Errata to FDA Briefing Document
for the June 24, 2008 meeting of the
Cardiovascular and Renal Drugs Advisory Committee

The committee will discuss safety considerations in the development of ultrasound contrast agents. Four items are modified to provide updated information and clarification.

Item 1) Page 7, third bullet point:

Current:

- " FDA has finalized the risk management plan with the manufacturer of Definity and has approved labeling changes that remove most of the contraindications cited in the October, 20007 modification, as well as focused monitoring procedures upon patients with underlying pulmonary hypertension or unstable cardiopulmonary conditions. FDA is working with the manufacturer of Optison to effect similar changes to the label and to finalize a risk assessment and management program."

Replaced with (updated text to reflect actions that took place following preparation of the briefing background material):

- " FDA has finalized the risk management plan with the manufacturer of Definity and Optison and has approved labeling changes that remove most of the contraindications cited in the October, 20007 modification, as well as focused monitoring procedures upon patients with underlying pulmonary hypertension or unstable cardiopulmonary conditions."

Item 2) Page 23:

Current: Contains Optison product labeling, as of the due date for the background briefing material.

Replaced with: On June 6, 2008 FDA approved revised labeling for Optison. This revised labeling is attached to this Errata document (copied from http://www.fda.gov/cder/foi/label/2008/020899s011lbl.pdf, "Drugs at FDA").

Item 3) Page 6, second major bullet, second sub-bullet:

Current:

" - animal study findings appeared to duplicate the pattern of serious cardiopulmonary reactions observed in humans; administration of Optison and SonoVue was reported to cause transient but marked pulmonary hypertension and systemic hypotension in pigs at clinically relevant doses of the contrast agents."

Replaced with:

" - some dog and pig study hemodynamic findings provided a plausible pathophysiologic correlate to the pattern of serious cardiopulmonary reactions observed in humans; administration of Optison, Definity and SonoVue was reported to cause transient but marked pulmonary hypertension and systemic hypotension in pigs at clinically relevant doses of the contrast agents."

Item 4) Page 6, second major bullet, third sub-bullet:

Current:

"- the precedent for SonoVue. SonoVue is a product marketed in Europe that is contraindicated for use in patients with recent acute coronary syndromes, clinically unstable ischemic cardiac disease, acute cardiac failure, class 3/4 cardiac failure or severe rhythm disorders."

Replaced with:

" - the precedent for SonoVue. SonoVue is a product marketed in Europe for echocardiography, imaging of peripheral vasculature and for the characterization of focal lesions of the breast and liver. The cardiac indication was suspended for four months following some reports of serious adverse events and subsequently reinstated with contraindications for the use of SonoVue in patients with recent acute coronary syndromes, clinically unstable ischemic cardiac disease, acute cardiac failure, class 3/4 cardiac failure or severe rhythm disorders."

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

WARNING: Serious Cardiopulmonary Reactions

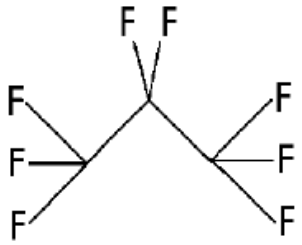
Serious cardiopulmonary reactions, including fatalities, have occurred during or following perflutren-containing microsphere administration.

- **Assess all patients for the presence of any condition that precludes OPTISON 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 OPTISON administration (see WARNINGS).**
- **Always have resuscitation equipment and trained personnel readily available.**

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_3F_8 and it has the following structural formula:



Each mL of OPTISON contains 5.0-8.0x10^8 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% ± 23% (mean ± SD), and the pulmonary elimination half-life was 1.3 ± 0.69 minutes (mean ± 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.

Pharmocodynamics
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 $2.0m^2$ (range: 1.4 to $2.6m^2$). 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 [a, b]

	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.

Table 3
Intensity of Left Ventricular Opacification[a]
Before and After OPTISON™ [b,c]

	Mid-Chamber		Apex	
	Intensity at End-Diastole	Intensity at End-Systole	Intensity at End-Diastole	Intensity at End-Systole

OPTISON 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

a Intensity measured by videodensitometry in arbitrary gray scale units (0-255).
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.
c An intent-to-treat analysis, with non-favorable values imputed for missing patients, provided qualitatively similar results.

INDICATIONS

OPTISON 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 with exercise stress or pharmacologic stress testing have not been established.

CONTRAINDICATIONS

Do not administer OPTISON to patients with known or suspected:

- Right-to-left, bi-directional, or transient right-to-left cardiac shunts,
- 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 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 OPTISON administration. In the absence of these underlying conditions, observe patients closely during and following OPTISON 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 OPTISON administration and monitor all patients for acute 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 (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 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 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 reactions to blood, blood products, albumin or a prior OPTISON administration (see CONTRAINDICATIONS and WARNINGS);

3. may be pregnant or are nursing an infant.

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.

Table 4
SELECTED ADVERSE EVENTS REPORTED IN ≥ 0.5%
OF THE SUBJECTS WHO RECEIVED OPTISON™
IN CONTROLLED CLINICAL STUDIES (1)(2)

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 ≥ 0.5%.
Details are not shown if the subsystem is not ≥ 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.

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

Distributed by
GE Healthcare Inc.
Princeton, NJ 08540

Manufactured by
Mallinckrodt Inc.
St. Louis, MO 63042

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