Joint Meeting of the Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committees

2 May 2011

OPTISON™

Perflutren Protein-Type A Microspheres Injectable Suspension, USP

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1 TABLE OF CONTENTS

1 TABLE OF CONTENTS 2

2 LIST OF TABLES AND FIGURES 4

3 LIST OF ABBREVIATIONS 5

4 EXECUTIVE SUMMARY 7

5 BACKGROUND OVERVIEW 14

5.1 Objective 14
5.2 Organization of the Briefing Document 14
5.3 Regulatory Background 14
5.4 Fundamental Concepts of Ultrasound Contrast Agents 17
5.4.1 OPTISON™ Product Information 17
5.4.2 Principle 17
5.4.3 Effects of Size 17
5.4.4 Effects of Gas and Shell Type 18

6 UTILITY AND MEDICAL NEED OF ULTRASOUND CONTRAST AGENTS 19

7 SAFETY PROFILE OF OPTISON 25

7.1 Sponsor-Conducted Post-Marketing Safety Studies 25
7.1.1 Study GE-191-003 25
7.1.2 Study GE-191-004 28
7.1.3 Study GE-191-005 33
7.2 Post-Marketing Surveillance Data 40
7.2.1 Determination of Seriousness for Adverse Event Reports 40
7.2.2 GE Healthcare Pharmacovigilance Database 40
7.2.3 Patient Exposure 40
7.2.4 Adverse Event Reports 41
7.2.4.1 Non-Serious Reports 41
7.2.4.2 Serious Reports 41
7.2.5 Overall Safety Evaluation from Post-Marketing Surveillance 43
7.3 Safety of OPTISON Reported in Published Literature 43
7.3.1 Search Characteristics 43
7.3.2 Published Studies 44
7.4 Preclinical Safety of OPTISON 45

8 THE OPTISON PRODUCT LABEL 46

8.1 Proposed Changes to the Current Product Label 46
8.2 Consequences of Restricting the Use of Contrast Agents 46

9 OVERALL CONCLUSIONS 48

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10 REFERENCES 49

APPENDIX A INFORMATION FOR HEALTHCARE PROFESSIONALS: MICRO-BUBBLE CONTRAST AGENTS (MARKETED AS DEFINITY (PERFLUTREN LIPID MICROSPHERE) INJECTABLE SUSPENSION AND OPTISON (PERFLUTREN PROTEIN-TYPE A MICROSPHERES FOR INJECTION).....56

APPENDIX B OPTISON PRODUCT LABEL 60

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2 LIST OF TABLES AND FIGURES

Table 1 Principal Components of Five Contrast Agents for Ultrasound Imaging..... 18

Table 2 Post-marketing Safety Studies 25

Table 3 Serious Adverse Events: Study GE-191-003 26

Table 4 Adverse Events by MedDRA Preferred Term: Study GE-191-003..... 27

Table 5 Mean Values and Mean Changes for Vital Signs by Observation Time: Study GE-191-003 28

Table 6 Summary of Pulmonary Artery Systolic Pressure and Pulmonary Vascular Resistance (Wood Units) by Stratum and Treatment, Hemodynamic Population: Study GE-191-004..... 30

Table 7 Statistical Analysis of PASP and PVR, Hemodynamic Population: Study GE-191-004..... 32

Table 8 Unstable Cardiopulmonary Conditions Used to Define Critically Ill Patients: Study GE-191-005 35

Table 9 Distribution of Propensity Score Matches: Study GE-191-005..... 36

Table 10 Alternative Analysis: Rate of Same-day and Two-day, All-cause, In-hospital Mortality Between Patients Administered OPTISON and Patients who did not Have a Contrast Agent Using a 1:4 Match by First Matching Within Clinical Condition: Study GE-191-005 38

Table 11 Alternative Sensitivity Analysis: Rate of Same-day and Two-day, All-cause, In-hospital Mortality Between Patients Administered OPTISON and Patients who did not Have a Contrast Agent Using a 1:1 Match by First Matching Within Clinical Condition : Study GE-191-005 38

Table 12 Per Protocol Analysis: Rate of Same-day and Two-day, All-cause, In-hospital Mortality Between Patients Administered OPTISON and Patients who did not Have a Contrast Agent Using a 1:4 Match - Study GE-191-005.... 39

Table 13 Per Protocol Sensitivity Analysis: Rate of Same-day and Two-day, All-cause, In-hospital Mortality Between Patients Administered OPTISON and Patients who did not Have a Contrast Agent Using a 1:1 Match: Study GE-191-005 39

Figure 1 Contrast and Quantitative Assessment of Left Ventricular Systolic Function: Comparison of Ability to Calculate LVEF with Fundamental, Harmonic, and Contrast Echocardiography 20

Figure 2 Contrast Echocardiography as a Percentage of Total Echocardiography (Arlington Medical Resources)..... 47

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3 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ACR	American College of Radiology
AE	Adverse event
ASE	American Society of Echocardiography
BP	Blood pressure
CAD	Coronary artery disease
CCI	Charlson Comorbidity Index
CCSI	Company Core Safety Information
CHF	Congestive heart failure
CT	Computed tomography
D	Diameter
DM-CCI	Deyo-modified Charlson Comorbidity Index
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	Heart rate
ICAEL	Intersocietal Commission for the Accreditation of Echocardiography Laboratories
ICU	Intensive care unit
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IV	Intravenous
LAD	Left anterior-descending
LOCM	Low-osmolality contrast media
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MHz	Megahertz

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Abbreviation	Definition
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NSAIDS	Non-steroidal anti-inflammatory drugs
PA	Pulmonary artery
PAP	Pulmonary artery pressure
PASP	Pulmonary artery systolic pressure
PCWP	Pulmonary capillary wedge pressure
PSUR	Periodic safety update report
PVR	Pulmonary vascular resistance
RA	Right atrial
SAE	Serious adverse event
SAR	Serious adverse reaction (defined as a related SAE)
STEMI	ST-segment elevation myocardial infarction
TTE	Transthoracic echocardiography
US	United States

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4 EXECUTIVE SUMMARY

Background Overview

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. 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. OPTISON was approved in the United States (US) in 1997 and is marketed by GE Healthcare. Since its approval, approximately 1.15 million doses of OPTISON have been administered to patients globally (data on file).

October 2007 Safety Alert

In October 2007, the Food and Drug Administration (FDA) issued a safety alert for micro-bubble contrast agents (marketed as Definity® and OPTISON™) based on reports received by the FDA of 11 deaths and an unspecified number of serious cardiopulmonary reactions following administration of these products. In the alert, the FDA stated that four of the deaths were related to cardiac arrest occurring during or within 30 minutes of administration of the contrast agent and that serious but non-fatal events also occurred within this time frame. Based on these reports, the FDA required manufacturers to revise their labeling by adding a boxed warning and modifying the "Contraindications" and "Warnings" sections of the package inserts as follows:

- A boxed warning was added to alert healthcare professionals about serious cardiopulmonary reactions, including fatalities that occurred during or within 30 minutes following administration of OPTISON.
- Directions were added to the boxed warning and the "Warnings" section to monitor all 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 of hypoxia.
- Directions were added to the boxed warning and the "Warnings" section to consider alternative diagnostic procedures for patients with pulmonary hypertension or unstable cardiopulmonary conditions and to monitor vitals signs, electrocardiography, and cutaneous oxygen saturation during and for at least 30 minutes after OPTISON administration.
- Contraindications were included: worsening or clinically unstable congestive heart failure, acute myocardial infarction or acute coronary syndromes, serious ventricular arrhythmias or high risk of arrhythmias due to prolongation of QT interval, respiratory failure, severe emphysema, pulmonary emboli or other conditions that cause pulmonary hypertension.

In addition, manufacturers were also required to modify the "Indication for Use" section of the label by stating that the safety and efficacy with exercise or pharmacological stress have not been established.

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July 2008 Safety Alert

In July 2008, another safety alert was issued by the FDA to healthcare professionals describing updates to the boxed warning and to the "Contraindications" and "Warnings" sections of micro-bubble contrast agent package inserts:

- The population to be monitored changed from all patients (implemented in October 2007) to high risk patients with pulmonary hypertension or unstable cardiopulmonary conditions.
- Contraindications added in October 2007 were removed.

At this time, FDA also required manufacturers to conduct new clinical studies to more thoroughly assess risks for serious cardiopulmonary reactions.

The FDA acknowledged that these changes reflected conclusions related to reviews of information received following the labeling changes in October 2007. In the July 2008 update, the FDA indicated that information from physicians and a review of published reports of hemodynamic measurements from patients undergoing heart surgery and/or congestive heart failure (CHF) evaluation suggested that these products might not carry as great a risk for pulmonary hypertension as was previously thought.

Information Following the Safety Alerts

Since the implementation of the boxed warning in 2007, new clinical safety data from the post-marketing commitment, as well as published data, have become available that support removing the boxed warning from the OPTISON product label.

In a letter from the FDA dated 26 January 2011, sponsors of microbubble ultrasound contrast agents were notified that the Cardiovascular and Renal Drugs and Drug Safety and Risk Management Advisory Committees will discuss safety considerations of ultrasound contrast agents particularly related to new information and developments since the prior Advisory Committee meeting on the same topic. (The prior meeting was a joint Cardio-Renal/Drug Safety & Risk Management Advisory Committee with invited Special Government Employees and was held on 24 June 2008.) The agency letter further noted that the Committee discussion will include results from required post-marketing safety studies, US and international post-marketing surveillance data, as well as other safety developments.

Utility and Medical Need of Ultrasound Contrast Agents

The accurate determination of left ventricular ejection fraction (LVEF) is critically important in clinical decision-making. Several studies indicate that contrast-enhanced 2D echocardiography has excellent correlation with radionuclide, magnetic resonance, and computed tomographic (CT) measurements of left ventricular volumes and LVEF, with improved inter-observer agreement and physician interpretation confidence (Thomson et.al., 2001; Hundley et. al., 1999; Malm et. al., 2004; Jenkins et. al., 2009). The underestimation of cardiac volumes by echocardiography is improved when contrast agents are used (Yu et. al., 2003).

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Clinical research and experience with ultrasound contrast agents show that suboptimal echocardiograms can be converted to diagnostic examinations in 75% to 90% of patients. In addition to improving image quality, the use of contrast agents also improves reproducibility and the accuracy of image interpretation for both experienced and inexperienced readers (Vlassak et. al., 2002; Malm et. al., 2004). The American College of Cardiology Foundation (ACCF), in partnership with the American Society of Echocardiography (ASE) and along with key specialty and subspecialty societies, conducted a review of common clinical scenarios where echocardiography is frequently considered and provided transthoracic and transesophageal echocardiography appropriateness criteria (Douglas et. al., 2011). These criteria include a recommendation that contrast agents be used when greater accuracy is needed. Further, contrast-enhanced echocardiography is considered reasonable when two or more contiguous left ventricular segments are not seen on non-contrast images. The Intersocietal Commission for the Accreditation of Echocardiography Laboratories (ICAEL) recommends the use of contrast in the presence of poor endocardial border definition for quantification of chamber dimensions, volumes, ejection fraction, and assessment of regional wall motion as it provides greater accuracy (ICAEL, 2010). ICAEL also recommends the use of contrast to assess conditions such as hypertrophic cardiomyopathy or when left ventricular thrombus is suspected. Senior et. al. provides similar evidence-based recommendations for the use of contrast echocardiography in patients with suboptimal images (Senior et. al., 2009). These recommendations are supported by the results from two multi-center, randomized, cross-over studies in 203 patients (Senior et. al., 2009). In comparison with non-contrast ultrasound, OPTISON significantly increased the length of the endocardial border that could be visualized both at end-systole and end-diastole. In addition, OPTISON significantly improved the ability to delineate qualitatively each of the left ventricular segments.

When the class labeling requirements, including the boxed warning, were implemented in 2007, a notable decrease in the use of contrast echocardiography was reported. Dolan et. al. reported that many institutions stopped using contrast agents as a result of the FDA warning (Dolan et. al., 2001). Limiting the use of OPTISON in critically ill patients, who may receive the most benefit from contrast-enhanced echocardiography, may result in incorrect treatment, adverse outcomes from incorrect or delayed diagnosis, and increased usage of other diagnostic tests that have well-documented risks.

Serious complications from ultrasound imaging agents are well documented and occur rarely. Moreover, the risks associated with these agents are similar to other diagnostic tests performed routinely for coronary artery disease (CAD). The rate of serious contrast reactions is 1 or 2 per 10,000 (0.01% to 0.02%) IV injections of CT/ X ray (low-osmolality contrast media [LOCM]) (ACR Manual, 2010). The incidence of a fatal outcome from an IV contrast media injection is not known with precision. The conservative estimate of 1 fatality per 170,000 LOCM administrations is therefore often quoted. Wei et. al. reported on the incidence of severe AEs after exposure to contrast ultrasound agents in a retrospective analysis of 78,383 administered doses, of which 12,219 doses were OPTISON (Wei et. al., 2008). There were no anaphylactoid reactions reported for OPTISON patients. The results from this study show that the incidence of

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serious adverse reactions (SAR) to ultrasound contrast agents is lower than, or similar to, that reported for contrast agents commonly used in other cardiac imaging tests.

Safety Profile of OPTISON

The safety profile of OPTISON is supported by the data collected from the post-marketing commitments (i.e., three clinical studies), as well as reports from post-marketing surveillance and safety reported in the published literature.

As part of the comprehensive risk management plan agreed to with the FDA, GE Healthcare conducted three post-marketing studies focusing on the safety of OPTISON. Study GE-191-003 was a prospective study designed to assess the safety of OPTISON in patients representative of those who would routinely be referred by their physicians for contrast ultrasound echocardiography. Study GE-191-004 assessed the hemodynamic assessments of pulmonary artery systolic pressure (PASP) and derived pulmonary vascular resistance (PVR). A total of 1069 patients were evaluable for safety (1039 patients in Study GE-191-003 and 30 patients in Study GE-191-004). Study GE-191-005 was a retrospective, case-controlled study that compared the rate of same-day and two-day, all-cause, in-hospital mortality between patients administered OPTISON and those who did not have a contrast agent administered.

