None of the serious adverse events were considered related to DEFINITY administration. The 8 deaths occurred several days after DEFINITY administration and were attributed to underlying disorders. The other serious adverse events reported were attributed to progression or treatment of underlying disorders.

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 experienced a hypersensitivity reaction with urticaria and pruritis and all the other patients experienced dizziness, chest pain, dyspnea or back pain. Adverse events 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.

Subanalyses by age, gender and race were performed. The overall incidence of AEs was similar for the <65 year age group and the ≥65 year age group, similar in males and in females, and similar among all racial or ethnic groups.

The most frequent adverse events were reported for the Central and Peripheral Nervous System (3.1%), Body as a Whole (2.4%) and Gastrointestinal System (1.8%).

The most frequently occurring treatment-related adverse experiences (AEs) were headache (2.3%), back/renal pain (1.2%), flushing (1.1%), and nausea (1.0%).

The incidence of all treatment-related new-onset adverse experiences occurring in ≥0.5% of all patients in DEFINITY studies are summarized in Table 1.

Table 1
Treatment-Related, New-Onset Adverse Experiences in Clinical Trials
Occurring in ≥0.5% of All Subjects

	PLACEBO		DEFINITY	
	n	**(%)**	**n**	**(%)**
Total Number of Subjects	183		1716	
Total Number of Subjects with an AE	13	(7.1)	144	(8.4)
Application Site Disorders	2	(1.1)	11	(0.6)
Injection Site Reactions	2	(1.1)	11	(0.6)
Body as a Whole - General Disorders	1	(0.5)	41	(2.4)
Back Pain	0	(0.0)	20	(1.2)
Chest Pain	0	(0.0)	13	(0.8)
Central and Peripheral Nervous System Disorders	5	(2.7)	54	(3.1)
Headache	4	(2.2)	40	(2.3)
Dizziness	1	(0.5)	11	(0.6)
Gastrointestinal System	2	(1.1)	31	(1.8)
Nausea	1	(0.5)	17	(1.0)
Vascular (extracardiac) disorders	1	(0.5)	19	(1.1)
Flushing	1	(0.5)	19	(1.1)

AE = Adverse Event n = number of subjects

Although headache was the most frequently reported adverse experience, its incidence was similar to placebo.

Data from clinical trials presented in the safety table has shown that DEFINITY, administered intravenously in the recommended dose as a bolus injection or as an infusion, was safe and well tolerated.

Other treatment-related adverse experiences that occurred in < 0.5% of the DEFINITY-dosed patients 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, monocytosis, 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 and abnormal urine
Laboratory Abnormalities:	Increased bilirubin, AST/SGOT, SGPT/ALT, creatine phosphokinase, LDH, creatinine, glucose and non-protein nitrogen
Miscellaneous:	Lymphadenopathy

Clinical Trials Experience During Stress

A total of 2455 patients were evaluated in clinical trials of activated DEFINITY in stress echocardiography. In this group, 1236 (50.6%) were male and 1208 (49.4%) were female, 1888 (77.2%) were White, 377 (15.4%) were Black/African American, and 176 (7.2%) were classified as other racial or ethnic groups. The mean age was 58.7 years (range 21 to 90). There were 11 serious adverse events and 9/2445 patients (0.4%) discontinued because of an adverse event.

Of the 1866 patients with data on non-serious adverse events, 460 (24.7%) had at least one treatment-related adverse reaction (Table 2). For all adverse events, the overall incidence of adverse events was 21.8% for the <65 year age group and 30.8% for the ≥65 year age group. Incidences of adverse events were higher in males (31.0%) than in females (18.9%). The most common events were headache (0.9%) and back pain (0.5%).

Deaths and Serious Adverse Events:

Among the 2445 DEFINITY patients, there were no deaths and 10 (0.4%) experienced a total of 11 serious adverse events. All of the serious adverse events, which appeared between dosing and 7 days after drug administration, appeared to be a progression of underlying cardiac and non-cardiac disease.

Discontinuations:

There were 9 discontinuations reported. Three patients experienced hypertension, 2 experienced bradycardia, and all other events associated with discontinuation were cardiac arrest, chest pain, fatigue, back disorder, back pain, muscle spasms, headache, syncope, pruritus, or flushing. Adverse events appeared within minutes (3 – 36 min) of DEFINITY administration.

Table 2 Treatment-Related Adverse Events Reported by at Least 0.5% of Patients in Either Treatment Group by Incidence in Placebo-Controlled Stress Echocardiography Efficacy Trials (N [%])

Preferred Term	Placebo Treatment	DMP 115 Treatment
Patients treated	167	344
Patients with any new-onset AE	1 (0.6%)	14 (4.1%)
Headache	0 (0.0%)	8 (2.3%)
Loose stools	0 (0.0%)	3 (0.9%)
Fatigue	1 (0.6%)	1 (0.3%)
Nausea	0 (0.0%)	2 (0.6%)
Dyspnoea	1 (0.6%)	0 (0.0%)

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during the post-approval use of DEFINITY. 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.

In postmarketing use, rare but serious reactions observed during or shortly following DEFINITY administration included fatal cardiac or respiratory arrest, hypotension, hypertension, chest pain, myocardial infarction, cardiac ischemia, syncope, symptomatic arrhythmias (bradycardia, atrial fibrillation, supraventricular tachycardia, ventricular tachycardia or fibrillation), hypoxia, respiratory distress or decreased oxygenation and loss of consciousness or convulsions (see ADVERSE REACTIONS and WARNINGS).

