

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 RT and any potential adverse effects on the breastfed infant from DEFINITY RT or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of activated DEFINITY RT have not been established in the pediatric population.

The safety of injecting activated DEFINITY RT in neonates and infants with immature pulmonary vasculature has not been studied.

The pharmacokinetics of activated DEFINITY RT in pediatric subjects has not been studied.

8.5 Geriatric Use

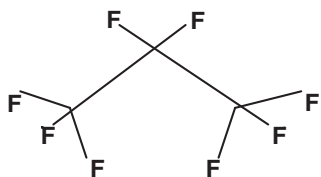
In clinical trials, the overall incidence of adverse reactions was similar for the <65 year age group and the ≥65 year age group. Of the total number of subjects in clinical trials of DEFINITY, 144 (33%) were 65 and over. No overall differences in safety or effectiveness were observed between these subjects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

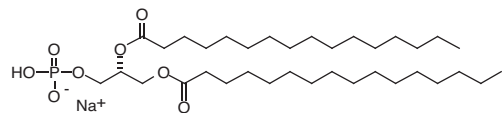
DEFINITY RT (Perflutren Lipid Microsphere) Injectable Suspension is an ultrasound contrast agent. The DEFINITY RT vial contains components that upon activation and dilution yield perflutren lipid microspheres. The unactivated vial contains a colorless, uniformly clear to translucent (hazy), viscous, sterile, non-pyrogenic solution, which upon activation with the aid of a VIALMIX RFID and dilution with 0.9% Sodium Chloride Injection, USP, provides a homogeneous, hypertonic, milky white injectable suspension of perflutren lipid microspheres. The suspension of activated DEFINITY RT 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)-α-[6-hydroxy-6-oxido-9-[(1-oxohexadecyl)oxy]-5,7,11-trioxa-2-aza-6-phosphahexacos-1-yl]-ω-methoxypropyl(ox-1,2-ethanediyl), monosodium salt; commonly called N-(methoxypolyethylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-sn-glycero-3-phosphatidylethanolamine, monosodium salt (abbreviated MPEG5000 DPPE).

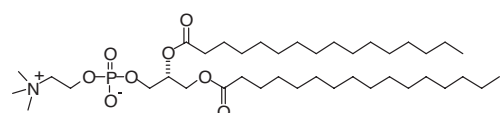
Octafluoropropane is chemically characterized as 1,1,1,2,2,3,3,3-octafluoropropane. It has a molecular weight of 188, empirical formula of C₃F₈ and has the following structural formula:



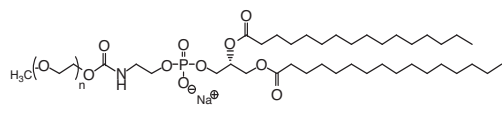
DPPA has a molecular weight of 670, empirical formula of C₂₆H₅₀O₈PNa, and following structural formula:



DPPC has a molecular weight of 734, empirical formula of C₄₀H₉₀NO₈P, and following structural formula:



MPEG5000 DPPE has an approximate molecular weight of 5750 represented by empirical formula C₂₆₆H₅₂₇NO₁₂₃PNa, contains <100ppm Ca²⁺ and the following structural formula:



Prior to activation, the DEFINITY RT vial contains 6.52 mg/mL octafluoropropane in the headspace which is confirmed by positive IR spectroscopic testing in every vial. Each mL of the viscous solution contains 3.75 mg lipid blend (consisting of 0.225 mg DPPA, 2.005 mg DPPC, and 1.520 mg MPEG5000 DPPE), 517.5 mg propylene glycol, 631 mg glycerin, 0.370 mg anhydrous sodium acetate, and 0.030 mg glacial acetic acid. The pH is 5.2 to 6.4. DEFINITY RT does not contain bacterial preservative.

After activating the contents of the vial in a VIALMIX RFID and diluting with 1.4 mL of preservative-free 0.9% Sodium Chloride, Injection, USP, each mL of the milky white suspension contains 0.045 mg DPPA, 0.401 mg DPPC, 0.304 mg MPEG5000 DPPE, 0.074 mg anhydrous sodium acetate, 0.006 mg glacial acetic acid, a maximum of 1.2 X 10¹⁰ perflutren lipid microspheres, and about 80 microL/mL (0.65 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 RT 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 intravenous 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 RT 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 intravenous bolus doses of either 0.9% Sodium Chloride Injection, USP (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 0.9% Sodium Chloride Injection, USP 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 RT is supplied as a single patient use 2 mL clear glass Radio Frequency Identification (RFID)-tagged vial containing a colorless, uniformly clear to translucent (hazy) viscous solution in packages of twenty (20) single patient use vials.

- One (1) 2 mL RFID-tagged vial - NDC (11994-017-01)
- Twenty (20) 2 mL RFID-tagged vials per kit - NDC (11994-017-20)

16.2 Storage and Handling

Store at Room Temperature 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

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 RT administration, including rash, wheezing, or shortness of breath.

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