Study GE-191-003

This prospective, multi-center, post-marketing safety surveillance study was conducted to collect safety information on OPTISON as used in clinical practice and to better understand the frequency of serious adverse reactions (SARs), defined as a serious adverse event (SAE) that was considered causally related to OPTISON by the investigator. Patients were eligible to participate in the study if they were scheduled for a stress or non-stress OPTISON-enhanced echocardiography examination. The primary safety endpoint in Study GE-191-003 was the occurrence of SARs. There were no SARs reported in this study; however, five patients had SAEs, all of which resolved and were considered related to underlying heart disease. There were no deaths in the study. Non-serious adverse events (AEs) were reported for 16.8% (175/1039) of patients during the study; this incidence rate was consistent with that reported from the original clinical studies of OPTISON and reported in the product label. The most frequently occurring AEs were dyspnea, tachycardia, hypertension, chest pain, ventricular arrhythmia, abnormal T-wave, and chest discomfort. The majority of these AEs were mild in intensity and considered to be unrelated to OPTISON. Two AEs were reported as possibly related to OPTISON: mild prolonged QT interval and moderate worsening shortness of breath; both AEs resolved.

Study GE-191-004

This was a single-blind, two-period cross-over, placebo-controlled clinical study of OPTISON and 5% dextrose (control) conducted in 30 subjects, aged 18 years and older, referred for cardiac catheterization for clinical reasons. The primary endpoint in Study GE-191-004 comprised the hemodynamic assessments of PASP and derived PVR. Patients were stratified based on a screening PASP obtained by echocardiography within 30 days prior to study drug administration:

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- Stratum 1: Normal PASP (≤35 mmHg)
- Stratum 2: Elevated PASP (>35 mmHg)

The results demonstrated that both OPTISON and control had no statistically significant effects on PASP and PVR changes from baseline at all but one of the post-injection time points. At 10 minutes after injection for subjects in the elevated PASP stratum, there was a statistically significant difference in PASP between the OPTISON and control data; however the difference was not clinically relevant. The mean changes from baseline in PASP and PVR were small for both treatments, both strata, and overall, across all three post-baseline time points. There were no clinically relevant changes observed in any other hemodynamic parameters, vital signs, oxygen saturation, clinical laboratory tests, or electrocardiogram (ECG) findings. There were no deaths, SAEs, or significant AEs reported during the study.

Study GE-191-005

Study GE-191-005 utilized an existing database to compare in-hospital mortality in critically ill patients undergoing echocardiography with and without OPTISON. The database consisted of samples from over 500 hospitals in the US with a 93% hospital retention rate. Data were available from 209,950 critically ill patients who met all of the eligibility criteria and were admitted to the hospital for one of six unstable cardiopulmonary conditions, of which 2,884 received OPTISON. A propensity score matching algorithm was used to match each of the 2,884 patients who received OPTISON to four control patients who did not have a contrast agent administered. This retrospective, case-controlled study compared the rate of same-day and two-day, all-cause, in-hospital mortality between patients administered OPTISON (n=2,884) and those who did not have a contrast agent administered (n=11,536). The per protocol analysis used the propensity score matching approach to control for the differences in observable covariates and to reduce the selection bias that can occur in case-control studies (Rosenbaum and Rubin, 1985). This method reduced the variability between matched controls. The propensity score matching algorithm did not include the specific clinical condition as a baseline covariate. Therefore, after careful consideration, it was determined that an alternative method to match OPTISON patients to control patients was to first match by clinical condition and then match on the similarity of the propensity score, thereby guaranteeing that OPTISON patients with one cardiopulmonary condition would be matched to control patients with the same cardiopulmonary condition. The specific conditions were worsening or clinically unstable CHF, acute myocardial infarction (MI), serious ventricular arrhythmias, respiratory failure, pulmonary emboli, and pulmonary hypertension. This method provided the most reliable assessment for the event rate in the control population for this study. The results based on this analysis demonstrated that there was no clinically or statistically meaningful increase in same-day or two-day all-cause mortality in the patients receiving OPTISON. A sensitivity analysis supported these results.

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Other Safety Data

Other safety data on OPTISON has been collected by GE Healthcare since the 2008 Advisory Committee meeting from post-marketing surveillance and published literature reports. The data collected from post-marketing surveillance between January 2008 and December 31, 2010 encompasses approximately 55,000 patient exposures to OPTISON. During this period, there were two spontaneous reports of minor allergy-type reactions: hypersensitivity (rash) and anaphylactoid reaction (increased heart rate [HR] of 125 bpm, shortness of breath, and sweating). These reports did not represent an increase in the reporting rate of allergy-type events.

Reports from the published literature are consistent with data collected by the sponsor-conducted studies. A retrospective data review from Hennepin County Medical Center was published by Herzog, 2008. A total of 3051 patients received OPTISON between February 1998 to February 2002; no AEs were reported for these patients. Wei et. al. reported on the incidence of severe AEs after exposure to contrast ultrasound agents in a retrospective analysis of 78,383 administered doses, of which 12,219 doses were OPTISON; contrast use accounted for 5% of transthoracic and 28% of stress echocardiographic procedures (Wei et. al., 2008). Severe reactions occurred in four (0.006%) patients who received OPTISON. There were no deaths and no SAEs reported. The results from this study showed that the incidence of SARs to ultrasound contrast agents was lower than, or similar to, that reported for contrast agents commonly used in other cardiac imaging tests. Abdelmoneim et. al. reported safety results from a 4-year single-center cohort study of patients who received a contrast agent during stress echocardiography (Abdelmoneim et. al., 2009). A total of 26,774 subjects were evaluated between 1 November 2003 and 31 December 2007. A total of 10,792 patients received a contrast agent and 15,982 had no contrast administered; 14% (1511/10792) of the contrast patients received OPTISON. The authors concluded that patients who had undergone stress echocardiography with contrast agents were not at increased risk of death or MI compared with those who had not received contrast agents. Overall, there were few AEs reported and the incidence of acute anaphylactoid reaction was 0.03% (approximately 3 of 10,000 patients).

Overall Conclusions

- Since its approval, approximately 1.15 million doses of OPTISON have been administered to patients and it has been shown to be safe and well-tolerated.
- The ACCF, in partnership with the ASE, along with key specialty and subspecialty societies, as well as the ICAEL, recommend the use of contrast agents when greater accuracy in diagnosis is needed because of poor image quality.
- Serious contrast reactions are rare and the incidence of SARs to ultrasound contrast agents is lower than, or similar to, that reported for contrast agents commonly used in other cardiac imaging tests.
- The boxed warning may have the effect of limiting the use of OPTISON in critically ill patients who may receive the most benefit from contrast-enhanced echocardiography with the potential for incorrect treatment, adverse outcomes from

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incorrect or delayed diagnosis, and increased usage of other diagnostic tests that have well-documented risks.

- Data from three mandated post-marketing studies, continued post-marketing surveillance, and published literature collectively demonstrate that there is no need for the current boxed warning; consequently, the OPTISON product label should be revised.

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5 BACKGROUND OVERVIEW

5.1 Objective

A boxed warning was imposed in 2007 because of 11 deaths and an unspecified number of serious cardiopulmonary reactions that occurred after administration of ultrasound contrast agents. Subsequently, the FDA indicated in July 2008 that information from physicians and a review of published reports suggested that these products might not carry as great a risk for pulmonary hypertension as was previously thought. Since 2008, GE Healthcare has collected data from post-marketing studies, post-marketing surveillance, and published literature that support the removal of the boxed warning from the OPTISON label.

5.2 Organization of the Briefing Document

In response to the upcoming joint Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, this Briefing Document details information of interest, including the safety profile of OPTISON.

This document is organized as follows:

1. **Section 5.3** and **Section 5.4**: A brief summary of the regulatory background leading to the upcoming Advisory Committee meeting is provided, as well as the fundamental concepts of ultrasound contrast imaging agents.

2. **Section 6**: Because it is important to place the safety of OPTISON in the context of its clinical use, the section presents the overall utility of ultrasound contrast agents, including medical need for these important diagnostic agents.

3. **Section 7**: Safety information for OPTISON collected by GE Healthcare since the last Briefing Document (2008) is summarized in accordance with the request of the FDA; all sponsor-conducted studies, post-marketing safety surveillance, and published reports are presented from 2008 through December 2010.

4. **Section 8**: A proposal for changes to the OPTISON product label is presented and supported by the clinical implications of the current label.

5.3 Regulatory Background

This Briefing Package has been prepared for the joint meeting of the Cardiovascular and Renal Drugs and the Drug Safety and Risk Management Advisory Committees to be held 2 May 2011 at the request of the FDA.

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OPTISON was approved in the US in 1997 and obtained marketing authorization in the European Union through the Centralised procedure. Currently, OPTISON is on the market in seven countries (US, Denmark, Finland, Norway, Sweden, United Kingdom, and Germany).

October 2007 Safety Alert

In October 2007, the FDA issued a safety alert for micro-bubble contrast agents (marketed as Definity® and OPTISON™) based on reports received by the FDA of 11 deaths and an unspecified number of serious cardiopulmonary reactions following administration of these products. In the alert, the FDA stated that four of the deaths were related to cardiac arrest occurring during or within 30 minutes of administration of the contrast agent and that serious, but non-fatal events, also occurred within this time frame. Based on these reports, the FDA required manufacturers to revise their product labeling by adding a boxed warning to alert healthcare professionals about serious cardiopulmonary reactions, including fatalities occurring during or within 30 minutes following administration of perflutren-containing microspheres. Healthcare professionals were advised to:

- Assess all patients for the presence of any condition that precludes OPTISON administration (added to the "Contraindications" section)
- 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 of hypoxia; to have resuscitation equipment and trained personnel readily available (added to the "Warnings" section)
- Consider alternative diagnostic procedures for patients with pulmonary hypertension or unstable cardiopulmonary conditions and to monitor vitals signs, electrocardiography, and cutaneous oxygen saturation during and for at least 30 minutes after OPTISON administration (added to the "Warnings" section)

The following contraindications were added:

- Do not administer OPTISON by intra-arterial injection and do not administer OPTISON in patients with known or suspected:
  - Right-to-left, bi-directional, or transient right-to-left cardiac shunts (originally, these patients were covered under the "Warnings" section)
  - Worsening or clinically unstable CHF
  - Acute MI or acute coronary syndromes
  - Serious ventricular arrhythmias or high risk for arrhythmias due to prolongation of the QT interval
  - Respiratory failure, as manifest by signs or symptoms of carbon dioxide retention or hypoxemia
  - Severe emphysema, pulmonary emboli or other conditions that cause pulmonary hypertension due to compromised pulmonary arterial vasculature
  - Hypersensitivity to perflutren, blood, blood products or albumin

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July 2008 Safety Alert

In July 2008, another safety alert was issued by the FDA to healthcare professionals describing updates to the boxed warning and to the "Contraindications" and "Warnings" sections of micro-bubble contrast agent package inserts. The boxed warning was modified and the requirement to monitor all patients for at least 30 minutes after OPTISON administration was limited to monitoring only patients with pulmonary hypertension and or unstable cardiopulmonary conditions. The statement to consider alternative procedures in patients with pulmonary hypertension or unstable cardiopulmonary conditions was removed. The following "Contraindications" added in October 2007 were removed: worsening or clinically unstable congestive heart failure, acute myocardial infarction or acute coronary syndromes, serious ventricular arrhythmias or high risk of arrhythmias due to prolongation of QT interval, respiratory failure, severe emphysema, pulmonary emboli or other conditions that cause pulmonary hypertension.

Related changes were made to the "Warnings" section of the package insert requiring monitoring of vital signs and echocardiography in patients with pulmonary hypertension or unstable cardiopulmonary conditions (instead of for all patients) and removing the statement to consider alternative diagnostic procedures in these patients.

The FDA acknowledged that these changes reflected conclusions related to reviews of information received following the labeling changes in October 2007. In the July 2008 update, the FDA indicated that information from physicians and a review of published reports of hemodynamic measurements from patients undergoing heart surgery and/or congestive heart failure evaluation suggested that these products might not carry as great a risk for pulmonary hypertension as was previously thought. The FDA issued an *Information for Healthcare Professionals* on 18 July 2008 explaining the changes described above and the reasons for the changes (a copy of this letter is provided in Appendix A).

Information Following the 2008 Safety Alert

In addition to product labeling changes, the FDA requested that sponsors of these products commit to comprehensive risk management plans that included clinical studies to evaluate product safety, as well as the utilization of safety monitoring boards to evaluate AE data. GE Healthcare met this commitment with two prospective post-marketing studies that evaluated the safety of OPTISON in 1069 patients, and one retrospective study that evaluated OPTISON use in 2,884 patients. The studies were conducted between June 2008 and July 2010.

In a letter from the FDA dated 26 January 2011, sponsors of microbubble ultrasound contrast agents were notified that the committees will discuss safety considerations of ultrasound contrast agents particularly related to new information and developments since the prior Advisory Committee meeting on the same topic. (The prior meeting was a joint Cardio-Renal/Drug Safety & Risk Management Advisory Committee with invited Special Government Employees and was held on 24 June 2008.) The agency letter further noted that the Committee discussion will include results from required post-

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marketing safety studies, US and international post-marketing surveillance data, as well as other safety developments.

5.4 Fundamental Concepts of Ultrasound Contrast Agents

5.4.1 OPTISON™ Product Information

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; it 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. OPTISON was approved in the US in 1997 and is marketed by GE Healthcare. Since its approval, approximately 1.15 million doses of OPTISON have been administered to patients.

5.4.2 Principle

The concept of contrast for ultrasound imaging was discovered by Gramiak and Shah, 1968 who observed enhancement of echo during intra-cardial injections of indocyanide green, saline and dextrose. Kremkau et. al. later confirmed that the observed contrast enhancement was due to formation of small gas bubbles during rapid injection of solutions (Kremkau et. al., 1970). This is the principle physical contrast creating mechanism of all ultrasound contrast agents; the scattering of ultrasound from small envelopes of gas as they undergo volume oscillations in the sound beam. Due to the high compressibility of gases and their ability to resonate when insonated, a population of microspheres is very effective in scattering incident ultrasound compared to surrounding blood or tissue. During ultrasound scanning, body cavities and compartments containing microspheres will appear white compared to regions without contrast agent.