Always have cardiopulmonary resuscitation equipment and trained personnel readily available prior to DEFINITY administration and observe all patients for acute reactions for at least 30 minutes following the use of DEFINITY (see WARNINGS).

In addition, acute allergic type reactions (e.g. anaphylactoid/anaphylactic reactions and angioedema) have been reported very rarely as part of ongoing post-marketing surveillance (see WARNINGS – Hypersensitivity Reactions). Central nervous system reactions, including altered consciousness, seizures, and/or seizure like reactions have also been reported very rarely and may or may not be associated with immediate hypersensitivity reactions. Musculoskeletal reactions have included muscle cramps, musculoskeletal discomfort, myalgia and neck pain.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

During clinical trials there was no incidence of an overdose with DEFINITY (perflutren injectable suspension). Should an overdose be suspected, supportive measures should be taken in response to symptoms.

DOSAGE AND ADMINISTRATION

For Single Use Only

DEFINITY (perflutren injectable suspension) contains no 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 preparation of DEFINITY carefully and to adhere to strict aseptic procedures during preparation.

The DEFINITY vial must be activated prior to use with a mechanical shaking device (Vialmix™). Upon activation, DEFINITY appears as a milky white suspension. The activated product has an initial concentration of perflutren of 150±100 µL/mL.

Bolus Administration

The recommended dose for DEFINITY is a single dose of 10 µL/kg of the activated product by intravenous bolus injection over 30-60 seconds, followed by a 10 mL saline flush. If necessary, a second 10 µL/kg dose may be administered 5 minutes after the first injection to prolong contrast enhancement.

Infusion

DEFINITY may also be administered via an I.V. infusion of 1.3 mL added to 50 mL of preservative-free saline. The rate of infusion is suggested to be initiated at 4.0 mL/minute and could be titrated as necessary to achieve optimal image enhancement but should not exceed 10 mL/min. The total dose administered per kg will range from

approximately 14.4 µL/kg (90 kg person) to 21.7 µL/kg (60 kg person). Note: DEFINITY should be used immediately after dilution with preservative-free saline.

Instructions for Preparation of DEFINITY (Perflutren Injectable Suspension)

1. Allow the vial to warm to room temperature.

2. Activate DEFINITY by shaking the vial using the Vialmix™. Immediately after shaking, DEFINITY appears as a milky white suspension. **The contents of the vial are not to be administered to the patient without first undergoing the mechanical activation procedure.**

3. Withdraw DEFINITY from the vial using an 18- to 20-gauge syringe needle. The needle should be positioned to withdraw the material from the middle of the liquid in the inverted vial. **Do not inject air into the vial.**

4. If the product is allowed to sit for more than 5 minutes after Vialmix™ shaking, it should be resuspended with 10 seconds of hand agitation prior to syringe withdrawal.

Following activation (steps 1, 2), DEFINITY can be stored at room temperature and should be used within 12 hours of preparation.

The contents of the vial are intended only for use in the preparation of DEFINITY and are not to be administered directly to the patient without first undergoing the preparative procedure (steps 1-4).

The contents of the vial are intended for use in a single patient.

PHARMACEUTICAL INFORMATION

Drug Substance

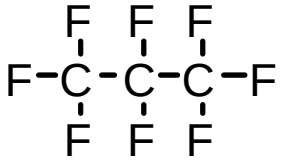
Common Name: Perfluoropropane

Chemical Name: 1,1,1,2,2,3,3,3-Octafluoropropane

Molecular Formula: C_3F_8

Molecular Weight: 188.02 g/mol

Structural Formula:



Description: Colourless gas

Composition

DEFINITY (perflutren injectable suspension) comes in a 2 mL clear vial containing a 1.5 mL fill volume. Each mL of DEFINITY contains:

Sodium Chloride, USP	4.87 mg
Propylene Glycol, USP	103.5 mg
Glycerin, USP	126.2 mg
Water for Injection, USP	QS to 1.0 mL
Lipid Blend*	0.75 mg
Sodium phosphate monobasic, monohydrate, ACS	2.34 mg
Sodium phosphate dibasic, heptahydrate, ACS	2.16 mg
Perfluoropropane Gas	perflutren 150±100 µL/mL when shaken (activated)

* The Lipid Blend is composed of the following lipids in a mole % ratio of 10:82:8: 1,2-**d**i**p**almitoyl-*sn*-glycero-3-**p**hosphatidic **a**cid, monosodium salt (DPPA); 1,2-**d**i**p**almitoyl-*sn*-glycero-3-**p**hosphatidyl**c**holine (DPPC); *N*-(**m**ethoxy**p**oly**e**thylene **g**lycol **5000** carbamoyl)-1,2-**d**i**p**almitoyl-*sn*-glycero-3-**p**hosphatidyl**e**thanolamine, monosodium salt (MPEG5000 DPPE).

Stability and Storage Recommendations

Store in a refrigerator (2-8°C) prior to activation.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used.

Following activation, DEFINITY can be stored at room temperature and should be used within 12 hours of preparation.

The activated vials are for single use only and unused portions should be discarded.

When activated, DEFINITY appears as a milky white suspension. If allowed to sit for more than 5 minutes after Vialmix™ shaking, it should be resuspended with 10 seconds of hand agitation prior to administration. (See INSTRUCTIONS FOR PREPARATION OF DEFINITY).

AVAILABILITY OF DOSAGE FORMS

DEFINITY (perflutren injectable suspension) is supplied as a sterile and non-pyrogenic liquid in a 2 mL glass vial. Each package contains four (4) single-use vials.

The VialMix™ will be provided with the initial DEFINITY order.

