

## Attachments to the FDA Backgrounder

1. [Definity label](#)
2. [Optison label](#)
3. [FDA statement from October, 2007](#)
4. [Bibliography](#)

## Definity Label

### DEFINITY<sup>®</sup>

#### Vial for (Perflutren Lipid Microsphere) Injectable Suspension

For Intravenous Use

#### WARNING: Serious Cardiopulmonary Reactions

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

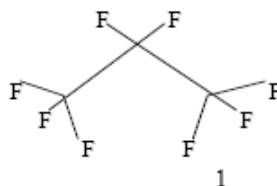
- Assess all patients for the presence of any condition that precludes DEFINITY<sup>®</sup> administration (see CONTRAINDICATIONS).
- In patients with pulmonary hypertension or unstable cardiopulmonary conditions, monitor vital sign measurements, electrocardiography and cutaneous oxygen saturation during and for at least 30 minutes after DEFINITY<sup>®</sup> administration (see WARNINGS).
- Always have resuscitation equipment and trained personnel readily available.

#### DESCRIPTION

The DEFINITY<sup>®</sup> vial contains components that upon activation yield perflutren lipid microspheres, a diagnostic drug that is intended to be used for contrast enhancement during the indicated echocardiographic procedures. The vial contains a clear, colorless, sterile, non-pyrogenic, hypertonic liquid, which upon activation with the aid of a Vialmix<sup>®</sup>, provides a homogeneous, opaque, milky white injectable suspension of perflutren lipid microspheres. The suspension of activated DEFINITY<sup>®</sup> is administered by intravenous injection.

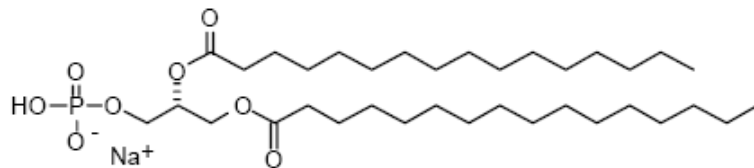
The perflutren lipid microspheres are composed of octafluoropropane encapsulated in an outer lipid shell consisting of (R) – hexadecanoic acid, 1-[(phosphonoxy)methyl]-1,2-ethanediyl ester, monosodium salt (abbreviated DPPA); (R) - 4-hydroxy-N,N,N-trimethyl-10-oxo-7-[(1-oxohexadecyl)oxy]-3,4,9-trioxa-4-phosphapentacosan-1-aminium, 4-oxide, inner salt (abbreviated DPPC); and (R)- $\alpha$ -[6-hydroxy-6-oxido-9-[(1-oxohexadecyl)oxy]-5,7,11-trioxa-2-aza-6-phosphahexacos-1-yl]- $\omega$ -methoxypoly(ox-1,2-ethanediyl), 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<sub>3</sub>F<sub>8</sub> and has the following structural formula:

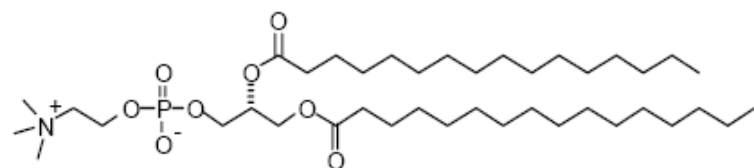


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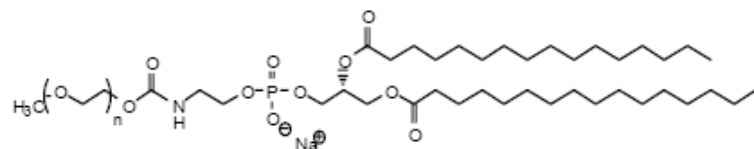
DPPA has a molecular weight of 670, empirical formula of  $C_{35}H_{68}O_8PNa$ , and following structural formula:



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  $C_{265}H_{527}NO_{123}PNa$ , and the following structural formula:



Prior to Vialmix<sup>®</sup> activation, the DEFINITY<sup>®</sup> vial contains 6.52 mg/mL octafluoropropane in the headspace. Each mL of the clear liquid contains 0.75 mg lipid blend (consisting of 0.045 mg DPPA, 0.401 mg DPPC, and 0.304 mg MPEG5000 DPPE), 103.5 mg propylene glycol, 126.2 mg glycerin, 2.34 mg sodium phosphate monobasic monohydrate, 2.16 mg sodium phosphate dibasic heptahydrate, and 4.87 mg sodium chloride in Water for Injection. The pH is 6.2-6.8.

After activating the contents of the vial in a Vialmix<sup>®</sup>, each mL of the milky white suspension contains a maximum of  $1.2 \times 10^{10}$  perflutren lipid microspheres, and about 150  $\mu\text{L/mL}$  (1.1 mg/mL) octafluoropropane. The microsphere particle size parameters are listed in Table 1 below:

Table 1: Microsphere Size Distribution	
	Microsphere particle size parameters
Mean diameter range	1.1 $\mu\text{m}$ – 3.3 $\mu\text{m}$
Percent less than 10 $\mu\text{m}$	98%
Maximum diameter	20 $\mu\text{m}$

See DEFINITY<sup>®</sup> Activation, Preparation, and Handling Instructions.

## CLINICAL PHARMACOLOGY

### PHARMACODYNAMICS

After activation of DEFINITY<sup>®</sup> and intravenous injection, the physical acoustic properties of activated DEFINITY<sup>®</sup> (see DESCRIPTION) provide contrast enhancement of the endocardial borders during echocardiography. The perflutren lipid microspheres exhibit lower acoustic impedance than blood and enhance the intrinsic backscatter of blood.

In animal models the acoustic properties of activated DEFINITY<sup>®</sup> 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.

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  $\mu\text{L/kg}$  bolus and was approximately 7.1 minutes during the continuous infusion of 1.3 mL activated DEFINITY<sup>®</sup> in 50 mL saline at a rate of 4 mL/min.

### PHARMACOKINETICS

Human pharmacokinetics information is not available for the intact or degassed lipid microspheres. The pharmacokinetics of octafluoropropane gas (OFP) were evaluated in healthy subjects (n=8) after the IV administration of activated DEFINITY<sup>®</sup> at a 50  $\mu\text{L/kg}$  dose.

#### Octafluoropropane (OFP) Protein Binding

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) were 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.

Microspheres may obstruct the vasculature of some patients. See WARNINGS for use in subjects with cardiac shunts and pulmonary hypertension.

The pharmacokinetics of activated DEFINITY<sup>®</sup> has not been studied in subjects with hepatic diseases or congestive heart failure.