5.4.3 Effects of Size

The main drive for the development of a safe and efficacious compound has been to produce stable microspheres of a pre-defined, biologically acceptable size, which will pass through capillary beds and thus allow for imaging throughout the cardiovascular system. The average diameter of the lung capillaries has been reported to be approximately 7 µm with approximately 95% being equal or larger than 4 µm (Hogg, 1987). To optimize for free flow and avoid potential capillary embolism, the size of microspheres in ultrasound contrast agents should preferably be smaller than 4 µm.

Another important aspect of microsphere size is its influence on product efficacy; the ability of any given microsphere to scatter ultrasound is strongly dependent on the diameter (D). For a typical microsphere the scattering efficacy per bubble volume (at 2 MHz) is a monotonically increasing function of size scaling as D^3 up to some 7 µm before dropping sharply scaling as D^{-2} (Sontum et. al., 1999; Sontum, 2008).

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Unfortunately these two effects (potential capillary retention and product efficacy) pull the optimal size in different directions. Products with bigger microspheres are more efficacious, but there is a greater potential for capillary retention.

5.4.4 Effects of Gas and Shell Type

Various formulation concepts have been explored in developing an ultrasound contrast agent with suitable properties. Early products investigated the stabilization of air bubbles, either by release *in vivo* from micro-porous crystalline sugar structures as with Levovist® (Schering AG) or by stabilizing individual envelopes of air by a shell of denatured human serum albumin as with Albunex® (Mallinckrodt Inc.). Both concepts were successful in bringing microspheres through the capillary bed of the lungs, producing contrast in the bulk volume of the left heart chamber after an IV injection. Their stability *in vivo* (and hence the contrast persistency) was insufficient and their clinical utility limited. A primary cause for the poor stability of air-based ultrasound contrast agents is that the small molecules of the air easily diffuse across the stabilizing structure. As air is relatively soluble in the surrounding matrix (i.e, blood), the microspheres dissolve too quickly after injection. To improve the stability of the contrast agents, a concept of encapsulating air with a more solid, polymer-based, shell was investigated (Bjerknes et. al., 1997). In this case, however, the stiffness of the shell lowered the physical, *in vitro* acoustic efficacy of the compound to such a degree that the substance did not deliver the necessary imaging quality (Hoff et. al., 2000). An alternative approach for increasing the stability of the contrast agent is based on the type of gas used. The life span of a non-stabilized bubble in a liquid matrix is proportional to the density, and inversely proportional to the solubility/diffusivity, of the gas in question. Using a denser, more slowly diffusing, low solubility gas increases the stability of microspheres, without the need for a rigid stabilizing structure (Dugstad et. al., 1996). Gases such as sulphur-hexafluoride or low molecular weight perfluoro-carbons in combination with various flexible stabilizing structures are now used in several (2nd generation) products. The main components of five ultrasound contrast agents are listed in Table 1.

Table 1 Principal Components of Five Contrast Agents for Ultrasound Imaging

Product	Shell Material	Encapsulated Gas
Albunex®	Protein	Air
OPTISON	Protein	Octafluoropropane
Sonovue®	Lipids	Sulphur-hexafluoride
Definity®	Lipids	Octafluoropropane
Sonazoid™	Lipids	Perfluorobutane

Note: Only OPTISON and Definity® are available in the US market.

As apparent from the discussion above, for ultrasound contrast agents the *physical state* of the active ingredient may be more important to product performance than its mass content or chemical structure. In this context it may be more correct to refer to a contrast enhancing *system* rather than a *substance* (i.e., gas or shell) since the *in vivo* performance is related to a number of parameters of the formulation as a *physical entity*.

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6 UTILITY AND MEDICAL NEED OF ULTRASOUND CONTRAST AGENTS

The use of contrast agents for left ventricular opacification improves the accuracy and reproducibility of echocardiography for the qualitative and quantitative assessment of left ventricular structure at rest and during exercise and pharmacologic stress (Kirkpatrick et. al., 2004; Masugata et. al., 1999; Kimura et. al., 1999; Terasawa et. al., 1993; Nakatani et. al., 1992). Ultrasound contrast agents have been used effectively in echocardiographic studies performed in the emergency department, Intensive Care Units (ICU), interventional cardiology suite, and the operating room. The efficient implementation of contrast medium use in the echocardiography laboratory results in procedural optimization and may contribute to improved patient care outcomes (Thanigaraj et. al., 2001; Castello et. al., 2003).

Image Accuracy

The accurate determination of LVEF is critically important in clinical decision making to determine the need for placement of intracardiac defibrillators and biventricular pacing systems. Initially, fundamental (i.e., non-harmonic) imaging equipment was used and in later studies harmonic imaging equipment was used (Feinstein et. al., 1990; Cohen et. al., 1998; Allen et. al., 1999; Kitzman et. al., 2000). Emerging ultrasound technologies are enhanced by using IV echocardiographic contrast agents (Yu et. al., 2003; Takeuchi et. al., 2006). Studies indicate that contrast-enhanced 2D echocardiography has excellent correlation with radionuclide, magnetic resonance, and computed tomographic measurements of left ventricular volumes and LVEF, with improved inter-observer agreement and physician interpretation confidence (Thomson et. al., 2001; Hundley et. al., 1999; Malm et. al., 2004; Jenkins et. al., 2009). Figure 1 illustrates the increasing accuracy of LVEF measurements when contrast imaging is used to improve border definition (Yu et. al., 2003). The underestimation of cardiac volumes by echocardiography is significantly improved when contrast agents are used (Yu et. al., 2003).

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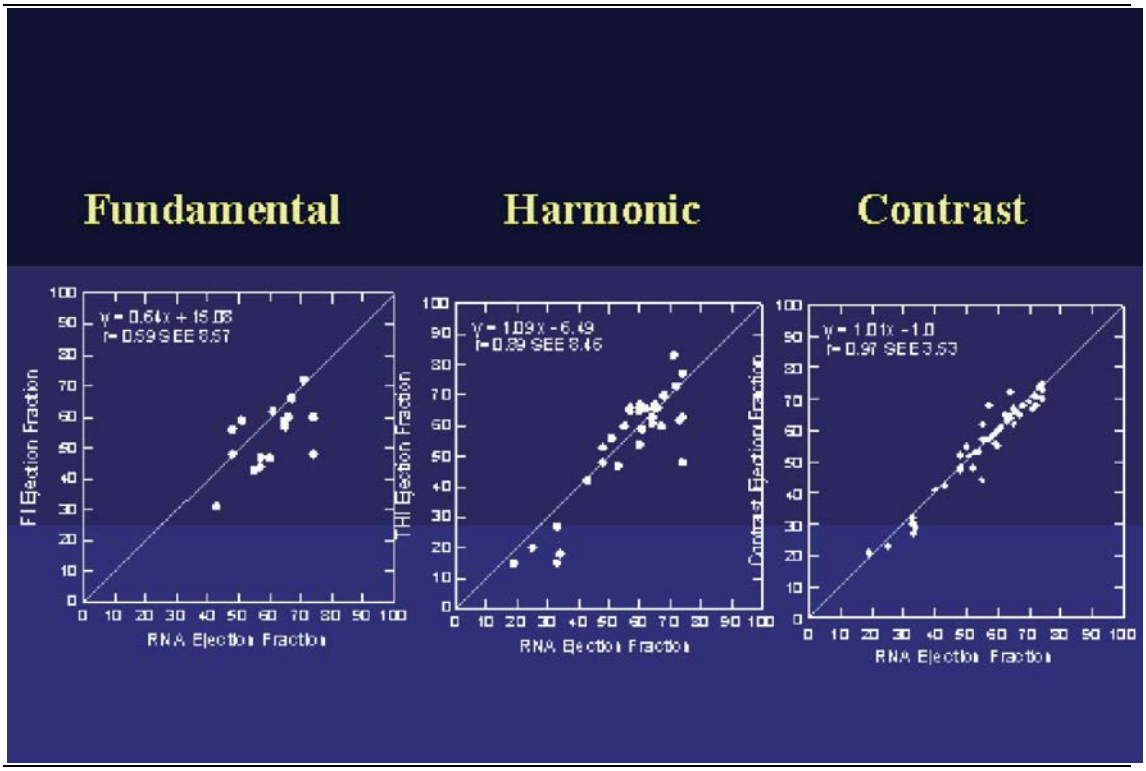
Figure 1 Contrast and Quantitative Assessment of Left Ventricular Systolic Function: Comparison of Ability to Calculate LVEF with Fundamental, Harmonic, and Contrast Echocardiography



FI, Fundamental imaging; RNA, radionuclide angiography; SEE, standard error of the estimate for correlation; THI, tissue harmonic imaging.

Source: ASE Consensus Statement: American Society of Echocardiography Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography, 2008.

Conversion of Low-quality Images to High-quality Images

Despite marked improvements in ultrasound transducer technology and signal processing algorithms, as many as 20% of transthoracic echocardiographic studies remain technically difficult when standard resting echocardiographic imaging is applied (Mulvagh et. al., 2000), which often occurs in patients who are obese, have lung disease, are critically ill, or are receiving ventilator care (Mulvagh et. al., 2008**).** In such patients, the image quality remains suboptimal unless a contrast agent is used, and the use of a contrast agent provides substantial benefit to such studies by improving image quality, confidence of interpretation, and accuracy (Hundley et. al., 1999; Thomson et. al., 2001; Dolan et. al., 2001; Plana et. al., 2008). The use of contrast agents also improves study reproducibility and the accuracy of image interpretation for both experienced and inexperienced readers (Vlassak et. al., 2002; Malm et. al., 2004).

Clinical research and experience with ultrasound contrast agents show that suboptimal echocardiograms can be converted to diagnostic examinations in 75% to 90% of patients. In addition to improving image quality, the use of contrast agents also improves

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reproducibility and the accuracy of image interpretation for both experienced and inexperienced readers (Vlassak et. al., 2002; Malm et. al., 2004). The ACCF, in partnership with the ASE and along with key specialty and subspecialty societies, conducted a review of common clinical scenarios where echocardiography is frequently considered and provided transthoracic and transesophageal echocardiography appropriateness criteria (Douglas et. al., 2011). These criteria include a recommendation that contrast agents be used when greater accuracy is needed. Further, contrast-enhanced echocardiography is considered reasonable when two or more contiguous left ventricular segments are not seen on non-contrast images. The ICAEL recommends the use of contrast in the presence of poor endocardial border definition for quantification of chamber dimensions, volumes, ejection fraction, and assessment of regional wall motion as it provides greater accuracy (ICAEL, 2010). ICAEL also recommends the use of contrast to assess conditions such as hypertrophic cardiomyopathy or when left ventricular thrombus is suspected. Senior et. al. provides similar evidence-based recommendations for the use of contrast echocardiography in patients with suboptimal images (Senior et. al., 2009). These recommendations are supported by the results from two multi-center, randomized, cross-over studies in 203 patients (Senior et. al., 2009). In comparison with non-contrast ultrasound, OPTISON significantly increased the length of the endocardial border that could be visualized both at end-systole and end-diastole. In addition, OPTISON significantly improved the ability to delineate qualitatively each of the left ventricular segments.

Stress Echocardiography

While GE Healthcare appreciates that OPTISON is not approved for use with stress echocardiography procedures, commercially available ultrasound contrast agents such as OPTISON are used in the medical community for such procedures and therefore warrant discussion here as it has a bearing on safety.

As reported by the ACC, approximately 30 million echocardiograms per year are performed in the US. Stress echocardiography is an established clinical tool with sensitivity and specificity for the diagnosis of CAD through detailed evaluation of regional wall motion, cavity size, and left ventricular function at rest and under stress induced by either exercise or pharmacologic means. Because the detection of CAD by stress echocardiography is based on the observation of contractile (wall thickening) dysfunction in any myocardial segment at rest or under stress, complete visualization of the entire left ventricular endocardial border is necessary to document or exclude abnormalities of regional myocardial wall thickening confidently.

Non-diagnostic or poor-quality images from echocardiography may occur in up to 30% of patients (Marwick et. al., 1992). Furthermore, suboptimal studies result in increased inter-observer variability and poor reproducibility, with inter-institutional observer variance in interpretation of stress echocardiograms reported to decline substantially as image quality is reduced from 100% agreement for good image quality to 43% agreement for studies with the lowest image quality.

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With contrast agents, complete left ventricular cavity opacification is reliably obtained, resulting in an improvement in endocardial borders delineation in up to 95% of patients at peak stress (Rainbird et. al., 2001; Moir and Marwick, 2004). More recently, Plana et. al. confirmed the logical extension of this observation: better visualization of the structures required for interpretation enhances test performance (Plana et. al., 2008). In the OPTIMIZE trial, the investigators enrolled 108 patients who underwent two dobutamine stress echocardiographic studies, one with and one without contrast enhancement; the majority of patients had coronary angiography within 30 days. As endocardial borders visualization and confidence in interpretation increased in the contrast-enhanced studies, a significant impact of contrast enhancement on the accuracy of dobutamine stress echocardiography was observed (p=0.01). The agreement between results from echocardiography and angiography for diagnosing CAD increased by 31% in patients with poor visualization of the endocardium without contrast (>2 of 17 segments not visualized), but the impact was more modest (5%) in patients for whom only one or two segments were not visualized (Plana et. al., 2008).

An evidence-based analysis was conducted with data from 23 observational studies that assessed the diagnostic accuracy of contrast echocardiography for the diagnosis of CAD (Ontario Health Technology Assessment Series, 2010). All these studies used stress echocardiography with contrast. In addition, nine retrospective chart reviews were identified that assessed the safety of stress echocardiography at rest or stress. The results of these studies, demonstrated that stress echocardiography with contrast has a higher diagnostic accuracy than echocardiography without contrast. In addition, stress echocardiography with contrast seems to have a similar diagnostic accuracy to 99 technetium SPECT and the addition of contrast in patients with suboptimal echocardiography results significantly improves interpretability of the results.

Collectively, the findings from this research support the ASE and the ACC recommendations for use of contrast enhancement in echocardiography and emphasize the importance of adequate visualization of all myocardial segments for interpreting echocardiograms confidently and reaching an accurate diagnosis.