INFORMATION FOR THE CONSUMER

Inform your physician if you are or may be pregnant or are nursing.

Some people are born with a rare condition which results in lengthening of the heartbeat on an electrocardiogram test (QT interval prolongation). If you or any of your family members have this condition, you should inform your health care professional.

On very rare occasions, serious reactions have occurred after administration of DEFINITY in patients with severe heart or lung conditions. Inform your physician if you have a congenital heart defect or recent worsening of a heart or lung condition.

Immediate, serious and very rare hypersensitivity (allergic) reactions, which could be life-threatening, have occurred with this product with symptoms such as swelling of the feet, mouth and throat, difficulty in breathing, low blood pressure and shock. Other very rare reactions, such as seizures, have also been reported.

If this occurs, immediately inform the attending healthcare professional conducting the procedure, or if these symptoms occur later, contact a doctor or emergency healthcare facility immediately.

PHARMACOLOGY

DEFINITY (perflutren injectable suspension) has no pharmacologic action; it produces its effect by increasing the backscatter of ultrasound.

In Vitro Pharmacology

Stability of Acoustic Response Over 12 Hours

The stability of the DEFINITY acoustic response has been assessed at various times post-preparation. The results showed that there was no significant difference in acoustic response for up to 12 hours following activation compared to the acoustic response obtained shortly after product activation. After standing for 5 minutes to 12 hours, a simple hand resuspension was all that was required to achieve an acoustic response comparable to the response observed immediately post-preparation. A study was also performed to assess the *in vitro* stability of the DEFINITY acoustic response in saline and blood. DEFINITY was significantly more stable to ultrasound exposure at normal and elevated pressures when it was in blood rather than saline.

Animal Pharmacology (*In Vivo*)

Assessment of Mode of Administration in Dogs

A study was performed to assess the various modes of administration of DEFINITY in the anesthetized open-chest dog. The results showed that DEFINITY administered as a bolus allows for assessment of left ventricular opacification (LVO) with an optimal dose of 3-10 µL/kg. In addition, DEFINITY administered over 2 minutes using an infusion pump or 30 minutes diluted in an intravenous (I.V.) bag, allows for the assessment of both LVO and gated harmonic myocardial perfusion (GHMP). Steady-state homogeneous enhancement without ventricular shadowing was achieved over 30 minutes with an I.V. dose of 9 µL/kg/min. Data from these studies suggest that DEFINITY administered as a continuous infusion may have clinical utility in assessment of both LVO and GHMP.

Assessment of Myocardial Perfusion Defects in Dogs

Studies have been performed to assess the ability of DEFINITY to accurately detect myocardial perfusion defects in the anesthetized open-chest canine using gated second harmonic imaging. DEFINITY was able to accurately detect the area of flow deficit as well as areas of increased flow during reactive hyperemia. Data from these studies suggest that DEFINITY may have clinical utility for the rapid diagnosis of myocardial

perfusion defects resulting from myocardial infarction or ischemia. These results are consistent with those found by Wei *et al.*, 1998 and Linder *et al.*, 1998.

Assessment of Physiologic Parameters

The effect of DEFINITY on hemodynamics, electrocardiograms (ECG), hematology, blood hemolysis, blood gases, and cerebral vasculature has been studied in rhesus and cynomologus monkeys, baboons, pigs, dogs, and rats. There were no significant effects on hematology parameters (red and white blood cell or platelet counts), cerebral vasculature (100 µL/kg I.A. administered into the carotid artery in rats), or ECGs. DEFINITY does not induce hemolysis in the presence or absence of clinically relevant levels of ultrasound power. Bubble sizes of 1-2 µm and 2-10 µm in DEFINITY had no effect on heart rate or mean arterial pressure. The only significant effects on hemodynamic parameters (LVP [left ventricular pressure], LVEDP [left ventricular end-diastolic pressure], dP/dtmax [maximum rate of change of left ventricular pressure], heart rate, mean arterial pressure, or pulmonary arterial pressure) were a transient fall in heart rate and blood pressure in one monkey at a dose of 1000 µL/kg, I.V. (50 times the recommended maximum human dose) and mild reversible elevation in pulmonary arterial pressure in pigs at 5 and 10 µL/kg, I.V. Effects in pigs are considered to be species specific.

Rat Pharmacokinetics of MPEG5000 DPPE in DEFINITY

The pharmacokinetics, distribution, metabolism and excretion of DEFINITY were studied in conscious Sprague-Dawley rats (3 rats/sex/dose group). Since the MPEG5000 DPPE is the only novel phospholipid, DEFINITY was prepared with ^{14}C-MPEG5000 DPPE and ^{14}C levels were determined at 5, 15, 30 min, and 1, 2, 4, 6, 24, 48, and 72 hours post-injection. The radiolabeled DEFINITY was found to clear from the blood in a manner that best fit a two compartment model (R=0.98). A summary of results can be found in Table 3.

Table 3
Summary of Pharmacokinetics, Distribution, Metabolism, and Excretion of ^{14}C-DEFINITY

Dose	Weight of rats	Initial t½	Terminal t½	Distribution at Steady State	Systemic Claerance	Cmax	Tmax	AUC
1 mL/kg (0,9 µCi/kg)	230-350g	0.3 hours	10.6 hours	0.17 L/kg	0.25 mL/ min/kg	0.02 µCi• hr/mL	0.08 hr	0.07 µCi• hr/mL

AUC = Area Under Curve (calculated from 0 to infinity)

The 14C-MPEG5000 DPPE indicated no major metabolism in plasma at 15 minutes post-injection. At 4 hours post-injection, 60% was in the form of 14C-MPEG5000 LPE and at 4 hours plasma levels were below the level of detection by HPLC. The metabolic profile in the urine at 4 hours showed 90% of the radioactivity in the form of 14C-

MPEG5000, and radioactivity in the feces was below the detectable limits.