**Gender:**

The effects of activated DEFINITY<sup>®</sup> appeared to be similar in men and women.

**Age/Race:**

The effects of age and race on the pharmacokinetics of activated DEFINITY<sup>®</sup> have not been studied.

**Pediatrics:**

The pharmacokinetics of activated DEFINITY<sup>®</sup> in pediatric subjects has not been studied. The safety of injecting activated DEFINITY<sup>®</sup> in neonates and infants with immature pulmonary vasculature has not been studied (see WARNINGS).

**Elderly:**

The pharmacokinetics of activated DEFINITY<sup>®</sup> in the elderly has not been studied.

**DRUG-DRUG INTERACTIONS**

Drug-drug interactions for activated DEFINITY<sup>®</sup> have not been studied.

## CLINICAL TRIALS

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 µL/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 I.V. bolus doses of either saline (placebo) or activated DEFINITY® 10 µL/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 2, compared to baseline, a single bolus dose of 10 µL/kg 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 µL/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 42-71% 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<sup>®</sup> 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<sup>®</sup> did not significantly improve the assessment of ejection fraction compared to the baseline images.**

<b>Table 2</b> <b>MEAN (SD) ENDOCARDIAL BORDER LENGTH (CM) BY BOTH APICAL 2- AND 4-CHAMBER VIEWS AT END-SYSTOLE AND END-DIASTOLE BY STUDY, EVALUABLE SUBJECTS</b>				
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
<b>Study A: (N = 67)</b>				
<u>Apical 2-chamber</u>				
Baseline	8.0(3.4)	4.7(2.8)	7.1(3.3)	4.3(2.6)
Post-DEFINITY <sup>®</sup>	12.8(5.2)*	5.8(2.6)*	10.6(5.0)*	4.4(2.3)
<u>Apical 4-chamber</u>				
Baseline	8.1(3.3)	4.5(2.6)	7.6(3.2)	4.5(2.7)
Post-DEFINITY <sup>®</sup>	13.5(5.2)*	6.8(3.3)*	11.5(4.4)*	5.3(3.1)
<b>Study B: (N = 59)</b>				
<u>Apical 2-chamber</u>				
Baseline	4.3(2.6)	7.8(5.3)	4.1(2.4)	6.5(5.1)
Post-DEFINITY <sup>®</sup>	5.7(4.7)*	8.2(6.5)	5.5(4.4)*	6.9(6.3)
<u>Apical 4-chamber</u>				
Baseline	4.0(2.7)	9.2(5.9)	3.8(2.6)	7.3(5.6)
Post-DEFINITY <sup>®</sup>	7.1(5.5)*	11.5(7.5)*	5.9(5.3)*	8.7(6.3)*
Activated DEFINITY <sup>®</sup> 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 µL/kg) and infusion (1.3 mL activated DEFINITY<sup>®</sup> in 50 mL saline at the rate of 4 mL/min) dosing of activated DEFINITY<sup>®</sup>. 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<sup>®</sup> doses and device settings for harmonic imaging have not been established.

## 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.

The safety and efficacy of DEFINITY® with exercise stress or pharmacologic stress testing have not been established.

## CONTRAINDICATIONS

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

- Right-to-left, bi-directional, or transient right-to-left cardiac shunts,
- Hypersensitivity to perflutren (see WARNINGS).

Do not administer DEFINITY® by intra-arterial injection.

## WARNINGS

### Serious Cardiopulmonary Reactions:

Serious cardiopulmonary reactions, including fatalities, have occurred during or following perflutren-containing microsphere administration. The risk for these reactions may be increased among patients with pulmonary hypertension or 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, monitor vital signs, electrocardiography, and cutaneous oxygen saturation during and for at least 30 minutes after DEFINITY® administration. In the absence of these underlying conditions, observe patients closely during and following DEFINITY® administration.

In postmarketing use, uncommon but serious reactions observed during or shortly following perflutren-containing microsphere administration included fatal cardiac or respiratory arrest, loss of consciousness, convulsions, symptomatic arrhythmias (atrial fibrillation, supraventricular tachycardia, ventricular tachycardia or fibrillation), hypotension, respiratory distress or cardiac ischemia (see ADVERSE REACTIONS).

Always have cardiopulmonary resuscitation personnel and equipment readily available prior to DEFINITY® administration and monitor all patients for acute reactions.



### **Anaphylactoid Reactions:**

Post-marketing reports of acute anaphylactoid reactions including shock, bronchospasm, upper airway swelling, loss of consciousness, urticaria and pruritus, have occurred in patients with no prior exposure to perflutren-containing microsphere products. Monitor all patients for signs and symptoms of anaphylactoid reactions (see ADVERSE REACTIONS).

### **Systemic Embolization of DEFINITY® in Patients with Cardiac Shunts:**

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

### **High Ultrasound Mechanical Index:**

High ultrasound mechanical index values may cause microsphere cavitation or rupture and lead to ventricular arrhythmias. Additionally, end-systolic triggering with high mechanical indices has been reported to cause ventricular arrhythmias. The safety of activated DEFINITY® at mechanical indices greater than 0.8 has not been evaluated. The safety of activated DEFINITY® with the use of end-systolic triggering has not been evaluated.

### **QTc Prolongation:**

ECG parameters for doses up to 10 µL/kg were monitored in 221 subjects at multiple time points from 1 hour to 72 hours after the first bolus injection. In the 221 subjects, QTc prolongations of >30 msec were noted in 64 (29%) subjects. Forty-six out of 64 subjects with QTc prolongations were further evaluated and 39% (18/46) showed associated cardiac rhythm changes. The effects of concomitant drugs were not studied.

## **PRECAUTIONS**

### **Information For Patients**

Patients receiving activated DEFINITY® should be instructed to inform their healthcare provider if they:

1. have a congenital heart defect, or recent worsening of heart or lung conditions,
2. have had prior reactions to DEFINITY® (see CONTRAINDICATIONS and WARNINGS),
3. may be pregnant, are trying to become pregnant, or are nursing.

## **Carcinogenesis, Mutagenesis, 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 up to 1 mL/kg (24x and 15x maximal human dose based on body surface area, respectively).

## **Pregnancy Category B**

Reproduction toxicity studies have been performed in rats and rabbits at up to 3 mL/kg and, 1 mL/kg (24x and 15x maximal human dose based on body surface area for rats and rabbits, respectively). The studies revealed no evidence of an effect of activated DEFINITY® treatment on the developing fetus. Adequate and well-controlled studies in pregnant women have not been conducted. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

## **Nursing Mothers**

Studies to detect if activated DEFINITY® is excreted in human milk have not been conducted. Because many drugs are excreted in human milk, caution should be exercised when activated DEFINITY® is administered to a nursing woman.