Detection of Intracardiac Masses

The detection and correct classification of intracardiac masses, including tumors and thrombi, are facilitated with the use of contrast agents during echocardiography. Although several echocardiographic criteria have been developed to define cardiac masses, diagnostic errors have been reported in the detection of other space-occupying lesions in the left ventricle, and misclassifications can lead to unnecessary surgery or inappropriate anticoagulation therapy. The use of contrast agents to better characterize cardiac masses can potentially avoid these unfortunate problems (Mulvagh et. al., 2008). The apex is the most common location for a left ventricular thrombus. An apical thrombus may be difficult to define clearly, or to exclude, especially if the view of the apex is foreshortened. However, left ventricular opacification through use of contrast allows complete visualization of the apical region enabling detection of a thrombus, if present. For example, Kurt et. al. reported a series of 632 consecutive patients with technically difficult studies who underwent contrast-enhanced echocardiography

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(Kurt et. al., 2009). A total of 35 patients were suspected to have an apical thrombus and three definitely to have one before contrast was used. After contrast enhancement, an apical thrombus was diagnosed in five more patients and excluded in all other patients except one in whom thrombus was still suspected but could not be confirmed. Thus, the number of patients with suspected thrombi decreased from 35 to only one after contrast utilization.

Use in Obese and Other Technically Difficult Patients

Castello et. al. reported on the use of OPTISON in a high-volume echocardiography laboratory. In their real-life clinical experience, access to contrast-enhanced echocardiography was not limited just to patients undergoing mechanical ventilation, patients in the ICU or patients undergoing stress testing (Castello et. al., 2003). Less than 40% of the studies were performed in any of these traditional "highly technically difficult" groups. The most common indication for use of contrast in their study was obesity: in their practice only 23% of the patients who received contrast were of normal weight; 19% were overweight (body mass index >27), and 58% were obese (body mass index >30).

In the future, as obesity increases, patients with increased body mass index will become more difficult to image by other modalities. Some of the value of echocardiography for these patients is its portability; the procedure can be done bedside and is a real-time non-invasive imaging method. Further, as consequence of aging in the general population, the number of patients with chronic obstructive pulmonary diseases will increase as well, and many of these patients would benefit from contrast-enhanced echocardiography for similar reasons.

Contrast Reactions and Complications

Serious complications from ultrasound imaging agents occur rarely and are well documented. Moreover, the risks associated with these agents are similar to other diagnostic tests performed routinely for CAD. Serious contrast reactions have occurred in 1 or 2 per 10,000 (0.01% to 0.02%) IV injections of CT/ X ray (low-osmolality contrast media [LOCM]) (ACR Manual, 2010). The incidence of a fatal outcome from an IV contrast media injection is not known with precision. The conservative estimate of 1 fatality per 170,000 LOCM administrations is therefore often quoted. Wei et. al. reported on the incidence of severe AEs after exposure to contrast ultrasound agents in a retrospective analysis of 78,383 administered doses, of which 12,219 doses were OPTISON (Wei et. al., 2008). In this study, eight serious AEs occurred, of which four were compatible with severe anaphylactoid or complement activation-related pseudoallergy reactions; this represents a total incidence of 1:16,541 (0.006%). All of these events occurred within 30 minutes of a bolus administration with another ultrasound contrast agent. There were no anaphylactoid reactions reported for OPTISON patients. The results from this study showed that the incidence of SARs to ultrasound contrast agents was lower than, or similar to, that reported for contrast agents commonly used in other cardiac imaging tests.

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Coronary angiography, exercise testing, cardiac magnetic resonance imaging (MRI), cardiac CT and nuclear scintigraphic examinations each have known risks. The mortality rate for diagnostic coronary angiography is approximately 1:1,000 (Johnson et. al., 1989), and x-ray and magnetic resonance contrast agents have documented AE profiles. Patients receiving gadolinium-based magnetic resonance contrast media have been shown to develop urticarial rash (0.04%) and anaphylactoid shock (0.01%) (Li et. al., 2006). Intravenously administered non-ionic iodinated contrast agents used for CT cause urticaria in up to 0.5% and severe reactions in 0.001% to 0.04% of patients (Caro et. al., 1991; Katayama et. al., 1990). Iodinated x-ray contrast media are also associated with a risk of contrast-induced nephropathy. The risk of MI or death with exercise treadmill stress testing is approximately 1:2,500 (Stuart and Ellestad, 1980), and the lifetime risk of fatal malignancy after rest-stress single-photon emission CT or a radionuclide ventriculogram examination is estimated at 1:1,000 to 1:10,000 (Einstein et. al., 2007). This latter risk is greatest in relatively young patients and in women. Recognizing the established safety profile of ultrasound contrast agents, their use should not be considered of any higher risk than other diagnostic tools.

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7 SAFETY PROFILE OF OPTISON

7.1 Sponsor-Conducted Post-Marketing Safety Studies

As part of the comprehensive risk management plan agreed to with FDA, GE Healthcare conducted three post-marketing studies focusing on the safety of OPTISON. The protocols were submitted for FDA review and comment and after addressing FDA's comments, the protocols were finalized. All three studies have been completed and the final reports have been submitted. A brief summary of the studies is provided in Table 2.

Table 2 Post-marketing Safety Studies

Study No.	Study Description	Study Design	Study Sites	Number of Subjects
GE-191-003	Determine the occurrence of serious adverse events among patients receiving OPTISON during routine medical care	Prospective, multi-center, open-label	18	1039
GE-191-004	Determine effects on pulmonary artery systolic pressure (PASP) and pulmonary vascular resistance (PVR), assessed by right heart cardiac catheterization techniques and assess overall safety	Single-blind, cross-over, placebo-controlled, randomized	4	30
GE-191-005	Retrospective database analysis of in-hospital mortality in critically ill patients	Retrospective, case-controlled, matched controls	NA Comparative Database 500 hospitals	2,884 (O) 11,536 (C)

O = Optison; C = Control (no contrast agent)

All studies were conducted in full accordance with the Declaration of Helsinki and the *Good Clinical Practice: Consolidated Guideline* approved by the International Conference on Harmonisation (ICH). The investigators were responsible for performing the study in accordance with the protocol and ICH E6-Good Clinical Practice (GCP), for collecting, recording, and reporting the data accurately and properly. Patient informed consent was obtained in compliance with 21 CFR §50 and Institutional Review Board (IRB) approval was obtained in compliance with 21 CFR §56.

7.1.1 Study GE-191-003

In accordance with the post-marketing commitment, this prospective, multi-center, post-marketing safety surveillance study was conducted to collect safety information on OPTISON as used in clinical practice and to better understand the frequency of SARs,

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defined as an SAE that was considered causally related to OPTISON by the investigator. The frequency of SAEs and cardiopulmonary AEs was also assessed. Patients were eligible to participate in the study if they were scheduled for a stress or non-stress OPTISON-enhanced echocardiography examination. The first patient entered the study on 4 June 2008 and the last patient completed on 14 March 2009. A total of 1039 subjects scheduled for an OPTISON-enhanced echocardiography examination were enrolled. The majority of subjects were male (62.4%) and Caucasian (83.2%). The average age of the subjects was 59.9 years (min, max: 20, 97). The majority of subjects were <65 years of age (64.6%).

There were no SARs reported in this study; however, five patients had SAEs, all of which resolved and were considered related to underlying heart disease (Table 3). There were no deaths in the study.

Table 3 Serious Adverse Events: Study GE-191-003

Patient Demographics	Event Term	Time to Resolution	Relationship to Optison	Outcome	Seriousness Criterion Met
57 year old female	Non sustained ventricular tachycardia	<1 minute	Not Suspected	Resolved when dobutamine stopped	Immediately life-threatening condition
57 year old female	Coronary artery disease	22 hours	Not suspected	Resolved with aspirin, beta blockers and increased statin dosage	Required/prolonged hospitalization
66 year old female	Left ventricular thrombus	8 days	Not suspected	Resolved after heparin and diuretic therapy	Required/prolonged hospitalization
31 year old male	Left ventricular mass requiring surgery	8 days	Not suspected	Resolved after open heart surgery to remove mass	Required/prolonged hospitalization
41 year old male	Fluid overload	5 days	Not suspected	Resolved after treatment with furosemide and bi-level positive airway pressure	Required/prolonged hospitalization
	Episodes of sustained ventricular tachycardia	7 days	Not suspected	Resolved after treatment with dofetilide, mexiletine and defibrillation from ICD	Required/prolonged hospitalization

Adverse events were reported for 16.8% (175/1039) of patients during the study (Table 4). The most frequently occurring AEs were dyspnea, tachycardia, hypertension, chest pain, ventricular arrhythmia, abnormal T-wave, and chest discomfort. The majority of

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these AEs were mild in intensity (243; 84.4%) and considered to be unrelated to OPTISON. Two AEs were reported as possibly related to OPTISON:

- One patient had mild prolonged QT interval, which lasted 2 minutes and resolved without treatment. Subsequently, the Data Safety Monitoring Board reviewed the patient's ECG and determined that there was no prolongation.
- One patient had moderate worsening shortness of breath, which lasted 15 minutes and resolved without treatment.

Table 4 Adverse Events by MedDRA Preferred Term: Study GE-191-003

	Total (N=1039)		
	No. of Subjects with an AE		
Event (MedDRA)	**n**	**%**	**No. of AEs**
Angina Pectoris	4	0.4	4
Arrhythmia supraventricular	1	0.1	1
Atrial fibrillation	1	0.1	1
Blood pressure abnormal	3	0.3	3
Bundle branch loss	1	0.1	1
Cardiac ventricular disorder	1	0.1	1
Chest discomfort	11	1.1	11
Chest pain	32	3.1	33
Coronary artery disease	1	0.1	1
Dizziness	4	0.4	5
Dyspepsia	1	0.1	1
Dyspnea	69	6.6	69
ECG QT interval abnormal	1	0.1	1
ECG T wave abnormal	14	1.3	14
Fatigue	4	0.4	4
Feeling abnormal	1	0.1	2
Fluid overload	1	0.1	1
Headache	1	0.1	1
Hypertension	37	3.6	37
Hypotension	3	0.3	3
Intracardiac thrombus	1	0.1	1
Left ventricular heave	1	0.1	1
Nausea	5	0.5	5
Nodal rhythm	2	0.2	2
Palpitations	2	0.2	2
SVT	1	0.1	1
Shoulder pain	1	0.1	1
Superventricular extrasystoles	1	0.1	1
Tachycardia	40	3.8	40
Tremor	2	0.2	2
Ventricular arrhythmia	27	2.6	30
Ventricular extrasystoles	1	0.1	1
Ventricular tachycardia	2	0.2	2
Vomiting	2	0.2	2
Weakness	2	0.2	2
Wheezing	1	0.1	1

N = Number of subjects evaluable for safety. n = number of subjects with a particular AE
MedDRA = Medical Dictionary for Regulatory Activities.

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Vital signs (systolic and diastolic blood pressure [BP], HR and respiration rate) measurements were generally stable from baseline until 1 hour post injection (Table 5). The slight changes in systolic BP and HR were more likely to be attributable to the study procedures rather than OPTISON administration. No clinically significant changes were apparent.

Table 5 Mean Values and Mean Changes for Vital Signs by Observation Time: Study GE-191-003

Vital Sign Parameter	Observation Time	N	Measured Values		Changes from Baseline	
			n	Mean (SD)	n	Mean (SD)
Systolic BP (mmHg)	Baseline	1039	818	130.4 (20.28)		
	5-15minutes	1039	813	133.7 (23.65)	811	3.4 (16.80)
	30 minutes	1039	809	131.6 (22.61)	808	1.2 (17.87)
	1 hour	1039	800	128.4 (18.91)	799	-2.1 (16.13)
Diastolic BP (mmHg)	Baseline	1039	818	73.8 (12.50)		
	5-15minutes	1039	812	72.8 (13.40)	810	-0.9 (10.90)
	30 minutes	1039	809	72.6 (13.26)	808	-1.2 (11.73)
	1 hour	1039	800	73.1 (11.73)	799	-0.6 (11.47)
Heart Rate (bpm)	Baseline	1039	818	73.0 (13.58)		
	5-15minutes	1039	814	81.1 (21.62)	812	8.1 (18.02)
	30 minutes	1039	809	82.2 (19.17)	808	9.2 (17.13)
	1 hour	1039	799	77.9 (14.76)	798	4.9 (11.99)
Respiration Rate (Breaths/min)	Baseline	1039	806	16.4 (3.54)		
	5-15minutes	1039	787	17.4 (4.23)	784	1.0 (3.02)
	30 minutes	1039	770	17.1 (3.75)	768	0.7 (2.79)
	1 hour	1039	786	16.6 (3.26)	784	0.2 (2.19)

SD = standard deviation; BP = blood pressure; bpm = beats per minute.
N = Total number of subjects evaluable for safety.
n = Total number of subjects evaluable for safety with non-missing values for that variable.

Conclusion

Based on the overall safety results, OPTISON was shown to be safe and well tolerated in this real world subject population.

7.1.2 Study GE-191-004

In accordance with the post-marketing commitment, this single-blind, two-period cross-over, placebo-controlled clinical study of OPTISON and 5% dextrose (control) was conducted in 30 subjects, aged 18 years and older, referred for cardiac catheterization for clinical reasons. Subjects were stratified based on a screening PASP obtained by echocardiography within 30 days prior to study drug administration as follows:

- Stratum 1: Normal PASP (≤35 mmHg)
- Stratum 2: Elevated PASP (>35 mmHg)

The primary objective was to compare the effects of OPTISON and a control solution on PASP and PVR, assessed by right heart cardiac catheterization techniques and the

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secondary objective of this study was to perform an overall assessment of the safety of OPTISON in study subjects.

Baseline pulmonary hemodynamic measurements were performed and recorded within 60 minutes of the first OPTISON/control injection, and hemodynamic measurements were then repeated at 2, 6, and 10 minutes after each injection. Continuous 3-lead ECG monitoring was performed from approximately 10 minutes before the first control/OPTISON injection until at least 30 minutes following the second injection of OPTISON/control. All subjects were monitored for safety during the injection and catheterization procedure and for approximately 1-3 hours after injection. A follow-up phone call was performed on Day 2, approximately 24 hours after the subject was discharged, for assessment of AEs and concomitant medication usage.