The tissue distribution and elimination of total radioactivity was determined. The five groups were euthanized at 0.5, 4, 24, 48, and 72 hours post-injection. Twenty-three tissues were collected from each rat at necropsy and the total radioactivity in each tissue was determined. Total radioactivity recovered can be found in Table 4.

Table 4
Total Radioactivity Recovered

Time (hours)	% Radioactivity
0.5	104
4	96
24	86
48	87
72	96*

* The majority of the activity was in the urine (71.5%) while the feces contained 10.5%. The remainder was in the cage wash (2%), liver (3.7%), skin (1.9%), muscle (1.4%) and the remaining 5% was distributed throughout other organs at <1% per organ.

The maximum concentration occurred in most tissues between 0 and 4 hours post-injection and decreased in all tissues between 4 and 72 hours. The tissues with the highest concentrations of activity were the liver (17.8% of the injected dose) and plasma (17.2% of the injected dose) at 4 hours post-injection.

Dog Pharmacokinetics

The *in vivo* kinetics of perfluoropropane (PFP) component of DEFINITY were studied following a single intravenous administration to dogs at three dose levels. The test article was administered to four naive male Beagle dogs in each dose group. PFP concentrations in blood and expired air were collected at a total of twelve timepoints up to 30 minutes post-dose.

The data were analyzed using a single compartment model. The mean area under the curve (AUC) was estimated to be 3.237 nL•sec/mL with a mean elimination half-life of 61 seconds, and a mean blood clearance of 19 mL/(kg•sec). The volume of distribution was estimated to be 1,720 mL/kg. The large volume of distribution was attributed to the rapid PFP clearance from the blood and never achieving steady state equilibrium of PFP in the blood.

PFP levels in expired air following the administration of the 10 µL/kg dose were also very low and approached the limit of quantification. At the 100 and 1000 µL/kg doses, an initial rapid excretion of PFP was observed with plateau levels attained by 2 or 4 minutes, respectively. Total PFP eliminated in expired air over the course of the study for these groups was estimated to represent approximately 117% of the theoretical total

administered. Mean lung clearance at the 1000 µL/kg dose was estimated to be 24.2 mL/(kg•sec).

Human Pharmacology

Human Pharmacokinetics

Doppler ultrasound measurements were performed with DEFINITY in conjunction with the pharmacokinetic evaluation of PFP. Doppler signal intensity corresponded well with measured and extrapolated PFP concentrations in blood. The time to maximum Doppler signal intensity tmax was shown to be similar to the PFP blood tmax (1.13 versus 1.77 minutes). The observed 99% drop in Doppler signal intensity within 10 minutes (t½ approximately 2 minutes) was in agreement with the decline in measurable blood levels of PFP.

Clinical Studies

Dose Selection Trials

DMP 115-901 was a Phase I trial to determine the safety and tolerability (primary objective) of DEFINITY given as multiple, IV bolus injections in healthy adult male subjects. This trial compared four ascending doses of DEFINITY (5, 10, 15, and 30 µL/kg) and compared each dose to placebo. A total of five injections (DEFINITY or placebo) were administered; the first IV bolus injection was followed by four additional injections at approximately 5, 10, 60, and 120 minutes following the first injection. DEFINITY was safe and well tolerated when administered at all doses. Early evaluation of cavity enhancement at higher (>15 µL/kg) doses found excessive attenuation. Doses of 5 to 15 µL/kg of DEFINITY were recommended for efficacy dose ranging studies in echocardiographic imaging.

DMP 115-902 was conducted in patients referred for diagnostic echocardiography. DEFINITY was administered as a single bolus IV injection at doses of 5, 10, or 15 µL/kg. At 5 µL/kg the mean duration of enhancement was limited to 54 to 102 seconds. Optimal enhancement was observed on an average for approximately 1.5 to 2 minutes in the 10 µL/kg dose group and for 2.5 minutes in the 15 µL/kg dose group. However, as a result of excessive contrast attenuation, the 15 µL/kg dose required a significant time delay (85 to 100 seconds) before clinically useful contrast-enhanced images could be obtained. Based on these findings, doses of 5 and 10 µL/kg were selected for the initial Phase III Cardiology trials. Results of this trial were published by Pantely *et al.*, 1998.

DMP 115-001 was a Phase II dose selection trial conducted in patients positive for at least one liver and/or kidney abnormality. DEFINITY was administered as a single IV bolus injection at doses of 10, 30, or 50 µL/kg. The 10 µL/kg dose was effective in some patients in this trial. The 30 µL/kg and 50 µL/kg dose groups both showed

adequate contrast enhancement. In addition, although a small number of patients were enrolled in each dose group, there appeared to be a dose-related increase in the incidence of new-onset AEs for the 50 µL/kg dose, without any increase in efficacy over the 30 µL/kg dose. Therefore, the higher dose (50 µL/kg) was dropped from further evaluation in Phase III trials. Consistent with the Phase II echocardiography trials, the duration of contrast enhancement in this Phase II trial revealed a dose relationship. Based on these considerations, doses of 10 µL/kg and 30 µL/kg were recommended for further investigation in patients referred for diagnostic ultrasound of the liver and kidney in the Phase III trials.