## **Pediatric Use**

The safety and effectiveness of activated DEFINITY® have not been established in the pediatric population (see WARNINGS).

## **ADVERSE REACTIONS**

### **Clinical Trials Experience**

A total of 1716 subjects were evaluated in pre-market clinical trials of activated DEFINITY®. In this group, 1063 (61.9%) were male and 653 (38.1%) were female, 1328 (77.4%) were White, 258 (15.0%) were Black, 74 (4.3%) were Hispanic, and 56 (3.3%) were classified as other racial or ethnic groups. The mean age was 56.1 years (range 18 to 93). Of these, 144 (8.4%) had at least one treatment-related adverse reaction (Table 3). There were 26 serious adverse events and 15 (0.9%) subjects discontinued because of an adverse event.

Deaths and serious adverse events: Among the 1716 activated DEFINITY® patients, 19 (1.1%) suffered serious cardiopulmonary adverse events including eight deaths. The deaths occurred

several days after activated DEFINITY® administration and appear to be related to the course of underlying disease. Of the 11 other serious adverse events, which appeared within days of the drug administration (2-15 days), all appeared to be a progression underlying cardiac and non-cardiac disease. However, a role for DEFINITY® in the initiation or course of these adverse events can not be ruled out.

Discontinuations: There were 15 discontinuations reported with a mean age of 41.5 years. Nine of these patients were discontinued after the first injection. One patient experienced a hypersensitivity reaction with urticaria and pruritus and all the other patients experienced dizziness, chest pain, dyspnea or back pain. 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.

For all adverse events, 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. As shown in Table 3, the most common adverse events were reported in the Central and peripheral nervous system (3.1%), Body as a Whole (2.4%) and Gastrointestinal system (1.8%). The most common events were headache (2.3%), back and renal pain (1.2%), flushing (1.1%) and nausea (1.0%).

**Table 3. Treatment-Related, New-Onset Adverse Experiences Occurring in  $\geq 0.5\%$  of All Activated DEFINITY<sup>®</sup>-Treated Subjects**

		All activated DEFINITY <sup>®</sup> (N=1716)
Total Number of Treatment-Related A.E.'s	269	
Total Number of Subjects with a Treatment-Related A.E.	144	(8.4%)
WHOART body system		
WHOART 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 <sup>®</sup>		
A.E.=Adverse Experience		
n=Number of subjects reporting at least one A.E.		

Other treatment-related adverse experiences that occurred in  $<0.5\%$  of the activated DEFINITY<sup>®</sup>-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, 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

**Miscellaneous:** Lymphadenopathy

## Post Marketing Experience

The following adverse reactions have been identified during the post-marketing use of perflutren-containing microsphere products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Fatal cardiac arrests and other serious but non-fatal adverse reactions were uncommonly reported. Most of these uncommon reactions included cardiopulmonary symptoms and signs such as cardiac or respiratory arrest, hypotension, supraventricular and ventricular arrhythmias, respiratory distress or decreased oxygenation. Reports also identified neurologic reactions (loss of consciousness or convulsions) as well as anaphylactoid reactions (see WARNINGS).

## OVERDOSAGE

The clinical consequences of overdosing with activated DEFINITY® are not known. Treatment of an overdose should be directed toward the support of all vital functions and prompt institution of symptomatic therapy (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

## DOSAGE AND ADMINISTRATION

**DEFINITY® IS INTENDED FOR ADMINISTRATION ONLY AFTER ACTIVATION IN THE VIALMIX® APPARATUS.** Before injection, this product must be activated and prepared according to the instructions outlined below. The Vialmix® apparatus should be ordered from Lantheus Medical Imaging, 331 Treble Cove Road, North Billerica, MA 01862. For customer orders call 1-800-299-3431.

DEFINITY® may be injected by either an intravenous bolus or infusion.

**Bolus:** The recommended dose for activated DEFINITY® is 10 microliters (µL)/kg of the activated product by intravenous bolus injection within 30-60 seconds, followed by a 10 mL saline flush. If necessary, a second 10 microliters (µL)/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 dose for activated DEFINITY® is via an IV infusion of 1.3 mL added to 50 mL of preservative-free saline. The rate of infusion should be initiated at 4.0 mL/minute, but titrated as necessary to achieve optimal image enhancement, not to exceed 10 mL/minute.

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.

**Imaging:** After baseline non-contrast echocardiography is completed, the mechanical index for the ultrasound device should be set at 0.8 or below (see WARNINGS). Then

inject activated DEFINITY<sup>®</sup> (as described above) and begin ultrasound imaging immediately. The activated DEFINITY<sup>®</sup> echocardiogram images should be evaluated in combination with the non-contrast echocardiogram images.

#### **DEFINITY<sup>®</sup> ACTIVATION, PREPARATION AND HANDLING INSTRUCTIONS:**

1. Allow the vial to warm to room temperature before starting the activation procedure.
2. Activate DEFINITY<sup>®</sup> by shaking the vial for 45 seconds using a Vialmix<sup>®</sup>.

Note: illustrations of this procedure are contained in the Vialmix<sup>®</sup> Users Guide.

**WARNING: DO NOT USE THIS DRUG UNLESS IT HAS COMPLETED A FULL 45 SECOND ACTIVATION CYCLE IN THE VIALMIX<sup>®</sup>. DEFINITY<sup>®</sup> WILL NOT BE PROPERLY ACTIVATED UNLESS THE FULL 45 SECOND ACTIVATION CYCLE IS COMPLETED. DO NOT REACTIVATE the vial if Vialmix<sup>®</sup> did not complete a full 45 second cycle. DO NOT REACTIVATE a successfully activated DEFINITY<sup>®</sup> vial (see step 3). DO NOT USE a Vialmix<sup>®</sup> that is not functioning properly. Refer to the "VIALMIX<sup>®</sup> User's Guide" for the "VIALMIX<sup>®</sup> CALIBRATION AND REPLACEMENT PROCEDURES" to ensure that a properly functioning Vialmix<sup>®</sup> is used.**

3. Immediately after activation in the Vialmix<sup>®</sup>, activated DEFINITY<sup>®</sup> appears as a milky white suspension and may be used immediately after activation. If the product is not used within 5 minutes of Vialmix<sup>®</sup> 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<sup>®</sup> may be used for up to 12 hours from the time of Vialmix<sup>®</sup>, but only after the microspheres are resuspended by hand agitation. Store the activated DEFINITY<sup>®</sup> at room temperature in the original product vial.
4. Invert the vial and withdraw the activated milky white suspension using the Intellipin<sup>™</sup> (Dispensing Pin) or 18 to 20 gauge syringe needle. Withdraw the material from the middle of the liquid in the inverted vial. **DO NOT INJECT AIR INTO THE DEFINITY<sup>®</sup> VIAL.**
5. Use the product immediately after its withdrawal from the vial; do not allow the product to stand in the syringe.