The average age of subjects was 57 years (min, max: 19, 78) and 53% (16/30) of subjects were female. All 30 subjects had a medical history consistent with cardiac disease. Overall, 19 subjects had pulmonary hypertension, as evidenced by a history of elevated baseline pulmonary arterial pressures.

There were no clinically relevant changes from baseline in mean PASP or PVR (Wood units) values for subjects in either the normal PASP stratum or elevated PASP stratum, or for all subjects combined (Table 6). Overall, in the OPTISON group, mean PASP values were about the same or decreased slightly from baseline (55.2 mmHg at baseline compared with 55.6 mmHg at 2 minutes after injection, 54.1 mmHg at 6 minutes after injection, and 54.6 mmHg at 10 minutes after injection). However, in the control group, mean PASP values were about the same or increased slightly from baseline (53.7 mmHg at baseline compared with 53.8 mmHg at 2 minutes after injection, 54.6 mmHg at 6 minutes after injection, and 54.9 mmHg at 10 minutes after injection).

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Table 6 Summary of Pulmonary Artery Systolic Pressure and Pulmonary Vascular Resistance (Wood Units) by Stratum and Treatment, Hemodynamic Population: Study GE-191-004

			Normal PASP (N=11)				Elevated PASP (N=19)				Overall			
			Optison (N=11)		Control (N=11)		Optison (N=19)		Control (N=19)		Optison (N=30)		Control (N=30)	
Parameter	Time Point		Observed	Change	Observed	Change	Observed	Change	Observed	Change	Observed	Change	Observed	Change
PASP (mm-Hg)	Baseline	N	11	NA	11	NA	19	NA	19	NA	30	NA	30	NA
		Mean	32.5		33.4		68.3		65.5		55.2		53.7	
		SD	9.4		11.2		27.0		26.6		28.1		27.1	
		Median	30.1		31.2		69.1		58.8		47.7		44.9	
		Min	22.4		20.5		33.5		34.2		22.4		20.5	
		Max	51.8		55.5		123.4		120.1		123.4		120.1	
	2 Min Post-injection	N	11	11	10	10	19	19	16	16	30	30	26	26
		Mean	33.9	1.3	35.1	0.5	68.2	–0.1	65.6	1.7	55.6	0.4	53.8	1.3
		SD	10.4	5.2	11.8	8.2	27.1	4.2	27.2	3.0	27.9	4.5	26.9	5.5
		Median	33.7	2.7	32.0	–0.9	60.4	1.2	55.9	1.8	46.9	1.4	46.6	0.6
		Min	20.5	–9.6	22.2	–7.7	33.4	–12.3	36.0	–3.1	20.5	–12.3	22.2	–7.7
		Max	52.1	9.0	52.9	21.5	125.0	4.6	125.7	7.0	125.0	9.0	125.7	21.5
	6 Min Post-injection	N	11	11	11	11	18	18	19	19	29	29	30	30
		Mean	33.0	0.5	34.1	0.7	66.9	–1.1	66.5	1.0	54.1	–0.5	54.6	0.9
		SD	10.7	5.4	11.1	5.0	27.7	3.3	27.6	4.0	28.1	4.2	27.7	4.3
		Median	31.2	–0.9	32.1	–1.5	61.0	0.4	60.4	0.9	45.2	0.2	48.9	0.5
		Min	19.2	–9.4	20.2	–6.0	34.5	–7.3	31.6	–7.9	19.2	–9.4	20.2	–7.9
		Max	53.6	10.8	59.1	10.1	123.9	2.1	128.6	8.5	123.9	10.8	128.6	10.1
	10 Min Post-injection	N	10	10	11	11	19	19	19	19	29	29	30	30
		Mean	32.8	0.04	33.2	–0.1	66.0	–2.3	67.5	2.0	54.57	–1.5	54.9	1.2
		SD	10.0	4.9	10.5	3.9	26.1	4.2	26.6	4.2	27.001	4.5	27.6	4.1
		Median	30.3	–1.0	31.0	–1.1	60.6	–1.6	59.3	2.1	47.60	–1.6	47.7	0.6
		Min	20.2	–8.4	19.7	–5.7	33.3	–11.7	33.5	–5.1	20.2	–11.7	19.7	–5.7
		Max	54.5	8.9	57.1	8.8	119.4	3.8	124.7	13.3	119.4	8.9	124.7	13.3
PVR (Wood units)	Baseline	N	10	NA	11	NA	17	NA	18	NA	27	NA	29	NA
		Mean	1.6		1.6		4.9		5.3		3.6		3.9	
		SD	0.6		0.4		3.1		4.5		2.9		4.0	
		Median	1.5		1.5		4.8		3.3		2.4		2.1	
		Min	0.7		0.9		0.7		0.5		0.7		0.5	
		Max	2.5		2.2		9.6		18.1		9.6		18.1	
	2 Min Post-injection	N	11	10	10	10	16	15	13	13	27	25	23	23
		Mean	1.8	0.2	1.8	0.2	5.0	–0.03	5.4	0.16	3.67	0.1	3.9	0.2
		SD	1.2	0.7	0.8	0.7	4.1	2.6	5.4	0.822	3.561	2.0	4.4	0.8
		Median	1.4	0.05	1.7	–0.1	3.5	–0.1	2.8	0.20	2.40	–0.1	2.3	0.0
		Min	0.4	–0.8	1.1	–1.0	0.6	–4.4	0.4	–1.0	0.4	–4.4	0.4	–1.0
		Max	3.7	1.2	3.5	1.4	15.5	7.4	19.7	1.6	15.5	7.4	19.7	1.6

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Table 6 Summary of Pulmonary Artery Systolic Pressure and Pulmonary Vascular Resistance (Wood Units) by Stratum and Treatment, Hemodynamic Population: Study GE-191-004 (Continued)

			Normal PASP (N=11)				Elevated PASP (N=19)				Overall			
			Optison (N=11)		Control (N=11)		Optison (N=19)		Control (N=19)		Optison (N=30)		Control (N=30)	
Parameter	Time Point		Observed	Change	Observed	Change	Observed	Change	Observed	Change	Observed	Change	Observed	Change
	6 Min Post-injection	N	11	10	9	9	15	14	17	17	26	24	26	26
		Mean	1.5	–0.04	1.5	–0.1	4.6	–0.3	5.14	–0.3	3.3	–0.2	3.87	–0.2
		SD	0.9	0.8	0.5	0.6	3.2	1.5	4.0	2.0	2.9	1.3	3.677	1.7
		Median	1.4	–0.3	1.5	–0.2	3.2	–0.2	3.60	0.1	2.0	–0.2	2.40	0.1
		Min	0.5	–1.2	0.9	–1.3	0.6	–4.2	0.1	–6.5	0.5	–4.2	0.1	–6.5
		Max	3.8	1.3	2.3	0.7	10.1	2.0	12.5	3.7	10.1	2.0	12.5	3.7
	10 Min Post-injection	N	10	10	9	9	16	15	16	16	26	25	25	25
		Mean	1.5	–0.02	1.4	–0.2	5.1	–0.1	4.7	–0.3	3.8	–0.04	3.5	–0.2
		SD	0.6	0.4	0.6	0.8	3.7	1.8	3.6	1.9	3.4	1.4	3.3	1.5
		Median	1.6	0.1	1.3	–0.1	3.5	0.1	2.9	0.2	2.2	0.1	2.5	0.1
		Min	0.6	–0.6	0.4	–1.8	0.8	–4.3	0.6	–6.7	0.6	–4.3	0.4	–6.7
		Max	2.6	0.5	2.3	0.7	11.9	3.3	12.3	1.5	11.9	3.3	12.3	1.5

Note: Baseline was the evaluation immediately prior to each injection (Optison or control). If the baseline for the second injection was missing or invalid, the most recent evaluation prior to the second injection was used as baseline. The summary was based on blind read data.
PASP = pulmonary artery systolic pressure; PVR = pulmonary vascular resistance.

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For the primary analysis, OPTISON and control had no statistically significant effects on the PASP and PVR changes from baseline at all but one of the post-injection time points. At 10 minutes after injection for subjects in the elevated PASP stratum, there was a significant difference in PASP between the OPTISON and control data, with a least-squares mean decrease of -1.97 mmHg for OPTISON patients and an increase of 2.29 mmHg for the control patients; the difference (95% confidence limits) was –4.26 (–7.55, –0.97) mmHg. The mean changes from baseline in PASP and PVR were small for both treatments, both strata, and overall, across all three post-baseline time points (Table 7).

Table 7 Statistical Analysis of PASP and PVR, Hemodynamic Population: Study GE-191-004

Parameter	Time Point	Stratum	Least-Square Mean				Least-Square Mean Difference (Optison to Control) (95% Confidence Interval)
			N	Optison	N	Control	
Change from baseline PASP (mm-Hg)	2 Min Post-Injection	Normal PASP	11	0.80	10	–0.09	0.89 (–3.26, 5.05)
		Elevated PASP	19	0.19	16	2.00	–1.81 (–5.02, 1.40)
		Combined	30	0.50	26	0.95	–0.46 (–3.08, 2.16)
	6 Min Post-Injection	Normal PASP	11	–0.02	11	0.26	–0.28 (–3.98, 3.42)
		Elevated PASP	18	–1.36	19	1.24	–2.60 (–5.42, 0.23)
		Combined	29	–0.69	30	0.75	–1.44 (–3.76, 0.89)
	10 Min Post-Injection	Normal PASP	10	–1.36	11	–0.60	–0.76 (–5.10, 3.58)
		Elevated PASP	19	–1.97	19	2.29	–4.26 (–7.55, –0.97)
		Combined	29	–1.66	30	0.84	–2.51 (–5.23, 0.22)
Change from baseline PVR (Wood units)	2 Min Post-Injection	Normal PASP	10	0.14	10	0.02	0.11 (–1.28, 1.51)
		Elevated PASP	15	0.03	13	0.17	–0.14 (–1.25, 0.97)
		Combined	25	0.08	23	0.10	–0.01 (–0.90, 0.88)
	6 Min Post-Injection	Normal PASP	10	–0.12	9	–0.18	0.05 (–1.34, 1.45)
		Elevated PASP	14	–0.31	17	–0.14	–0.18 (–1.25, 0.89)
		Combined	24	–0.22	26	–0.16	–0.06 (–0.94, 0.82)
	10 Min Post-Injection	Normal PASP	10	–0.10	9	–0.34	0.24 (–1.08, 1.55)
		Elevated PASP	15	–0.12	16	0.04	–0.16 (–1.17, 0.86)
		Combined	25	–0.11	25	–0.15	0.04 (–0.79, 0.87)

PASP = pulmonary artery systolic pressure; PVR = pulmonary vascular resistance.

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Conclusion

There were no clinically relevant changes from baseline in other hemodynamic parameters (i.e., mean RA pressure, PA diastolic pressure, PAP, PCWP, and cardiac index) for subjects in either the normal PASP or elevated PASP strata, or for all subjects combined.

There were no deaths, SAEs, or significant AEs reported during the study. One AE of procedural pain was reported during the study. There were no clinically relevant changes observed in any other hemodynamic parameters, vital signs, oxygen saturation, clinical laboratory tests, or ECG findings.

7.1.3 Study GE-191-005

Background

Study GE-191-005 fulfilled the required post-marketing safety commitment to assess safety by utilizing an existing database to compare in-hospital mortality in critically ill patients undergoing echocardiography with and without OPTISON. Critically ill patients were defined as those who have at least one of six unstable cardiopulmonary conditions: unstable heart failure, acute myocardial infarction, arrhythmia, respiratory failure, pulmonary embolism or emphysema, and pulmonary hypertension as the admitting diagnosis. This retrospective, case-controlled study compared the rate of same-day and two-day, all-cause, in-hospital mortality between patients administered OPTISON and those who did not have a contrast agent administered.

A propensity score matching approach was used to control for the differences in observable covariates and to reduce the selection bias that can occur in case-control studies (Rosenbaum and Rubin, 1985). This method reduced the variability between OPTISON patients and matched controls. This approach yielded the final sample that was used in the per protocol statistical analysis. Prior to conducting this analysis, the statistical approach was presented to the FDA, who agreed that the proposed methodology was appropriate.

As part of the initial analyses, there was an assessment of the distribution of the matched controls to the OPTISON patients by each of the six cardiopulmonary conditions. An analysis of the case-control matches using the propensity score matching approach demonstrated that a majority of the OPTISON patients were matched to non-contrast patients with a different cardiopulmonary condition. The propensity score matching algorithm did not include the specific cardiopulmonary condition as a baseline covariate. Therefore, after careful examination of the distribution of propensity score matches, the decision was made to stratify the cohorts by the six cardiopulmonary conditions. The propensity score matching algorithm describe above was then utilized within each stratum separately. This approach guaranteed that OPTISON patients with one of the six conditions would be matched to control patients with the same condition, thereby ensuring a greater level of similarity between patients.

Analyses were conducted with and without the matching of the cardiopulmonary conditions and results from both analyses are presented here. The results accounting for clinical condition provide the most reliable assessment for the event rate in the control population for this study.

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Both analyses demonstrated that there is no clinically or statistically significant association between OPTISON use and same-day or two-day mortality.

Data Source

The data source was Premier's Perspective Comparative Database. Premier uses a consistent and secure sample of over 500 hospitals in the US, with a 93% hospital retention rate. This database is the largest hospital-based, service-level comparative database in the US, providing detailed resource utilization and cost data along with patients' admitting diagnosis and procedure codes. Premier collects data directly from each hospital's cost accounting systems. Detailed service-level information is available for each hospital day and includes medication information and location within hospital. Data collected include patient demographics (age, gender, and race/ethnicity) along with the hospital's teaching status, urban/rural location, and geographic region. Premier controls the consistency and quality of the data submissions and works closely with the hospitals to ensure accuracy and completeness of the data. The database goes through rigorous quality/integrity checks ensuring a high level of data reliability. This is also the case for reporting in-hospital mortality.