Rest Echocardiography

Five pivotal Phase III multicenter clinical trials were performed in a total of 401 patients with 2 or more non-evaluable segments in either the apical 2- or 4-chamber view: 42 patients were scheduled to receive placebo and 359 patients were scheduled to receive DEFINITY, 85 of whom were scheduled to receive two 5 µL/kg doses of DEFINITY and 274 of whom were scheduled to receive two 10 µL/kg doses of DEFINITY. The mean age was 55.0 (±16.3) years. These studies are summarized in Table 5.

Of the patients receiving a 10 µL/kg dose of DEFINITY, 174 (63.5%) were male and 100 (36.5%) were female.

Table 5
Cardiology Efficacy Studies Summary

Study	Study Design	Dose	Outcome - Indication
DMP 115-004 and DMP 115-005	A Phase III Randomized, Double-Blind, Multicenter, Placebo-Controlled Trial Two echocardiographic imaging sessions on the same day with safety follow-up visits at 24, 48, and 72 hours	Two IV bolus injections: one per imaging session Placebo or DMP 115, 5 or 10 µL/kg Doses separated by a minimum of 30 min	Contrast-enhanced echocardiographic imaging of cardiac structure (ventricular chambers and endocardial borders)
DMP 115-006 and DMP 115-007	A Phase III, Open-Label, Multicenter Trial One MRI session followed by two echocardiographic imaging sessions on the same day over approximately 3 hrs with a 24-hr safety follow-up visit	Two IV bolus injections of DMP 115 1st imaging session: 10 µL/kg 2nd imaging session: 10µL/kg diluted to 2mL with saline Sessions separated by at least 20 min	Contrast-enhanced echocardiographic imaging of cardiac structure (ventricular chambers and endocardial borders) and function (regional wall motion)
DMP 115-017	A Phase III, Multicenter, Open-Label Crossover Trial Two baseline and two echocardiographic imaging sessions (A and B); separated by 24 to 72 hrs, followed by a 24 to 72 hr safety follow-up visit Patients randomized to Session A or B on treatment Day 1 and the alternate session on treatment Day 2	Dosing session A: Single IV infusion of DMP 115 - 1.3mL in 50mL saline Dosing session B: Two IV bolus injections of DMP 115 - 10µL/kg each with ≤5 min between the two doses Sessions A and B separated by 24 to 72 hrs	Contrast-enhanced echocardiographic imaging of cardiac structure (ventricular chambers and endocardial borders) Compare images from IV infusion vs. Slow bolus injection

Qualitative evaluations of adequate or full cavity enhancement was demonstrated by multiple Institutional and Blinded Readers (Table 6). Institutional Reads were performed by the clinical investigator and Blinded Reads were performed by independent physician/readers who did not have any clinical or diagnostic information available. Adequate or full left ventricular cavity enhancement was demonstrated in 90.5% of the patients based on the combined Institutional Read data and in 42.9% to 96.9% of patients assessed during the Blinded Reads, compared to 0% of patients who received a placebo-saline injection. Quantitative measures of videodensitometry confirmed the qualitative assessments.

The improvement in endocardial border delineation with DEFINITY was examined by a variety of measures: (1) the percentage change in the number of evaluable myocardial

segments, (2) the percentage of patients showing at least a 1-segment improvement in evaluable endocardial borders, (3) the percentage of patients showing at least a 2-segment improvement in evaluable endocardial borders, (4) the percentage of patients demonstrating salvage of echocardiography examinations (a reduction from 4 or more non-evaluable cardiac segments to ≤ 1 non-evaluable segment), and (5) the absolute change in the measurable contiguous endocardial border length. All measures of endocardial border delineation in these trials showed substantial improvement with DEFINITY versus baseline examinations.

Incorporating an intent-to-treat analysis, the Institutional and Blinded Read data revealed a significant positive improvement in the number of unevaluable segments that were scored as evaluable after DEFINITY administration (Table 7). The Institutional Read data demonstrated 20.8% to 54.9% improvement in the net percentage of segments that demonstrated a positive change in evaluability, which clinically corresponds, on average, to a 2- to 3-segment improvement in visualization. For the unpaired Blinded Read, the median values for the net percentage of segment improvement in the five trials ranged from 9.4% to 37.2% (or net improvement in ~1 to 2 segments).

For functional assessment, a statistically significant improvement in the percentage of segmental wall-motion scores that agreed with the comparator test of MRI was demonstrated for both Institutional and Blinded Readers (Table 8). When segments were categorized by type of wall motion (exact match with MRI), the improvement in agreement with MRI for DEFINITY-enhanced segmental wall motion relative to baseline was 21.3% for the combined Institutional Read data. The median values for Blinded Read data in the two trials for difference in segmental wall motion agreement versus MRI comparator were 7.9% and 29.0% (or correct wall-motion assessment in 1 to 2 additional segments after DEFINITY).

Left Ventricular Cavity Enhancement

Table 6
Percentage of Patients with Adequate or Full Left Ventricular Cavity Enhancement Based on the Patients' Qualifying View[a]

Trial	Institutional Read				Blinded Read[c]			
	N	Placebo %	N	DEFINITY	N	Placebo %	N	DEFINITY
DMP 115-004	18	0	34	82.4**	18	0.0 (0.0, 0.0)	33	60.6** (60.6**, 63.6**)
DMP 115-005	24	0	50	96.0**	24	0.0 (0.0, 0.0)	49	61.2** (42.9**, 77.6**)
DMP115-017[b]	–	–	64	90.6	–	–	64	96.9 (85.9, 98.4)
Combined	42	0	148	90.5**	–	–	–	–

** Statistically significant difference from placebo ($p \leq 0.01$)
N =Sample size for Blinded Read, this is the N of the median value. DEFINITY dose = 10 µL/kg.
[a] In Trials DMP 115-004 and -005, ventricular cavity enhancement results are based on images obtained from the qualifying view *(either apical 4-chamber or 2-chamber view) with at least two non-evaluable segments. In Trial DMP 115-017, the apical 4-chamber view for all patients with at least two non-evaluable segments.
[b] Equivalent results were obtained following administration of DEFINITY as an infusion of 1.3 mL added to 50 mL of saline.
[c] Results are displayed as the median and range (minimum, maximum) for the three blinded readers in each trial.