**FOR SINGLE USE ONLY:** DEFINITY<sup>®</sup> does not contain bacterial preservative. Bacterial contamination with the risk of post-administration septicemia can occur following the puncture of the elastomeric septum. It is essential to follow directions for activation of DEFINITY<sup>®</sup> carefully and to adhere to strict aseptic procedures during preparation.

## HOW SUPPLIED

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

## STORAGE

Store between 2-8°C (36°-46°F) in a refrigerator.

CAUTION: Federal law prohibits dispensing without prescription.

Distributed By  
Lantheus Medical Imaging  
331 Treble Cove Road  
N. Billerica, Massachusetts 01862 USA  
For ordering, tel. toll free: 800-225-1572  
All Other Business: 800-362-2668  
(For Massachusetts and International,  
call 978-667-9531)

515188-0408

## OPTISON™

(Perflutren Protein-Type A Microspheres Injectable Suspension, USP)

### WARNING: Serious Cardiopulmonary Reactions

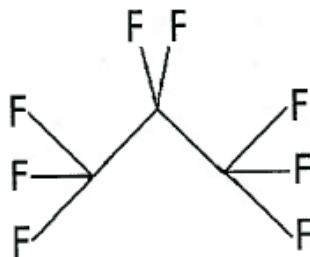
Serious cardiopulmonary reactions, including fatalities, have occurred during or within 30 minutes following perflutren-containing microsphere administration.

- Assess all patients for the presence of any condition that precludes OPTISON™ administration (see CONTRAINDICATIONS).
- Monitor patients during and for 30 minutes following OPTISON™ administration, including vital sign measurements and electrocardiography in all patients and cutaneous oxygen saturation in patients at risk for hypoxemia. Always have resuscitation equipment and trained personnel readily available (see WARNINGS).

### DESCRIPTION

OPTISON™ (Perflutren Protein-Type A Microspheres Injectable Suspension, USP) is a sterile non-pyrogenic suspension of microspheres of human serum albumin with perflutren for contrast enhancement during the indicated ultrasound imaging procedures. The vial contains a clear liquid lower layer and a white upper layer that, after resuspension by gentle mixing, provides a homogeneous, opaque, milky-white suspension for intravenous injection.

Perflutren is chemically characterized as 1,1,1,2,2,3,3,3-perflutren with a molecular weight of 188, an empirical formula of C<sub>3</sub>F<sub>8</sub> and it has the following structural formula:



Each mL of OPTISON™ contains 5.0-8.0x10<sup>8</sup> protein-type A microspheres, 10 mg Albumin Human, USP, 0.22 ± 0.11 mg/mL perflutren, 0.2 mg N-acetyltryptophan, and 0.12 mg caprylic acid in 0.9% aqueous sodium chloride. The headspace of the vial is filled with perflutren gas. The pH is adjusted to 6.4-7.4. The protein in the microsphere shell makes up approximately 5-7% (w/w) of the total protein in the liquid. The microsphere particle size parameters are listed in Table 1.



Table 1 Microsphere Particle Size Parameters	
Mean diameter (range)	3.0-4.5µm (max. 32.0µm)
Percent less than 10µm	95%

## CLINICAL PHARMACOLOGY

### General

The OPTISON™ microspheres create an echogenic contrast effect in the blood.

### Pharmacokinetics

Studies in humans have evaluated the pharmacokinetics of the perflutren component of the OPTISON™ microspheres. After injection of OPTISON™, diffusion of the perflutren gas out of the microspheres is limited by the low partition coefficient of the gas in blood that contributes to the persistence of the microspheres. The diffusion rate has not been studied.

In an anesthetized dog model, the acoustic properties of OPTISON™ were established at 0.6 mechanical index and 2.5 MHz frequency.

Neither the pharmacokinetics of the intact microspheres or of the human albumin component have been evaluated in humans.

### Metabolism

Perflutren is a stable gas that is not metabolized. The human albumin component of the microsphere is expected to be handled by the normal metabolic routes for human albumin.

### Perflutren Elimination

Following a single intravenous dose of 20 mL OPTISON™ to 10 healthy volunteers (5 men and 5 women), most of the perflutren was eliminated through the lungs within 10 minutes. The recovery was  $96\% \pm 23\%$  (mean  $\pm$  SD), and the pulmonary elimination half-life was  $1.3 \pm 0.69$  minutes (mean  $\pm$  SD). The perflutren concentration in expired air peaked approximately 30-40 seconds after administration.

### Perflutren Protein Binding

The binding of perflutren to plasma proteins or its partitioning into blood cells have not been studied. However, perflutren protein binding is expected to be minimal due to the low partition coefficient of the gas in blood.

### Special Populations

The pharmacokinetics of OPTISON™ have not been studied in patients with hepatic or respiratory diseases.

**Gender, Age, Race**

The effects of gender, age, or race on the pharmacokinetics of OPTISON™ have not been studied.

**Drug-Drug Interactions**

Drug-drug interactions for OPTISON™ have not been studied.

**Pediatrics**

The pharmacokinetics of OPTISON™ in pediatric patients have not been studied.

**Pharmacodynamics**

The general acoustic properties of OPTISON™ are similar to those of ALBUNEX®. The acoustic impedance of the OPTISON™ microspheres is much lower than that of the blood. Therefore, impinging ultrasound waves are scattered and reflected at the microsphere-blood interface and ultimately may be visualized in the ultrasound image. At the frequencies used in adult echocardiography (2-5 MHz), the microspheres resonate which further increases the extent of ultrasound scattering and reflection.

As assessed by the unblinded investigators in clinical studies, the median duration of OPTISON™ contrast enhancement for each of the four doses of OPTISON™ (0.2, 0.5, 3.0, and 5.0 mL) were approximately one, two, four, and five minutes, respectively (see CLINICAL TRIALS section).