Patient Population

The population of interest comprised hospitalized patients from the database who underwent at least one clinically indicated ECG during the period from 1 January 2003 to 1 November 2005, and who were 18 years of age or older during administration of the procedure. This time period was selected because OPTISON marketing was temporarily suspended in November 2005 for manufacturing reasons.

Critically ill patients were defined as those who had at least one of six unstable cardiopulmonary conditions as shown in Table 8. ICD-9-CM codes were used to determine criticality.

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Table 8 Unstable Cardiopulmonary Conditions Used to Define Critically Ill Patients: Study GE-191-005

Description	Percent Distribution
Worsening or clinically unstable congestive heart failure	47.7%
Acute myocardial infarction or acute coronary syndrome	34.8%
Serious ventricular arrhythmias or high risk for arrhythmia due to prolongation of the QT interval	3.4%
Respiratory failure, as manifest by signs and symptoms of hypoxemia	10.8%
Severe emphysema, pulmonary emboli or other conditions that may cause pulmonary hypertension	3.1%
Pulmonary hypertension	0.2%

Covariates

The propensity score matching algorithm utilized a pre-defined set of 23 covariates to match the OPTISON patients to the non-contrast patients. Covariates included a set of demographic and clinical variables that were available for each patient in the study population. There were also a set of hospital-specific variables; teaching status, urban/rural location, and geographic region. Variables to indicate the use of anti-coagulants and NSAIDs were also included.

To assess the morbidity level for each patient individual elements of the Deyo-modified Charlson Comorbidity Index (DM-CCI) were used. The DM-CCI was created to weight patients by their comorbid conditions in order to assess their risk of mortality (Charles et. al., 1987). The CCI was later modified by Deyo and colleagues, who matched the conditions to ICD-9-CM diagnosis codes (Deyo et. al., 1992). The DM-CCI is widely used as an adjustor to control for comorbidities in retrospective database analyses.

Propensity Score Matching Algorithm

A propensity score matching algorithm was used to match each of the patients who received OPTISON to four control patients who did not have a contrast agent administered. For each OPTISON patient, four matched control patients were selected with similar propensity scores that were generated from the propensity score matching algorithm which analyzed the 23 baseline covariates. This selection was based on the smallest difference between propensity scores among the OPTISON patients and controls.

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There were 207,066 non-contrast patients and 2,884 OPTISON patients who met all of the eligibility criteria for the study. The propensity score matching algorithm was used to match the OPTISON patients to similar non-contrast patients on the basis of pre-defined baseline covariates. This methodology was used to reduce the potential bias in the retrospective selection of matched controls. Prior to the matching, there were 25 of 29 (23 of which were used in the propensity score matching algorithm) baseline covariates that differed statistically between the cohorts. After matching on propensity score, the difference was reduced to four, reducing the potential for bias. The final sample used in the statistical analysis consisted of 2,884 OPTISON patients and 11,536 matched controls.

The propensity score matching algorithm did not include the specific clinical condition as a baseline covariate. Thus, the propensity score matching algorithm resulted in a majority of OPTISON patients that were matched to non-contrast patients with a different clinical condition. Table 9 displays the matching percentages for OPTISON patients with non-contrast patients in the 1:4 matching procedure for each of the six clinical conditions separately. Slightly more than half of the OPTISON patients with worsening or clinically unstable CHF are matched to non-contrast patients with the same clinical condition. The same is true for OPTISON patients with acute MI. OPTISON patients with the remaining four conditions are matched to non-contrast patients with the same condition much less than 50% of the time. For example, OPTISON patients with serious ventricular arrhythmias (code 3) are matched with similar non-contrast patients only 8% of the time, and OPTISON patients with pulmonary hypertension (code 6) did not match to any non-contrast patients with pulmonary hypertension.

Table 9 Distribution of Propensity Score Matches: Study GE-191-005

OPTISON (N=2884)				NON-CONTRAST (N=11,536)		
Clinical Condition Category Code[a]	N	%		Clinical Condition Category Code[a]	N	%
1	1205	41.78		1	2571	53.34
				2	1506	31.24
				3	149	3.09
				4	448	9.29
				5	139	2.88
				6	7	0.15
				TOTALS:	4820	
2	1083	37.55		1	1333	30.77
				2	2290	52.86
				3	192	4.43
				4	425	9.81
				5	87	2.01
				6	5	0.12
				TOTALS:	4332	
3	132	4.58		1	185	35.04
				2	221	41.86
				3	43	8.14
				4	73	13.83
				5	5	0.95
				6	1	0.19

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Table 9 Distribution of Propensity Score Matches: Study GE-191-005 (Continued)

OPTISON (N=2884)				NON-CONTRAST (N=11,536)		
Clinical Condition Category Code[a]	N	%		Clinical Condition Category Code[a]	N	%
				TOTALS:	528	
4	398	13.80		1	507	31.85
				2	434	27.26
				3	112	7.04
				4	496	31.16
				5	41	2.58
				6	2	0.13
				TOTALS:	1592	
5	59	2.05		1	109	46.19
				2	72	30.51
				3	11	4.66
				4	31	13.14
				5	10	4.24
				6	3	1.27
				TOTALS:	236	
6	7	0.24		1	13	46.43
				2	10	35.71
				3	0	0
				4	4	14.29
				5	1	3.57
				6	0	0
				TOTALS:	28	

[a]Clinical Condition Codes: 1=Worsening or clinical unstable CHF; 2=Acute Myocardial Infarction; 3=Serious Ventricular Arrhythmias; 4=Respiratory Failure; 5=Pulmonary Emboli; 6=Pulmonary Hypertension

Given the large number of possible matched controls and that this study was retrospective, it was crucial that the non-contrast patients selected were as similar as possible to the OPTISON patients in their baseline characteristics. The propensity score matching algorithm did not include the specific cardiopulmonary condition as a baseline covariate. Therefore, the pre-specified propensity score matching algorithm was utilized within each cardiopulmonary condition separately to match OPTISON patients to control patients. This approach (i.e., alternative matching strategy) guaranteed that OPTISON patients with one condition would be matched to control patients in the same condition, thus ensuring a greater level of similarity between patients.

Statistical Analysis Using Alternative Matching Strategy

The primary outcome in this study was all-cause, same-day mortality; the secondary outcome was all-cause two-day (same-day or next-day) mortality. One limitation of the dataset is that mortality and procedures were listed by date, not date/time, preventing the calculation of 24-hour mortality.

The pre-specified statistical methodology for analyzing the primary and secondary endpoints was performed after first matching on clinical condition category. Table 10 displays the primary and secondary endpoints after first matching within clinical condition and then matching within clinical condition by nearest propensity score. As shown in Table 10, there

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were no significant differences between the OPTISON patients and the matched controls for same-day (p=0.3199) or two-day (p=0.0818) all-cause mortality when first matching within clinical condition and then matching on propensity score.

Table 10 Alternative Analysis: Rate of Same-day and Two-day, All-cause, In-hospital Mortality Between Patients Administered OPTISON and Patients who did not Have a Contrast Agent Using a 1:4 Match by First Matching Within Clinical Condition: Study GE-191-005

	Odds Ratio	95% Confidence Intervals		P-value
OPTISON Treatment - Primary Outcome: Same Day Mortality (165 events: OPTISON n=38, Non-contrast n=127)	1.208	0.833	1.752	0.3199
OPTISON Treatment - Secondary Outcome: Same Day or Next Day Mortality (256 events: OPTISON n=62, Non-contrast n=194)	1.302	0.967	1.752	0.0818

The pre-specified sensitivity analyses were also performed for the primary and secondary endpoints using the alternative matching strategy to determine the effect of choosing a 1:4 ratio between OPTISON patients and the matched controls. The sensitivity analyses were performed using a 1:1 ratio between OPTISON patients and the matched controls. Therefore, only the best match to the OPTISON patient was used in the sensitivity analyses. Table 11 presents the results of the 1 to 1 matching by first matching within clinical condition. Results from the sensitivity analyses demonstrated that there was no increase in same-day or two-day all-cause mortality using OPTISON.

Table 11 Alternative Sensitivity Analysis: Rate of Same-day and Two-day, All-cause, In-hospital Mortality Between Patients Administered OPTISON and Patients who did not Have a Contrast Agent Using a 1:1 Match by First Matching Within Clinical Condition : Study GE-191-005

	Odds Ratio	95% Confidence Intervals		P-value
OPTISON Treatment - Primary Outcome: Same Day Mortality (71 events: Optison n=38, Non-contrast n=33)	1.161	0.718	1.877	0.5417
OPTISON Treatment - Secondary Outcome: Same Day or Next Day Mortality (111 events: Optison n=62, Non-contrast n=49)	1.310	0.876	1.957	0.1882

Results of the Per Protocol Analysis

As shown in Table 12, there were no significant differences between the OPTISON patients and the matched controls for same-day (p=0.0760) or two-day (p=0.1086) all-cause mortality when matching on propensity score.

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Table 12 Per Protocol Analysis: Rate of Same-day and Two-day, All-cause, In-hospital Mortality Between Patients Administered OPTISON and Patients who did not Have a Contrast Agent Using a 1:4 Match - Study GE-191-005

	Odds Ratio	95% Confidence Intervals		P-value
		Lower	Upper	
Optison™ Treatment - Primary Outcome: Same Day Mortality (147 events: Optison n = 38, No-Contrast n = 109)	1.400	0.965	2.030	0.0760
Optison™ Treatment - Secondary Outcome: Same Day or Next Day Mortality (259 events: Optison n = 62, No-Contrast n = 197)	1.268	0.949	1.695	0.1086

Sensitivity analyses were performed for the primary and secondary endpoints to determine the effect of choosing a 1:4 ratio between OPTISON patients and the matched controls. The sensitivity analyses were performed using a 1:1 ratio between OPTISON patients and the matched controls. Table 13 presents the results of the 1 to 1 matching by propensity score. Results from the sensitivity analyses demonstrated that there was no increase in same-day or two-day all-cause mortality using OPTISON.

Table 13 Per Protocol Sensitivity Analysis: Rate of Same-day and Two-day, All-cause, In-hospital Mortality Between Patients Administered OPTISON and Patients who did not Have a Contrast Agent Using a 1:1 Match: Study GE-191-005

	Odds Ratio	95% Confidence Intervals		P-value
		Lower	Upper	
Optison™ Treatment - Primary Outcome: Same Day Mortality (64 events: Optison n = 38, No-Contrast n = 26)	1.462	0.887	2.407	0.1360
Optison™ Treatment - Secondary Outcome: Same Day or Next Day Mortality (110 events: Optison n = 62, No-Contrast n = 48)	1.298	0.887	1.899	0.1792

Discussion

One limitation is the observational nature of the study. Treatment selection was non-random and there were large differences between the OPTISON group and the non-contrast group. However these differences were dramatically reduced after the propensity score matching.

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Another limitation is the measurement of the time of death. Both treatment and mortality are measured at the day level rather than time of day, and cause of death was not available. Ideally this database would have also provided the clinical indication for the echocardiogram. Finally, cause of death was not included in the dataset. Therefore, mortality likely was not limited to cardiovascular, cerebrovascular, or pulmonary causes. These limitations, however, did not influence the reliability of the analysis results or the conclusions from this study.

Conclusion

Based on the totality of the evidence from the statistical analyses performed in this retrospective study, there is not a statistically or clinically meaningful increase in same-day or two-day all-cause mortality for the patients receiving OPTISON.

7.2 Post-Marketing Surveillance Data

All spontaneously reported AEs from January 2008 to 31 December 2010 are presented. These reports were retrieved from the GE Healthcare Pharmacovigilance global safety database to prepare Periodic Safety Update Reports (PSURs); data shown are summarized from the PSURs for 2008, 2009, and 2010.

7.2.1 Determination of Seriousness for Adverse Event Reports

Manufacturers classify AE reports as serious or non-serious based on a standard regulatory definition. The regulatory classifications are different from medical or other classifications. By regulatory definition an AE is serious if it is fatal, immediately life-threatening, causes or prolongs hospitalization, causes disability, or is a congenital anomaly. Additionally, if the AE puts the patient in jeopardy or requires intervention to prevent one of the other criteria, it should be considered serious as an "other important medical condition."

7.2.2 GE Healthcare Pharmacovigilance Database

The GE Healthcare Pharmacovigilance organization uses an electronic database software to record, store, analyze, and report AEs for all company products. This database was searched using the company drug name "OPTISON" to identify cases for inclusion in PSURs.

7.2.3 Patient Exposure

During the reporting interval, approximately 55,000 vials of OPTISON were sold world-wide, which represents an estimated 55,000 patient exposures.

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7.2.4 Adverse Event Reports

7.2.4.1 Non-Serious Reports

There were two spontaneous reports of non-serious listed reactions. Both patients experienced minor allergy-type reactions: hypersensitivity (rash), and anaphylactoid reaction (increased HR 125 bpm, shortness of breath, sweating).

These do not represent an increase in the reporting rate of allergy-type events occurring in association with OPTISON administration.

7.2.4.2 Serious Reports

No spontaneous reports of SAEs were received.

Six reports of serious unlisted reactions were identified in the literature: four events were reported by Wei et. al. (2008) and two events were reported by Abdelmoneim et. al., (2009).

Wei et. al. described four patients who experienced ventricular tachycardia of short duration that resolved spontaneously or with treatment (Wei et. al., 2008). In the publication, the events were reported as not related to the contrast agent and, therefore, were not considered serious. Notwithstanding the statement by Wei et. al. that no SAEs were reported, GE Healthcare considers that a ventricular arrhythmia potentially jeopardizes the patient and accordingly classifies these AEs as serious. The AEs reported by Wei were assessed by GE Healthcare Pharmacovigilance as labeled per the US product label. Accordingly, the events were not alert reports to the FDA and were reported in the PSUR. Brief narratives prepared by GE Healthcare Pharmacovigilance for each patient are presented below.