Endocardial Border Delineation

Table 7
Endocardial Border Delineation - Net Percentage of Segments with Change in Evaluability[a]

Trial	Institutional Read				Blinded Read (Unpaired)[c]			
	N	Placebo %	N	DEFINITY	N	Placebo %	N	DEFINITY
DMP 115-004	18	- 1.9	34	26.2*#	18	-1.9 (-4.2, 0.0)	32	9.4# (2.3, 24.0*#)
DMP 115-005	24	0.3	50	40.3*#	24	4.9 (-1.4, 4.9)	49	13.4# (13.1*, 13.8#)
DMP 115-006	–	–	67	35.9#	–	–	67	25.2# (20.9#, 49.6#)
DMP 115-007	–	–	59	20.8#	–	–	59	17.7# (0.7, 41.8#)
DMP 115-017[b]	–	–	64	54.9#	–	–	64	37.2# (27.3#, 51.3#)

* Statistically significant difference from placebo ($p \leq 0.05$)
# Statistically significant change in evaluability ($p \leq 0.05$)
N =Sample size for Blinded read, this in the N of the median value for all three readers. DEFINITY dose = 10µL/kg
[a] In Trials DMP 115-004,-005,-006, and -007, each of the 12 cardiac segments was graded; in Trial DMP 115-017, each of the 6 cardiac segments was graded. The Net % of segments with change in Evaluability equals the % Change in the visualization of segmental endocardial borders before and after DEFINITY administration.
[b] Equivalent results were obtained following administration of DEFINITY as an infusion of 1.3 mL added to 50 mL of saline.
[c] Results are displayed as the median and range (minimum, maximum) for the three blinded readers in each trial.

Wall Motion

Table 8
Improvement in Segmental Wall-Motion Percentage with DEFINITY - Exact Match with MRI‡

Trial	Institutional Read		Unpaired Blinded Reada	
	N	DEFINITY	N	DEFINITY
DMP 115-006	64	29.9*	64	20.0* (23.2*, 38.0*)
DMP 115-007	58	12.0*	59	7.9* (1.3, 25.1*)
Combined	123	21.3*	–	–

* Statistically significant difference between baseline and contrast segmental wall motion percentage ($p \leq 0.05$)
‡ Exact match with MRI = Percentage difference in segmental wall motion between baseline and DEFINITY contrast-enhanced images relative to MRI. Segments were scored by MRI and echocardiography as normal/hyperkinetic, hypokinetic, akinetic, dyskinetic, or non-evaluable.
N =Sample size for Blinded read; this is the N of the median value for all three readers. DEFINITY dose = 10 µL/kg.
[a] Results are displayed as the median and range (minimum, maximum) for the three blinded readers in each trial.

Stress Echocardiography

The efficacy of DEFINITY administration during stress echocardiography was assessed in a prospective independent blinded read evaluation of non-contrast and DEFINITY contrast images for endocardial border delineation (ie, segment evaluability) and left ventricular opacification from the combined data of five multicenter, randomized clinical studies that utilized similar patient populations, study designs, and imaging procedures. Of the 465 patients with imaging data available (312 DEFINITY and 153 placebo/unenhanced), 247 patients (167 DEFINITY and 80 placebo/unenhanced) had all three apical views available (ie, apical 2-, apical 3-, and apical 4-chamber views) and 218 patients (145 DEFINITY and 73 placebo) had at least one apical view missing for assessment.

Improved endocardial border delineation was assessed for both the combined and individual study data, as defined by an improvement of the visualization of at least two segments in a patient from baseline non-contrast to stress echocardiography using the 16-segment cardiac model. Both the combined and individual study results in patients with all three apical views available demonstrated that the proportion of patients with improved endocardial border delineation determined by an average of blinded readers' results in the DEFINITY group was significantly higher than that of the placebo group (70.5% and 25%, respectively; $p < 0.001$). Similar results of improved endocardial border delineation with DEFINITY were demonstrated in patients that had at least one apical view missing for assessment for the pooled and individual clinical study data for stress echocardiography as compared to the placebo group (mean 12.4 segments visualized vs. 7.4 segments visualized; $p < 0.001$).

The proportion of images determined to be of adequate quality, as determined by the average of all readers, was significantly higher DEFINITY group (86.8%) compared to the placebo group (46.3%)($p < 0.001$).

Endocardial border length of the apical 2- and apical 4-chamber views was also assessed as part of this blinded read evaluation. Endocardial Border Length was measured as a continuous length from the mitral annulus through the apex to the other side of the annulus. A comparison of variance was performed to provide an estimate of variability in the endocardial border length read between treatment groups in both diastole and systole and in the apical 2- and apical 4-chamber views. Comparison of average variance of all readers for endocardial border length measurements using apical 2- and 4-chamber views during either systole or diastole was significantly higher in placebo groups as compared to the DEFINITY groups during peak stress. This is in contrast to the absence of statistical significances in the comparison of variance between the DEFINITY and placebo groups at baseline.