**CLINICAL TRIALS**

The efficacy of OPTISON™ was evaluated in two identical multicenter, dose escalation, randomized, cross-over studies of OPTISON™ and ALBUNEX®. The test drugs were administered single blind and the image analysis was double blind. Eligible patients were undergoing routine echocardiography and all patients were required to have at least two of six segments of the left ventricular endocardial border that were not well delineated in the apical 4-chamber view. In these studies, the 203 patients (Study A: n=101, Study B: n=102) received at least one dose of study drug had the following characteristics: 79% men, 21% women, 64% White, 25% Black, 10% Hispanic, and 1% other race or ethnic group. The patients had a mean age of 61 years (range: 21 to 83 years), a mean weight of 196 lbs (range: 117 to 342 lbs), a mean height of 68 inches (range: 47 to 78 inches), and a mean body surface area of 2.0m<sup>2</sup> (range: 1.4 to 2.6m<sup>2</sup>). Approximately 23% of the patients had chronic pulmonary disease, and 17% had congestive and dilated cardiomyopathy with left ventricular ejection fractions (LVEFs) of between 20% and 40% (by previous echocardiography). Patients with a LVEF of less than 20% or with New York Heart Association Class IV heart failure were not included in the studies.

The study test drugs were four doses of OPTISON™ (0.2, 0.5, 3.0 and 5.0 mL) and two doses of ALBUNEX® (0.08 and 0.22 mL/kg). The two test drugs were administered to the patients in a random sequence, with two to ten days between each drug. After non-contrast imaging, the test doses were administered in ascending order with at least ten minutes between each dose. Ultrasound settings were optimized for the baseline (non-

contrast) apical four-chamber view and remained unchanged for the contrast imaging. Static echocardiographic images and video-tape segments were interpreted by a reader who was blinded to the patient's clinical history and to the identity and dose of the test drug. The primary efficacy endpoint was left ventricular endocardial border delineation, assessed before and after OPTISON™ administration, by the measurement of visualized endocardial border length. The six segments of the left ventricular endocardial border were also assessed qualitatively (i.e., not well delineated, average delineation, good delineation, excellent delineation) before and after OPTISON™ administration.

In comparison to non-contrast ultrasound, OPTISON™ significantly increased the length of endocardial border that could be visualized both at end-systole and end-diastole (see Table 2). In these patients there was a trend towards less visualization in women. Similarly, in comparison to non-contrast ultrasound, OPTISON™ significantly improved the qualitative ability to delineate each of the left ventricular segments, though the effect was less for the septal segments. As assessed by videodensitometry, OPTISON™ increased left ventricular opacification (peak intensity) in the mid-chamber and apical views (see Table 3). In subset analysis, OPTISON™ tended to enhance the quality of the spectral Doppler signal of the pulmonary veins. The imaging effects of OPTISON™ on endocardial border delineation and left ventricular opacification tended to be qualitatively similar in patients with and without pulmonary disease or dilated cardiomyopathy.

In these studies, quantitative measures of left ventricular function (e.g., ejection fraction), quantitative measurements of anatomical structures (e.g., wall thickness), or the evaluation of myocardial perfusion were not performed.

Table 2 Left Ventricular Endocardial Border Length Before and After OPTISON™ <sup>a, b</sup>				
	Length at End-Systole (cm)		Length at End-Diastole (cm)	
OPTISON™ dose	n	mean ± S.D.	n	mean
Study A (n=101)				
0 mL (baseline)	87	7.7 ± 3.0	86	9.3 ± 3.4
0.2 mL	85	11.7 ± 4.3	85	15.7 ± 3.8
0.5 mL	86	12.0 ± 4.9	91	15.8 ± 5.1
3.0 mL	87	12.3 ± 4.4	88	16.7 ± 4.0
5.0 mL	89	12.7 ± 4.9	90	16.6 ± 4.3
Study B (n=102)				
0 mL (baseline)	89	8.1 ± 3.4	89	9.6 ± 3.7
0.2 mL	90	11.3 ± 4.5	95	15.0 ± 5.3
0.5 mL	95	12.4 ± 4.9	97	16.4 ± 4.6
3.0 mL	94	12.6 ± 4.8	99	16.5 ± 4.7
5.0 mL	92	13.0 ± 4.5	95	16.2 ± 5.1
a The differences in the number of enrolled patients and evaluated patients at each dose reflects exclusions based on withdrawal from the trial, or those with technically inadequate or missing images. b An intent-to-treat analysis, with non-favorable values imputed for missing patients, provided qualitatively similar results.				

<p align="center"><b>Table 3</b>  <b>Intensity of Left Ventricular Opacification<sup>a</sup></b>  <b>Before and After OPTISON<sup>TM</sup> <sup>b,c</sup></b></p>								
	Mid-Chamber				Apex			
	Intensity at End-Diastole		Intensity at End-Systole		Intensity at End-Diastole		Intensity at End-Systole	
OPTISON <sup>TM</sup> dose	n	mean ± S.D.	n	mean ± S.D.	n	mean ± S.D.	n	mean ± S.D.
Study A (n = 101)								
0 mL (baseline)	91	39.5 ± 16.9	91	40.0 ± 18.1	91	46.7 ± 19.7	91	46.9 ± 20.1
0.2 mL	91	56.7 ± 26.2	91	55.4 ± 26.6	91	63.2 ± 28.9	91	61.1 ± 28.5
0.5 mL	91	57.3 ± 26.8	90	57.4 ± 26.7	91	67.0 ± 30.1	90	64.1 ± 30.2
3.0 mL	90	53.9 ± 22.5	90	55.8 ± 24.3	90	66.1 ± 28.2	90	61.8 ± 26.8
5.0 mL	89	54.7 ± 24.0	89	57.9 ± 28.3	89	69.1 ± 30.4	89	63.7 ± 28.9
Study B (n = 102)								
0 mL (baseline)	95	40.4 ± 17.4	95	40.9 ± 17.5	95	43.7 ± 19.9	95	45.0 ± 19.6
0.2 mL	97	52.5 ± 21.0	97	51.5 ± 20.6	97	58.4 ± 22.2	97	56.0 ± 22.2
0.5 mL	97	53.3 ± 20.7	96	53.6 ± 21.0	97	64.4 ± 25.3	96	61.6 ± 26.7
3.0 mL	99	51.2 ± 23.6	99	55.6 ± 24.5	99	65.4 ± 26.3	99	62.7 ± 25.7
5.0 mL	95	51.8 ± 23.8	95	55.6 ± 24.8	95	65.2 ± 28.1	95	62.8 ± 28.1
<p>a Intensity measured by videodensitometry in arbitrary gray scale units (0-255).</p> <p>b The differences in the number of enrolled patients and evaluated patients at each dose reflects exclusions based on withdrawal from the trial, or those with technically inadequate or missing images.</p> <p>c An intent-to-treat analysis, with non-favorable values imputed for missing patients, provided qualitatively similar results.</p>								

## INDICATIONS

OPTISON<sup>TM</sup> is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricle and to improve the delineation of the left ventricular endocardial borders. The safety and efficacy of OPTISON<sup>TM</sup> with exercise stress or pharmacologic stress testing have not been established.