Patient 1
On an unknown date, a 63 year-old male patient received an IV administration of OPTISON and dobutamine for stress echocardiography to determine a strategy of palliative chemotherapy and radiotherapy versus surgery and radiotherapy. The patient's medical history was significant for esophageal squamous cell cancer, chronic pancreatitis, gastroesophageal reflux disease, CAD, a possible MI. During the procedure, the patient developed chest discomfort and then developed sustained ventricular tachycardia. The patient was treated with IV metoprolol and reverted to normal sinus rhythm.

Patient 2
A 58 year-old female patient received an administration of OPTISON for exercise-stress echocardiographic investigation of atypical chest pain. Medical history was significant for ST-segment elevation MI (STEMI), and percutaneous transluminal angioplasty, both 8 years before the procedure. Baseline HR and BP were 76 bpm and 144/80 mmHg, respectively. At stage-2 of the protocol, the HR was 150 bpm and the BP was 150/84 mmHg. At this time, she experienced a 1-minute episode of sustained ventricular tachycardia. Echocardiography showed ischemia in the left anterior-descending (LAD) artery territory and the patient underwent cardiac catheterization which showed 3-vessel coronary artery disease. Coronary artery bypass graft surgery was performed without complication and the patient discharged home.

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Patient 3
A 68 year-old male patient received an administration of OPTISON for exercise-stress echocardiographic investigation of vague cardiac symptoms. Medical history was significant for known coronary artery disease, percutaneous coronary intervention (2 years before procedure), cerebrovascular accident, obesity, type 2 diabetes mellitus, and increased cholesterol. Baseline HR and BP were 69 bpm and 140/80 mmHg respectively. The procedure was discontinued at stage 3 of the protocol, at which time the HR was 157 bpm and BP was 194/90 mmHg. At this time, he experienced increased shortness of breath and non-sustained ventricular tachycardia. Shortly thereafter, he experienced a 1-minute episode of sustained ventricular tachycardia which resolved spontaneously. Echocardiography showed ischemia in the LAD artery territory and the patient underwent cardiac catheterization which showed 80% stenosis of the LAD and occlusion of the posterior descending artery. Coronary artery bypass graft surgery was performed without complication and the patient discharged home.

Patient 4
A 74 year-old male patient received an intravenous administration of OPTISON for echocardiographic investigation of abdominal aortic aneurysm as part of the repair procedure. Medical history was significant for coronary artery bypass graft, aortic valve replacement, paroxysmal atrial fibrillation, and endarterectomy (multiple). Concomitant medications were not reported. Subsequent to administration, during post-operative recovery, the patient experienced a 2-minute episode of ventricular tachycardia which resolved. Abdominal aortic aneurysm repair was completed without complication. Echocardiography was indicative of severe coronary artery disease and the patient underwent cardiac catheterization that showed complete occlusion of the right circumflex, left anterior descending, and the origin of the circumflex, arteries. Coronary artery bypass graft surgery was performed and the patient was discharged home.

Abdelmoneim et. al. described two patients who experienced serious unlisted events (MI) following OPTISON (Abdelmoneim et. al., 2009).

Patient 1
A 65-year-old man with diabetes mellitus, hypertension, and hyperlipidemia; he underwent dobutamine stress echocardiography before orthopedic surgery. Baseline transthoracic echocardiography (TTE) showed a peak tricuspid regurgitant velocity of 2.4 m/second, which corresponds to an estimated right ventricular systolic pressure of 28 mmHg. Stress echocardiography results were markedly positive for ischemia in the left anterior descending coronary artery distribution. Ventricular fibrillation developed during the stress echocardiography recovery period and required emergent defibrillation. Three hours after the stress echocardiography, the cardiac troponin T level was elevated (0.05 ng/mL, reference range ≤0.03 ng/mL). The patient underwent urgent coronary angiography and stenting of the totally occluded LAD coronary artery.

While a temporal relationship exists, the sponsor considers the most plausible cause for this event to be the patient's pre-existing medical condition of myocardial ischemia in the LAD distribution. A contributing role of dobutamine-induced myocardial stress is possible, but a causal role for OPTISON is not thought to be credible.

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Patient 2
A 73-year-old woman who smoked and had diabetes mellitus, hypertension, and hyperlipidemia; she underwent dobutamine stress echocardiography before orthopedic surgery. Baseline TTE showed a peak tricuspid regurgitant velocity of 2.9 m/second, which corresponds to an estimated right ventricular systolic pressure of 44 mmHg. Stress echocardiography was negative for myocardial ischemia. Four hours after stress echocardiography, the patient underwent hip replacement. On the second postoperative day, she had chest pain and an elevated cardiac troponin T level (0.23 ng/mL). Non–STEMI was diagnosed; she underwent coronary angiography post-operatively, and a high-grade stenosis of the obtuse marginal branch of the left circumflex artery was stented.

The sponsor opined that the event was unrelated to the administration of OPTISON and likely related to peri-operative ischemia that occurred during the high-risk surgery performed on a patient with pre-existing high-grade stenosis.

These are historical events from a published retrospective study of doses administered between 2003 and 2007, i.e., not newly occurring during the present reporting interval. They are isolated incidents and represent neither an increase in the reporting rate of, nor a change in the nature of, cardiovascular events occurring in association with OPTISON administration.

7.2.5 Overall Safety Evaluation from Post-Marketing Surveillance

Based on the two spontaneously reported events (described above) and the six events reported in the literature (described above), GE Healthcare has assessed the data collected during the period of review and finds there was no significant change in:

- Serious unlisted reactions
- Non-serious unlisted reactions
- The characteristics of listed reactions (Severity, outcome, or target population)
- Increased reporting frequency of listed reactions

No significant new information has been received regarding:

- Drug interactions
- Experience with overdose, deliberate or accidental, and its treatment
- Drug abuse or misuse
- Positive or negative experiences during pregnancy or lactation
- Experience in special patient groups (e.g. children, elderly, organ impaired)
- Effects of long-term treatment (not applicable for contrast agents intended for single use)

7.3 Safety of OPTISON Reported in Published Literature

7.3.1 Search Characteristics

A literature search was conducted by GE Healthcare using Science Direct and the US National Library of Medicine's literature database, PubMed. The search period was from May 2008 to

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31 December 2010. The search resulted in identifying four large retrospective safety studies of contrast agents and one assessment of several observational studies. One of the identified articles was published by Exuzides et. al. and reports on the GE data derived from Study GE-191-005 (Exuzides et. al., 2010); the study data from the Clinical Study Report are included in Section 7.1.3 and not shown again here. The remaining three studies, as well as the review of observational studies, are summarized here.

7.3.2 Published Studies

A retrospective data review from Hennepin County Medical Center was published by Herzog. The database, which was started in 1986, contains data from over 112,000 echocardiographs and includes information on use and complications (Herzog, 2008). A separate non-electronic file of AEs reported by the nursing staff was accessed and events occurring within 30 minutes of injection were identified. Electronic charts for patients experiencing an AE were reviewed. Non-fatal AEs considered to be related to stress testing were omitted from the analysis. The database includes data for both OPTISON and Definity™ administration. The author states that from February 1998 to February 2002, 3051 patients received OPTISON and no AEs were reported for the OPTISON patients.

Wei et. al. reported on the incidence of severe AEs after exposure to contrast ultrasound agents in a retrospective analysis of 78,383 administered doses, of which 12,219 doses were OPTISON (Wei et. al., 2008); contrast use accounted for 5% of transthoracic and 28% of stress echocardiographic procedures. Severe reactions occurred in four (0.006%) OPTISON patients (these events are described in Section 7.2.4.2.). There were no deaths and no SAEs reported. The results from this study showed that the incidence of SARs to ultrasound contrast agents was lower than, or similar to, that reported for contrast agents commonly used in other cardiac imaging tests.

Abdelmoneim et. al. reported safety results from a 4-year single-center cohort study of patients who received a contrast agent during stress echocardiography (Abdelmoneim et. al., 2009). A total of 26,774 patients were evaluated during the period between 1 November 2003 and 31 December 2007. A total of 10,792 patients received a contrast agent and 15,982 had no contrast administered; 14% (1511/10792) of the contrast patients received OPTISON. The authors concluded that patients who had undergone stress echocardiography with contrast agents were not at increased risk of death or MI compared with those who had not received contrast agents. Few AEs were reported overall (narratives for two subjects are provided in Section 7.2.4.2). The incidence of acute anaphylactoid reaction was 0.03% (approximately 3 of 10,000 patients).

An evidence-based analysis was conducted with data from 23 obs ervational studies that assessed the diagnostic accuracy of contrast echocardiography for the diagnosis of CAD (Ontario Health Technology Assessment Series, 2010). All these studies used stress echocardiography with contrast. In addition, nine retrospective chart reviews were identified that assessed the safety of stress echocardiography at rest or stress. Based on the results of these studies, there was not a statistically significantly higher mortality rate in patients who receive contrast compared to those who did not.

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7.4 Preclinical Safety of OPTISON

No preclinical studies have been performed by GE Healthcare since 2008. In addition, a search of published preclinical literature revealed that there have been no published reports of preclinical studies with OPTISON.

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8 THE OPTISON PRODUCT LABEL

8.1 Proposed Changes to the Current Product Label

Based on the safety data presented in this Briefing Document, the boxed warning is not necessary to ensure patient safety. The boxed warning was added in 2007 after reports of deaths with a temporal association to contrast agent administration. Since the 2008 Advisory Committee Meeting, safety data have been collected; review of these data consistently shows that OPTISON is safe and well-tolerated. A copy of the current product label is provided in Appendix B.

Physicians are provided adequate and clear instructions for safe administration of OPTISON in the "Warnings" and "Precautions" section of the current product label. The "Warnings" and "Precautions" section is sufficient for the physician to make an informed decision on the use of a contrast agent. The "Contraindications" section clearly describes patients for whom OPTISON is not appropriate. As stated in 21 CFR §201.57: "The boxed warning ordinarily must be based on clinical data…" Data collected subsequently indicates that a boxed warning is no longer justified.

8.2 Consequences of Restricting the Use of Contrast Agents

Physicians using OPTISON are well versed on its benefits and limitations. In addition, physicians are cautious and prudent when administering such agents, and follow the information provided in the product label. When the class labeling requirements, including the boxed warning, were implemented in 2007, a notable decrease in the use of contrast echocardiography was reported. In fact, it has been reported that many institutions stopped using contrast agents as a result of the FDA warning (Dolan et. al., 2001). As illustrated in Figure 2, prior to this labeling change, contrast echocardiography was used more frequently when compared to its use after class labeling was implemented (Arlington Medical Resources). Continuing the boxed warning may have the effect of limiting the use of OPTISON in critically ill patients who may receive the most benefit from contrast-enhanced echocardiography with the potential for incorrect treatment, adverse outcomes from incorrect or delayed diagnosis, and increased usage of other diagnostic tests that have well-documented risks.

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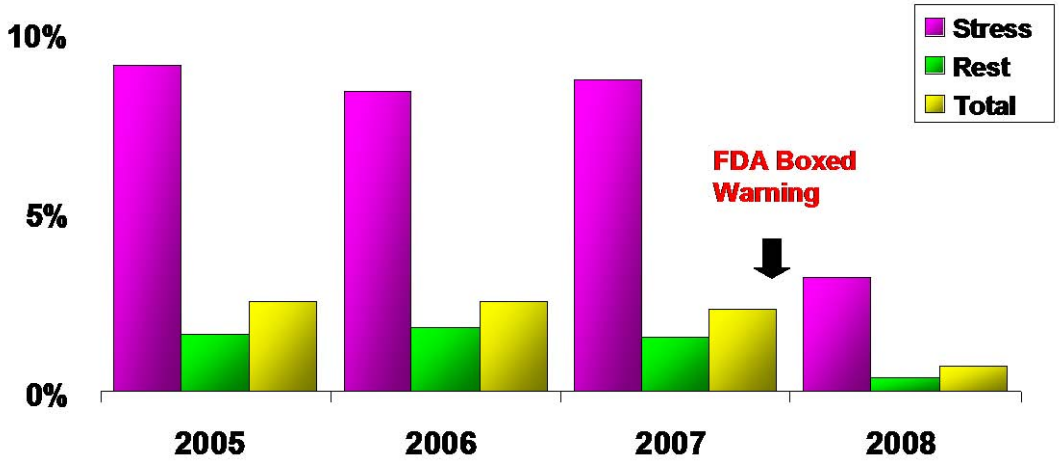
Figure 2 Contrast Echocardiography as a Percentage of Total Echocardiography (Arlington Medical Resources)



The clinical utility and medical need were outlined in detail in Section 6. From the data presented, it is clear that restricting the use of ultrasound contrast agents has already resulted in profound implications for physicians and patients. As presented previously, avoiding the use of an ultrasound contrast agent because of concerns regarding the potential risks may be inappropriate because the alternative procedures, such as MRI, CT, and radionuclide ventriculogram, to contrast-enhanced echocardiography could place the patient at an equivalent or higher risk (Main et. al., 2007). Patients receiving gadolinium-based magnetic resonance contrast media have been shown to develop urticarial rash (0.04%) and anaphylactoid shock (0.01%) (Li et. al., 2006). Intravenously administered non-ionic iodinated contrast agents used for CT cause urticaria in up to 0.5% and severe reactions in 0.001% to 0.04% of patients (Caro et. al., 1991; Katayama et. al., 1990). Iodinated x-ray contrast media are also associated with a risk of contrast-induced nephropathy. The risk of MI or death with exercise treadmill stress testing is approximately 1:2,500 (Stuart and Ellestad, 1980), and the lifetime risk of fatal malignancy after rest-stress single-photon emission CT or a radionuclide ventriculogram examination is estimated at 1:1,000 to 1:10,000 (Einstein et. al., 2007).

Moreover, restricting the use of contrast-enhanced ultrasound limits clinicians' ability to identify and characterize intracardiac masses, to differentiate cardiac structural variants such as apically displaced papillary muscles, artifacts, and to detect thrombi in the left ventricle. Research presented in this Briefing Document shows that the use of contrast ultrasound agents improves sensitivity and specificity of echocardiography; restricting its use with a boxed warning will reduce physicians' ability to provide a confident diagnosis and will reduce the access of contrast-enhanced echocardiography to an increasing number of patients that may benefit from it.

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GE Healthcare acknowledges that there are risks associated with the use of OPTISON, which were well characterized at the time of approval. The overall benefit-to-risk profile remains acceptable such that the boxed warning should be removed.