The safety of DEFINITY administration has been recently evaluated in several post-marketing clinical studies. In a prospective, multicenter, open-label registry of 1053 patients in routine clinical practice, there were no deaths, life-threatening reactions, or serious adverse events. Following DEFINITY administration at rest,13 (13/599; 2.17%) non-serious AEs occurred within the first 15 minutes, whereas 48 (11.4%) patients experienced at least one AE within 15 minutes of stress dose administration and an additional 23 (5.5%) of patients experienced an AE post-stress agent prior to DEFINITY dose. The most common AEs (i.e., ≥0.5%) were nausea 9 (0.9%), back pain 7 (0.7%), headache 13 (1.2%), and tremor 6 (0.6%).

In a retrospective observational Premier Perspective™ Database study in critically ill patients, discharge data collected between January 2002 and June 2008 were analyzed from 1,008,206 patients. Mortality in critically ill patients after DEFINITY echocardiography was 2.1% over the initial 48 hours, compared with 3.1% in the non-contrast echocardiography group. This represents a 32% reduction in the risk of mortality. Mortality at hospital discharge for the DEFINITY contrast group was 14.7% compared with 16.6% for the non-contrast group. In 23 major co-morbid disease states, there was no evidence for increased risk of mortality associated with DEFINITY echocardiography among patients with unstable cardiopulmonary syndromes, respiratory failure and need for mechanical ventilation, or in those with pulmonary hypertension.

A prospective, open-label safety study evaluated the effect of DEFINITY on pulmonary artery hemodynamics in patients with normal (≤ 35 mmHg, 16 patients) and elevated (> 35 mmHg, 16 patients) pulmonary artery systolic pressure (PASP) undergoing right heart catheterization.

Pulmonary artery hemodynamic measurements were conducted at baseline and up to 33 minutes after one dose of DEFINITY. DEFINITY administration did not result in any clinically or statistically significant change from baseline values in systemic and

pulmonary artery hemodynamic measurements in the patients with either normal or elevated PASP.

All patients had ECG monitoring during DEFINITY administration and no clinically significant variations were seen. No deaths, serious adverse events, or other significant adverse events occurred during this study.

Abdominal Ultrasound

DEFINITY was evaluated in two pivotal multicenter Phase III clinical trials (Trials DMP 115-009 and -010) enrolling a total of 209 patients. One hundred and thirty patients had suspected liver pathology and 79 had suspected kidney pathology.

Overall, 113 patients (54.1%) were male and 96 patients (45.9%) were female. The mean age was 54.9 (±14.3) years.

The two multicenter, Phase III, open-label, randomized, crossover trials compared two doses of DMP 115 (10 µL/kg and 30 µL/kg) to unenhanced ultrasound. Patients with suspected liver or kidney pathology were recruited to determine if DEFINITY contrast-enhanced ultrasound provided more diagnostic information (e.g., increased lesion conspicuity, detection of additional lesions, improved delineation of pathology, improved lesion characterization) relative to standard (non-contrast enhanced) ultrasound examinations. Ultrasound diagnoses were compared with comparative diagnostic tests (MRI, CT, surgery, etc.). The potential for DEFINITY contrast-enhanced imaging to affect patient management decisions when compared with unenhanced ultrasound imaging of the liver and kidney was also evaluated.

Dose findings found the 10 µL/kg dose essentially equivalent to the 30 µL/kg dose. It was determined that the 10 µL/kg dose would be the recommended dose for the abdominal ultrasound indication, and efficacy results were determined based on this dose.

Results for all readers (Blinded and Institutional) showed that the administration of 10 µL/kg of DEFINITY was clinically effective in providing additional diagnostic information relative to baseline non-contrast examination. Three out of four blinded readers demonstrated statistically significant positive results for additional diagnostic information with DEFINITY. DEFINITY contrast-enhanced images read by three of the four Blinded Readers provided additional diagnostic information in 60% to 76% of patients (Table 9). One blinded reader found DEFINITY enhanced exams provided additional diagnostic information in ~33% of cases. In addition, DEFINITY contrast-enhanced images read by institutional readers provided additional diagnostic information for 83% of patients in each trial.

Table 9
Percentage of Patients with Additional Diagnostic Information from the DEFINITY Ultrasound Study, Blinded Read and Institutional Read - All Patients (Trials DMP 115-009 and -010)

Blinded Read

Trial	N	% Patients with Additional Information	(95 % CI)
DMP 115-009			
Reader 3	108	75.9*	(66.6, 82.5)
Reader 4	108	68.5*	(58.8, 76.0)
DMP 115-010			
Reader 1	96	60.4*	(49.9, 69.1)
Reader 2	96	33.3	(24.2, 42.8)

* Indicates the percentage of patients with additional diagnostic information is statistically significantly greater than 50% ($p \leq 0.025$; Bonferroni's adjustment).

Institutional Read

Trial	N	% Patients with Additional Information	(95 % CI)
DMP 115-009	107	83.2**	(74.4, 88.6)
DMP 115-010	96	83.3**	(74.0, 88.9)
Combined	203	83.3**	(77.2, 87.5)

** Indicates the percentage of patients with additional diagnostic information is statistically significantly greater than 50% ($p \leq 0.01$)
N =Sample Size; CI = Confidence Interval.

Note:DEFINITY dose = 10 µL/kg.

Of patients with additional diagnostic information (Table 10), the combined Institutional Read data noted improved delineation of pathology in 29.0% of cases, detection of additional lesions in 8.9% of cases, improved lesion characterization in 31.4% of cases, and increased lesion conspicuity for 44.4% of patients. The blinded readers noted improved delineation of pathology for a median of 10.6% of patients, detection of additional lesions for a median of 5.2% of patients, improved lesion characterization for a median of 21.1% of patients, and increased lesion conspicuity for a median of 45.7% of patients.