## CONTRAINDICATIONS

Do not administer OPTISON<sup>TM</sup> to patients with known or suspected:

- o Right-to-left, bi-directional, or transient right-to-left cardiac shunts,
- o Worsening or clinically unstable congestive heart failure,
- o Acute myocardial infarction or acute coronary syndromes,
- o Serious ventricular arrhythmias or high risk for arrhythmias due to prolongation of the QT interval,
- o Respiratory failure, as manifest by signs or symptoms of carbon dioxide retention or hypoxemia,



- o Severe emphysema, pulmonary emboli or other conditions that cause pulmonary hypertension due to compromised pulmonary arterial vasculature, and
- o Hypersensitivity to perflutren, blood, blood products, or albumin (see WARNINGS).

Do not administer OPTISON™ by intra-arterial injection.

## **WARNINGS**

### **Serious Cardiopulmonary Reactions**

Serious cardiopulmonary reactions, including fatalities, have occurred during or within 30 minutes following perflutren-containing microsphere administration. Assess all patients for the presence of any condition that precludes OPTISON™ administration (see CONTRAINDICATIONS). Monitor patients during and for 30 minutes following OPTISON™ administration, including vital sign measurements and electrocardiography in all patients and cutaneous oxygen saturation in patients at risk for hypoxemia. Always have resuscitation equipment and trained personnel readily available.

In postmarketing use, four patients experienced fatal cardiac arrests either during or within 30 minutes of perflutren-containing microsphere administration; one patient received the product and underwent a cardiac stress test, two patients had severe congestive heart failure and the fourth was undergoing mechanical ventilation for respiratory failure. Other uncommon but serious reactions observed during or shortly following perflutren-containing microsphere administration included cardiac or respiratory arrest, loss of consciousness, convulsions, symptomatic arrhythmias (atrial fibrillation, supraventricular tachycardia, ventricular tachycardia or fibrillation), hypotension, respiratory distress or cardiac ischemia (see ADVERSE REACTIONS).

### **Anaphylactoid Reactions**

Postmarketing reports of acute anaphylactoid reactions including shock, bronchospasm, upper airway swelling, loss of consciousness, urticaria and pruritus, have occurred in patients with no prior exposure to perflutren-containing microsphere products. Monitor all patients for signs and symptoms of anaphylactoid reactions (see ADVERSE REACTIONS).

### **Systemic Embolization of OPTISON™ in Patients with Cardiac Shunts**

In patients with right-to-left, bi-directional, or transient right-to-left cardiac shunts perflutren-containing microspheres can bypass the pulmonary particle-filtering mechanisms and directly enter the arterial circulation resulting in microvascular occlusion and ischemia. Do not administer OPTISON™ by intra-arterial injection.

### **High Ultrasound Mechanical Index**

High ultrasound mechanical index values may cause microsphere cavitation or rupture and lead to ventricular arrhythmias. Additionally, end-systolic triggering with high mechanical indices has been reported to cause ventricular arrhythmias. The safety of OPTISON™ at mechanical indices greater than 0.8 has not been evaluated. The safety of OPTISON™ with the use of end-systolic triggering has not been evaluated.

## **PRECAUTIONS**

### **General**

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral disease. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral disease or CJD have ever been identified for albumin.

### **Laboratory Tests**

Immunologic tests of serum immunoglobulins, cytokines, and complement were monitored in a 3 week study of 20 healthy volunteers and 30 patients who received OPTISON™ or a 1% albumin control. Clinically relevant changes in the measured parameters were not noted. In another study 5 subjects received a skin test with OPTISON™ one year after receiving OPTISON™. One subject had a positive skin test and was not given a repeat dose of OPTISON™.

### **Information for Patients**

Patients receiving OPTISON™:

1. Inform your physician or health care provider if you may be pregnant or are nursing an infant.
2. Inform your physician if you ever have had an allergic or hypersensitivity reaction to blood, blood products, or albumin.
3. Inform your physician or health care provider if you have a congenital heart defect.

### **Carcinogenesis, Mutagenesis, and Impairment of Fertility**

Animal studies were not carried out to determine the carcinogenic potential of OPTISON™.

The result of the following genotoxicity studies with OPTISON™ were negative: 1) Salmonella/Escherichia coli reverse mutation assay, 2) in vitro mammalian chromosome aberration assay using Chinese hamster ovary cells (CHO) with and without metabolic activation, 3) CHO/HGPRT forward mutation assay, and 4) in vivo mammalian micronucleus assay.

### **Pregnancy Category C**

OPTISON™ administered intravenously to rats during organogenesis at doses of 0.25, 5.0 and 10.0 mL/kg/day was fetotoxic at 0.25 and 5.0 mL/kg (approximately 0.2 and 5 times the recommended maximum human dose, respectively, based on body surface area). Fetotoxicity was characterized by an increased incidence of reversible delayed pelvic ossification, the incidence of which was not related to dose. Signs of maternal toxicity at 5 mL/kg included respiratory and motor signs. Maternal death occurred at 10 mL/kg. A no observable adverse effect level (NOAEL) for fetotoxicity was not determined. Teratogenic effects were not observed at doses up to 10 mL/kg/day. The NOAEL for maternal toxicity was 0.25 mL/kg.

OPTISON™ administered intravenously to rabbits during organogenesis at doses of 0.25, 2.5 and 5.0 mL/kg/day was embryofetal toxic at 2.5 and 5.0 mL/kg (approximately 5 and 10 times the recommended maximum human dose, respectively, based on body surface area). Embryofetal toxicity was characterized by a decrease in fetal body weight and an increase in embryofetal death. Teratogenic effects (cleft palates and dilation of the lateral ventricles of the brain associated with skull abnormalities and compression deformities) were observed at 2.5 mL/kg but not 5 mL/kg. Neither the incidence nor the severity of embryofetal toxicity and teratogenicity exhibited a dose-dependent relationship. Maternal toxicity (significant suppression of body weight gain, abnormal stool) was observed at 2.5 and 5.0 mL/kg with the greatest effect observed at 2.5 mL/kg. The NOAEL for embryofetal and maternal toxicity was 0.25 mL/kg (approximately 0.5 times the recommended maximum human dose).

Adequate or well-controlled studies were not conducted in pregnant women. OPTISON™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### **Nursing Mothers**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk caution should be exercised when OPTISON™ is administered to a nursing woman.

#### **Pediatric Use**

Safety and efficacy have not been established in pediatric patients, or in patients with congenital heart disease (see WARNINGS).

### **ADVERSE REACTIONS**

#### **Clinical Trials Experience**

OPTISON™ was administered in clinical studies in 279 patients. Of these patients there were 192 (68.8%) men and 87 (31.2%) women. The racial demographics were 199 (71.3%) Caucasian, 52 (18.6%) Black, 24 (8.6%) Hispanic, and 4 (1.4%) other racial or ethnic groups.

In these patients, 47 (16.8%) reported at least one adverse event. Of these one event was serious and required treatment with antihistamines for hypersensitivity manifestations of dizziness, nausea, flushing and temperature elevation. Deaths were not reported during the clinical studies.

Of the reported adverse reactions following the use of OPTISON™ the most frequently reported were headache (5.4%), nausea and/or vomiting (4.3%), warm sensation or flushing (3.6%), and dizziness (2.5%). The most common adverse events observed in clinical studies of OPTISON™ are given in Table 4.



<p align="center">Table 4  SELECTED ADVERSE EVENTS REPORTED IN <math>\geq 0.5\%</math>  OF THE SUBJECTS WHO RECEIVED OPTISON™  IN CONTROLLED CLINICAL STUDIES <sup>(1)(2)</sup></p>		
No. of Patients Exposed to OPTISON™	279	
No. of Patients Reporting on Adverse Event	47	(16.8%)
Body as a Whole	38	(13.6%)
Headache	15	(5.4%)
Warm Sensation/Flushing	10	(3.6%)
Chills/fever	4	(1.4%)
Flu-like Symptoms	3	(1.1%)
Malaise/Weakness/Fatigue	3	(1.1%)
Cardiovascular System	12	(4.3%)
Dizziness	7	(2.5%)
Chest Pain	3	(1.1%)
Digestive System	12	(4.3%)
Nausea and/or Vomiting	12	(4.3%)
Nervous System	3	(1.1%)
Respiratory System	5	(1.8%)
Dyspnea	3	(1.1%)
Skin & Appendages	11	(3.9%)
Injection Site Discomfort	3	(1.1%)
Erythema	2	(0.7%)
Special Senses	9	(3.2%)
Altered Taste	5	(1.8%)
(1) Patients are counted separately within each body system.		
(2) The body system is reported if the aggregate is $\geq 0.5\%$ . Details are not shown if the subsystem is not $\geq 0.5\%$ .		

Adverse events reported in  $< 0.5\%$  of subjects who received OPTISON™ included: arthralgia, back pain, body or muscle aches, induration, urticaria, dry mouth, eosinophilia, palpitations, paresthesia, photophobia, premature ventricular contraction, pruritus, rash, irritableness, hypersensitivity, tinnitus, tremor, visual blurring, wheezing, oxygen saturation decline due to coughing, discoloration at the Heplock site, and burning sensation in the eyes.

Overall the reported adverse events with OPTISON™ were similar in type and frequency to those reported in the 199 patients who received ALBUNEX®.

In the clinical dose ranging studies of 40 normal volunteers, doses higher than those recommended in the DOSAGE AND ADMINISTRATION section tended to be associated with an increased frequency of reported adverse events.

### **Postmarketing Experience**

The following adverse reactions have been identified during the postmarketing use of perflutren-containing microsphere products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Four fatal cardiac arrests and other serious but non-fatal adverse reactions were uncommonly reported. Most of these uncommon reactions included cardiopulmonary symptoms and signs such as cardiac or respiratory arrest, hypotension, supraventricular and ventricular arrhythmias, respiratory distress or decreased oxygenation. Reports also identified neurologic reactions (loss of consciousness or convulsions) as well as anaphylactoid reactions (see WARNINGS).

### **DOSAGE AND ADMINISTRATION**

The recommended dose of OPTISON™ is 0.5 mL injected into a peripheral vein. This may be repeated for further contrast enhancement as needed. See individualization of dose below.

1. The injection rate should not exceed 1 mL per second.
2. Follow the OPTISON™ injection with a flush of 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP.
3. The maximum total dose should not exceed 5.0 mL in any 10 minute period.
4. The maximum total dose should not exceed 8.7 mL in any one patient study.

### **Individualization of Dose**

Image quality in cardiac ultrasound is a function of the acoustic window which is influenced by many variables including body habitus, intervening lung tissue, adequacy of transducer skin interface and other acoustic factors. These variables may influence the ultrasound contrast effect.

If the contrast enhancement is inadequate after the dose of 0.5 mL, additional doses in increments of 0.5 mL up to 5.0 mL cumulatively in a 10 minute period may be injected intravenously up to a maximum total dose of 8.7 mL in any one patient study.

### **DRUG HANDLING DIRECTIONS**

#### **FOR SINGLE USE ONLY.**

OPTISON™ does not contain preservatives. Bacterial contamination with the risk of post-infusion septicemia can occur if the container has been damaged or following puncture of the rubber cap. A single vial must not be used for more than one patient. Discard unused product properly.

**DO NOT USE** if the container has been damaged or the protective seal and/or rubber cap have been entered.

**DO NOT USE** if the upper white layer is absent. This indicates that the microspheres may have been damaged and may result in poor or no echo contrast.

**DO NOT INJECT** air into the vial.

1. Invert the OPTISON™ vial and gently rotate to resuspend the microspheres. This process will allow the product to come to room temperature before use.
  2. Inspect the vial for complete resuspension. Failure to adequately resuspend OPTISON™ may cause an under delivery of the microspheres, and may result in inadequate contrast.
  3. Do not use OPTISON™ if, after resuspension, the solution appears to be clear rather than opaque milky-white.
  4. Vent the OPTISON™ vial with a sterile vent spike or with a sterile 18 gauge needle before withdrawing the OPTISON™ suspension into the injection syringe.
- DO NOT USE** if after resuspending the OPTISON™, the product remains clear rather than appearing opaque and milky-white.

#### **INJECTION PROCEDURE:**

The time from resuspension of the OPTISON™ to injection must not exceed one minute. If one minute is exceeded, resuspend the microspheres in the syringe by gently rotating and inverting the syringe.