Table 10
Nature of Additional Diagnostic Information From the DEFINITY 2-D Gray Scale Ultrasound Study: Paired Blinded and Institutional Read Results for Patients with Additional Diagnostic Information - All Patients (Trials DMP 115-009 and -010)

Reader	N	Nature of Additional Diagnostic Information - All Patients			
		Improved Delineation (extent) of Pathology	Detection of Additional Lesions	Improved Lesion Characterization	Increased Lesion Conspicuity
		% Patients w/ Outcome			
DMP 115-009					
Blinded Reader 3	88	9.1	2.3	33	28.4
Blinded Reader 4	81	54.3	11.1	38.3	46.9
Institutional Read	89	38.2	9	40.4	49.4
DMP 115-010					
Blinded Reader 1	72	2.8	4.2	8.3	44.4
Blinded Reader 2	33	12.1	6.1	9.1	60.6
Institutional Read	80	18.8	8.8	21.3	38.8
Combined					
Institutional Read	169	29	8.9	31.4	44.4

Note : DEFINITY dose = 10 µL/kg
N = Sample Size

The administration of DEFINITY resulted in an improvement in diagnostic confidence for 28.2% of all patients by the combined Institutional Read and for 21.1% to 38.1% of all patients by the Blinded Readers. Overall, the addition of DEFINITY improved diagnostic quality for 23.4% to 39.8% of all ultrasound examinations for the blinded reader assessments relative to the unenhanced baseline examinations, when read in a blinded unpaired format.

The institutional readers also evaluated whether changes in patient management would be recommended based on the addition of DEFINITY to the ultrasound examinations. For cases with suspected liver pathology, 40.8% of patients in both trials combined would have had a change in patient management recommended, while 53.0% of patients with suspected kidney pathology in both trials combined would have had a change in patient management recommended based on the DEFINITY enhanced ultrasound examination. The most frequent (23.1% of patients with additional diagnostic information from the DEFINITY examination) change in patient management would have been a decision not to perform additional diagnostic testing. Additional changes recommended included alterations in patient therapy, surgical strategy or diagnostic workup.

TOXICOLOGY

Mutagenicity

There was no evidence of mutagenicity or clastogenicity in the following assays with DEFINITY (perflutren injectable suspension): 1) bacterial mutagenesis assay (Ames assay), 2) *in vitro* chromosome aberration assay (Chinese hamster ovary [CHO] cell assay) and 3) *in vivo* rat micronucleus assay.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Animal studies to evaluate the carcinogenic potential of DEFINITY have not been performed. There was no evidence of mutagenicity or clastogenicity in the following assays with DEFINITY: 1) bacterial mutagenesis assay (Ames assay), 2) *in vitro* chromosome aberration assay (Chinese hamster ovary [CHO] cell assay), and 3) in vivo rodent micronucleus assay.

Single- and Repeated-Dose Toxicity

Transient clinical signs consisting of abnormal respiration, heart rate changes and decreased activity were observed soon after administration of DEFINITY at doses ≥0.3 mL/kg in single- and repeat-dose toxicity studies in rats and monkeys. Higher doses of DEFINITY, typically ≥1 mL/kg, resulted in more severe signs including unresponsiveness and occasionally death. The no-effect doses for clinical signs in 1-month toxicity studies in rats and monkeys were 5 and 15 times, respectively, the recommended maximum clinical dose of 0.02 mL/kg (0.01 mL/kg with possible administration of a second dose of 0.01 mL/kg).

Rats given ≥0.1 mL/kg/day of DEFINITY for 1 month exhibited perivascular and peribronchiolar eosinophil infiltration, alveolar macrophage accumulation and increased goblet cell size and number in the lungs. The incidence and severity of these findings were dose related; the no-effect and minimum-effect doses were 1.5 and 5 times the clinical dose, respectively. The lung findings were reversible following a 1-month recovery period. There were no microscopic findings in other tissues from rats given DEFINITY for 1 month at doses ≤1 mL/kg/day (≤50 times the clinical dose). In addition, there were no lung findings in rats following a single dose of DEFINITY when evaluated at doses up to 15 times the clinical dose. There were no microscopic findings in lungs or other tissues from monkeys given single or repeated doses (up to 1-month) of ≤1 mL/kg/day of DEFINITY.

No hemolysis, and little or no potential for local irritation or antigen-stimulated immune response was observed in studies with DEFINITY that were designed to evaluate in vitro hemolysis in human blood, and vascular, muscular and ocular irritation in rabbits, and antigenicity in guinea pigs.

Reproduction and Teratology

There were no findings in gonads or other reproductive tissues in 1-month toxicity studies in rats and monkeys at doses ≤1 mL/kg/day.

Results from range-finding and definitive developmental (teratogenic) studies indicate that DEFINITY does not adversely affect fetal growth, survival or morphological development in rats or rabbits given doses up to and including 1.0 mL/kg/day, the highest dose evaluated. DEFINITY is not maternally toxic to rats given doses <1.0 mL/kg/day, but is maternally toxic to rabbits given doses ≥0.3 mL/kg/day. The toxicity (clinical signs) in pregnant and non-pregnant rats is similar. The no-effect dose for developmental toxicity in rats and rabbits (1.0 mL/kg/day) is 50 times the maximum recommended dose of 0.02 mL/kg for ultrasound imaging (0.01 mL/kg with possible administration of a second dose of 0.01 mL/kg).

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