Before injection, provide intravenous access in a peripheral vein with a 20-gauge or larger angiocatheter. Suggested methods of administration include: a short extension tubing, heparin lock, or intravenous line, all with a 3-way stopcock.

For short extension tubing or heparin lock: fill one syringe with 0.9% Sodium Chloride Injection, USP, and flush the line for patency before and after the injection of OPTISON™.

For a continuous intravenous line: open an intravenous line with 0.9% Sodium Chloride Injection, USP (or 5% Dextrose Injection, USP) at a slow infusion rate to maintain vascular patency. The line should be flushed immediately after injection of OPTISON™.

**DO NOT ASPIRATE** blood back into the OPTISON™ containing syringe before administration; this may promote the formation of a blood clot within the syringe.

#### **HOW SUPPLIED**

OPTISON™ (Perflutren Protein-Type A Microspheres Injectable Suspension, USP) is available in a carton of five 3 mL fills in single use 3 mL vials.

NDC 0407-2707-03

#### **STORAGE**

Store OPTISON™ refrigerated between 2°-8°C (36°-46°F).

Caution: Do not freeze.

**Rx ONLY**

GE Healthcare



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GE Healthcare Inc.  
Princeton, NJ 08540

Manufactured by  
Mallinckrodt Inc.  
St. Louis, MO 63042

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## Micro-bubble Contrast Agents (marketed as Definity (Perflutren Lipid Microsphere) Injectable Suspension and Optison (Perflutren Protein-Type A Microspheres for Injection))

**FDA ALERT [10/2007]** - FDA has received reports of deaths and serious cardiopulmonary reactions following the administration of ultrasound micro-bubble contrast agents used in echocardiography. Four of the 11 reported deaths were caused by cardiac arrest occurring either during infusion or within 30 minutes following the administration of the contrast agent; most of the serious but non-fatal reactions also occurred in this time frame. FDA has requested that a Boxed Warning and other warnings emphasizing the risk for serious cardiopulmonary reactions be added to the labeling for these products and that use of these products be contraindicated in patients with unstable cardiopulmonary status, including patients with unstable angina, acute myocardial infarction, respiratory failure, or recent worsening congestive heart failure.

*This information reflects FDA's current analysis of data available to FDA concerning this drug. FDA intends to update this when additional information or analyses become available.*

- **Healthcare Professional Information**

- [Information for Healthcare Professionals](#)
- [Labeling for Definity from Drugs@FDA](#)
- [Labeling for Optison from Drugs@FDA](#) (labeling will be updated soon)

### [Report Adverse Events to MedWatch](#)

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Date created: October 12, 2007

**Information for Healthcare Professionals**  
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*This information reflects FDA's current analysis of data available to FDA concerning this drug. FDA intends to update this when additional information or analyses become available.*

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*Report serious adverse events to FDA's MedWatch reporting system by completing a form online at <http://www.fda.gov/medwatch/report.htm>, by faxing (1-800-FDA-0178), by mail using the postage-paid address form provided online (5600 Fishers Lane, Rockville, MD 20852-9787), or by telephone (1-800-FDA-1088).*

### **Considerations**

Physicians who administer echocardiographic micro-bubble contrast agents should consider the following:

- Assess all patients for the presence of the following conditions that would preclude the use of these agents:
  - Right-to-left, bi-directional, or transient right-to-left cardiac shunts
  - Clinically unstable or recent worsening congestive heart failure
  - Acute myocardial infarction
  - Serious ventricular arrhythmias or at high risk for arrhythmias due to QT prolongation
  - Respiratory failure
  - Severe emphysema, pulmonary emboli or other conditions that compromise pulmonary arterial vasculature
- Monitor all patients receiving micro-bubble contrast agents for serious cardiopulmonary reactions during the infusion and for 30 minutes following completion of administration.

### **Information for the Patient**

- Tell the physician performing the echocardiogram if you:
  - have a congenital heart defect
  - have a heart or lung condition that has recently gotten worse
  - have ever had a reaction to a drug given to you during an echocardiogram

## Data Summary

Micro-bubble ultrasound contrast agents are a sterile suspension of perflutren gas microspheres that are indicated for use in patients with suboptimal echocardiograms. These products are used to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border. Definity and Optison are the only micro-bubble products approved for use in the United States. FDA approved Optison in 1997. The manufacturer of Optison voluntarily temporarily suspended marketing the product in 2005. Definity has been marketed since FDA approval in 2001. Most postmarketing reports are associated with the use of Definity.

FDA received postmarketing reports of 10 deaths following the administration of Definity and one death following Optison administration. Most of the reported deaths were patients with severe underlying conditions and occurred one to 12 hours following administration of the contrast agent. Some patients were also being treated with other medications that could have contributed to their death. Four deaths, following cardiac arrest, occurred either during or within 30 minutes of the administration of Definity. One patient received Definity and underwent a cardiac stress test while two patients had severe congestive heart failure and one patient was undergoing mechanical ventilation for respiratory failure.

FDA also received approximately 190 reports of serious non-fatal reactions following the administration of Definity and nine reports of serious non-fatal reactions following Optison administration. Many of these reports describe the acute onset of symptoms suggestive of an anaphylactoid reaction including dyspnea or urticaria. Other reports describe cardiopulmonary reactions with cardiac or respiratory arrest, loss of consciousness, convulsions, symptomatic arrhythmias (atrial fibrillation, supraventricular tachycardia, ventricular tachycardia or fibrillation), cardiac ischemia, hypotension, respiratory distress, and oxygen desaturation without signs or symptoms typical of an allergic reaction. Many of these serious reactions occurred either during or within minutes of administration of the ultrasound contrast agent.


The manufacturers of Definity and Optison have agreed to revise the labeling for these products in order to optimize their safe use by adding the following:

- **Boxed Warning** for cardiopulmonary reactions and **Warnings** for cardiopulmonary and hypersensitivity reactions that include recommendations to monitor vital signs, cardiac rhythm, oxygen saturation and to have equipment for resuscitation and trained personnel readily available.
- **Contraindications** for use in patients at particular at risk from cardiopulmonary reactions specifically patients with known cardiac shunts, clinically unstable or recent worsening of congestive heart failure, symptomatic arrhythmias or at high risk for arrhythmias due to QT prolongation, respiratory failure, severe emphysema, pulmonary emboli or other conditions that compromise pulmonary arterial vasculature.

- A statement in the ***Indications*** section cautioning that the safety and efficacy of the use of Definity with exercise or pharmacological stress testing have not been established.

The manufacturers will also conduct a postmarketing safety study to further assess the risks of serious cardiovascular reactions.

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