9 OVERALL CONCLUSIONS

- Since its approval, approximately 1.15 million doses of OPTISON have been administered to patients and it has been shown to be safe and well-tolerated.
- The ACCF, in partnership with the ASE, along with key specialty and subspecialty societies, as well as the ICAEL, recommend the use of contrast agents when greater accuracy in diagnosis is needed because of poor image quality.
- Serious contrast reactions are rare and the incidence of SARs to ultrasound contrast agents is lower than, or similar to, that reported for contrast agents commonly used in other cardiac imaging tests.
- The boxed warning may have the effect of limiting the use of OPTISON in critically ill patients who may receive the most benefit from contrast-enhanced echocardiography with the potential for incorrect treatment, adverse outcomes from incorrect or delayed diagnosis, and increased usage of other diagnostic tests that have well-documented risks.
- Data from three mandated post-marketing studies, continued post-marketing surveillance, and published literature collectively demonstrate that there is no need for the current boxed warning; consequently, the OPTISON product label should be revised.

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10 REFERENCES

Abdelmoneim et. al., 2009
Abdelmoneim SS, Bernier M, Scott CG. Dhoble A, Ness SA, et. Al. Safety of contrast agent use during stress echocardiography. JACC: Cardiovascular Imaging 2009: 2(9); 1048-56.

ACR Manual, 2010
ACR Manual on Contrast Media, Version 7. American College of Radiology Committee on Drugs and Contrast Media 2010. Accessed at http://www.acr.org/secondarymainmenucategories/quality_safety/contrast_manual.aspx

Allen et. al., 1999
Allen MR, Pellikka PA, Villarraga HR, Klarich KW, Foley DA, Mulvagh SL, et al. Harmonic imaging: echocardiographic enhanced contrast intensity and duration. Int J Card Imaging 1999;15:215-20.

Bjerknes et. al., 1997
Bjerknes K, Sontum PC, Smistad G, Agerkvist I. Preparation of polymeric microspheres: formulation studies and product characterisation. Int J Pharm 1997; 158: 129-136.

Charles et. al., 1987
Charles ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

Cohen et. al., 1998
Cohen JL, Cheirif J, Segar DS, Gillam LD, Gottdiener JS, Hausnerova E, et al. Improved left ventricular endocardial border delineation and opacification with Optison (FS069), a new echocardiographic contrast agent: results of a phase III multicenter trial. J Am Coll Cardiol 1998; 32:746-52.

Caro et. al., 1991
Caro JJ, Trindale E, McGregor M. The risks of death and of severe nonfatal reactions with high- vs low-osmolality contrast media: a meta-analysis. AJR Am J Roentgenol 1991;156:825-32

Castello et. al., 2003
Castello R, Bella JN, Rovner A, Swan J, Smith J, Shaw L. Efficacy and time-efficiency of a “sonographer-driven” contrast echocardiography protocol in a high-volume echocardiography laboratory. Am Heart J 2003;145:535-41.

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Dawson and Cockel, 1981
Dawson J, Cockel R. Oesophageal perforation at fibreoptic gastroscopy. Br Med J 1981;283:583.

Deyo et. al., 1992
Deyo RA, Cherkin DC, Ciol Ma. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45(6):613-9.

Dolan et. al., 2001
Dolan MS, Riad K, El-Shafei A, Puri S, Tamirisa K, Bierig M, et al. Effect of intravenous contrast for left ventricular opacification and border definition on sensitivity and specificity of dobutamine stress echocardiography compared with coronary angiography in technically difficult patients. Am Heart J 2001;142:908-15.

Douglas et. al., 2011
Douglas PS, Garcia MJ, Haines DE, et al. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 Appropriate Use Criteria for Echocardiography. A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance Endorsed by the American College of Chest Physicians. J Am Coll Cardiol;57:1126-66

Dugstad et. al., 1996
Dugstad H, Skurtveit R, Brænden J, Klavenes J, Rongved P. International Patent Application 9729783 1996 (priority February 19).

Einstein et. al., 2007
Einstein AJ, Moser KW, Thompson RC, Cerqueira MD, Henzlova MJ. Radiation dose to patients from cardiac diagnostic imaging. Circulation 2007;116:1290 –305.

Erb and Shanewise, 2001
Erb JM and Shanewise JS. Intraoperative contrast echocardiography with intravenous Optison does not cause hemodynamic changes during cardiac surgery. J Am Soc Echocardiography June 2001;14(6):595-600.

Exuzides et. al., 2010
Exuzides A, Main ML, Colby C, Grayburn PA, Feinstein SB, Goldman JH. A retrospective comparison of mortality in critically ill hospitalized patients undergoing echocardiography with and without an ultrasound contrast agent. JACC Cardiovasc Imaging 2010 Jun;3(6):578-85.

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Feinstein et. al., 1990

Feinstein SB, Cheirif J, ten Cate FJ, Silverman PR, Heidenreich PA, Dick C, et al. Safety and efficacy of a new transpulmonary ultrasound contrast agent: initial multicenter clinical results. J Am Coll Cardiol 1990;16:316-24.

Gramiak and Shah, 1968

Gramiak R. and Shah P. Echocardiography of the aortic root. Invest Radiol 1968; 3, 356-388.

Hoff et. al., 2000

Hoff L, Sontum PC, Hovem JM. Oscillations of polymeric microspheres: Effect of the encapsulating shell. J Acoust Soc Am 2000; 107: 2272-2280.

Hogg, 1987

Hogg JC. Neutrophil kinetics and lung injury. Phys Rev 1987; 67: 1249-1295.

Hundley et. al., 1999

Hundley WG, Kizilbash AM, Afridi I, Franco F, Peshock RM, Grayburn PA. Effect of contrast enhancement on transthoracic echocardiographic assessment of left ventricular regional wall motion. Am J Cardiol 1999;84:1365-8.

Herzog, 2008

Herzog C. Incidence of Adverse Events Associated With Use of Perflutren Contrast Agents for Echocardiography. JAMA 2008; V299, No, 18: 2023-5.

ICAEL, 2010

ICAEL Standards for Accreditation in Adult Echocardiography Testing. Intersocietal Commission for the Accreditation of Echocardiography Laboratories 2010. Accessed at http://www.icael.org/icael/main/icael_standards.htm.

Jenkins et. al., 2009

Jenkins C, Moir S, Chan J, Rakhit D, Haluska B, Marwick TH. Left ventricular volume measurement with echocardiography: a comparison of left ventricular opacification, three-dimensional echocardiography, or both with magnetic resonance imaging. Eur Heart J 2009;30:98-106.

Johnson et. al., 1989

Johnson LW, Lozner EC, Johnson S, et al. Coronary arteriography 1984–1987: a report of the Registry of the Society for Cardiac Angiography and Interventions. I. Results and complications. Cathet Cardiovasc Diagn 1989;17:5–10.

Katayama et. al., 1990

Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. Radiology 1990;157:621-8.

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Kimura et. al., 1999
Kimura BJ, Phan JN, Housman LB. Utility of contrast echocardiography in the diagnosis of aortic dissection. J Am Soc Echocardiogr 1999;12: 155-9.

Kirkpatrick et. al., 2004
Kirkpatrick JN, Wong T, Bednarz JE, Spencer KT, Sugeng L, Ward RP, et al. Differential diagnosis of cardiac masses using contrast echocardiographic perfusion imaging. J Am Coll Cardiol 2004;43:1412-9.

Kitzman et. al., 2000
Kitzman DW, Goldman ME, Gillam LD et al. Efficacy and safety of the novel ultrasound contrast agent perflutren (definity) in patients with suboptimal baseline left ventricular echocardiographic images. Am J Cardiol 2000;86:669 -74.

Kremkau et. al., 1970
Kremkau V., Gramiak R., Carstensen EL., Shah P. and Kramer DH. Ultrasonic detection of cavitation at catheter tips. Am. J. Roentgenol. 1970; 110, 177-183.

Kurt et. al., 2009
Kurt M, Shaikh KA, Peterson L, Kerrelmeyer KM, Shah G, et. al. Impact of contrast echocardiography on evaluation of ventricular function and clinical management in a large prospective cohort. . J Am Coll Cardiol 2009;53(9):803-10.

Li et. al., 2006
Li A, Wong CS, Wong MK, Lee CM, Au Yeung MC. Acute adverse reactions to magnetic resonance contrast media-gadolinium chelates. Br J Radiol 2006;79:368-71.

Main et. al., 2007
Main ML, Goldman JH, Grayburn PA. Thinking outside the “box”: the ultrasound contrast controversy. J Am Coll Cardiol 2007;50:2434-7

Malm et. al., 2004
Malm S, Frigstad S, Sagberg E, et al. Accurate and reproducible measurement of left ventricular volume and ejection fraction by contrast echocardiography. J Am Coll Cardiol 2004; 44 : 1030 -35.

Marwick et. al., 1992
Marwick TH, Nemec JJ, Pashkow FJ, Stewart WJ, Salcedo EE. Accuracy and limitations of exercise echocardiography in a routine clinical setting. J Am Coll Cardiol 1992;19:74-81.

Masugata et. al., 1999
Masugata H, Cotter B, Ohmori K, Kwan OL, Mizushige K, DeMaria AN. Feasibility of right ventricular myocardial opacification by contrast echocardiography and comparison with left ventricular intensity. Am J Cardiol 1999;84:1137-40.

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Moir and Marwick, 2004
Moir S, Marwick TH. Combination of contrast with stress echocardiography: a practical guide to methods and interpretation. Cardiovasc Ultrasound 2004 Aug;2:15.

Mulvagh et. al., 2000
Mulvagh SL, DeMaria AN, Feinstein SB, et al. Contrast echocardiography: current and future applications. J Am Soc Echocardiogr 2000;13:331– 42.

Mulvagh et. al., 2008
Mulvagh SL, Rakowski Harry, Vannan M et al. American Society of Echocardiography Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography. Journal of the American Society of Echocardiography November 2008.

Nakatani et. al., 1992
Nakatani S, Imanishi T, Terasawa A, Beppu S, Nagata S, Miyatake K. Clinical application of transpulmonary contrast-enhanced Doppler technique in the assessment of severity of aortic stenosis. J Am Coll Cardiol 1992;20:973-8.

Ontario Health Technology Assessment Series, 2010
Ontario Health Technology Assessment Series. An Evidenced Based analysis of Stress Echocardiography with Contrast for the Diagnosis of coronary Artery Disease. 2010; (10)10. Accessed at:
http://www.health.gov.on.ca/english/providers/program/mas/tech/ohtas/tech_cardit_9_20100615.html.

Plana et. al., 2008
Plana JC, Mikati IA, Dokainish H, Lakkis N, Abukhalil J, Davis R, et al. A randomized cross-over study for evaluation of the effect of image optimization with contrast on the diagnostic accuracy of dobutamine echocardiography in coronary artery disease: the OPTIMIZE trial. J Am Coll Cardiol Img 2008;1:145-52.

Rainbird et. al., 2001
Rainbird AJ, Mulvagh SL, Oh JK, McCully RB, Klarich KW, Shub C, et al. Contrast dobutamine stress echocardiography: clinical practice assessment in 300 consecutive patients. J Am Soc Echocardiogr 2001;14:378- 85.

Rosenbaum and Rubin, 1985
Rosenbaum PR and Rubin DB. Constructing a control group by multivariate matched sample methods that incorporate the propensity score. Am Stat 1985;39(1):33-8.

Senior et. al., 2009
Senior R, Becher H, Monaghan M, et al. Contrast echocardiography: evidence-based recommendations by European Association of Echocardiography. Eur J Echocardiogr 2009;10:194-212.

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Seward et. al., 1992
Seward JB, Khandheria BK, Oh JK, Freeman WK, Tajik AJ. Critical appraisal of transesophageal echocardiography: limitations, pitfalls, and complications. J Am Soc Echocardiogr 1992;5:228–305.

Sontum, 2008
Sontum PC. Physicochemical characteristics of Sonazoid™, a new contrast agent for ultrasound imaging. Ultrasound in Med. & Biol. 2008; 34, 5, 824–833.

Sontum et. al., 1999
Sontum PC, Østensen J, Dyrstad K, Hoff L. Acoustic properties of NC100100 and their relationship with the microsphere size distribution. Invest Radiol 1999; 34: 268-275.

Soman et. al., 2000
Soman P, Lahiri A, Senior R. Safety of an intravenous second generation contrast agent in patients with severe left ventricular dysfunction. Heart 2000;84(6):634-5.

Stuart and Ellestad, 1980
Stuart RJ Jr., Ellestad MH. National survey of exercise stress testing facilities. Chest 1980;77:94 –7.

Takeuchi et. al., 2006
Takeuchi M, Otani S, Weinert L, Spencer KT, Lang RM. Comparison of contrast-enhanced real-time live 3-dimensional dobutamine stress echocardiography with contrast 2-dimensional echocardiography for detecting stress-induced wall-motion abnormalities. J Am Soc Echocardiogr 2006;19:294-9.

Terasawa et. al., 1993
Terasawa A, Miyatake K, Nakatani S, Yamagishi M, Matsuda H, Beppu S. Enhancement of Doppler flow signals in the left heart chambers by intravenous injection of sonicated albumin. J Am Coll Cardiol 1993;21: 737-42.

Thanigaraj et. al., 2001
Thanigaraj S, Nease RF Jr, Schechtman KB, Wade RL, Loslo S, Perez JE. Use of contrast for image enhancement during stress echocardiography is cost-effective and reduces additional diagnostic testing. Am J Cardiol 2001;87:1430-2.

Thomson et. al., 2001
Thomson HL, Basmadjian AJ, Rainbird AJ, Razavi M, Avierinos JF, Pellikka PA et al. Contrast echocardiography improves the accuracy and reproducibility of left ventricular remodelling measurements: a prospective, randomly assigned, blinded study. J Am Coll Cardiol 2001;38:867-75

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Vlassak et. al., 2002
Vlassak I, Rubin DN, Odabashian JA, Garcia MJ, King LM, Lin SS, et al. Contrast and harmonic imaging improves accuracy and efficiency of novice readers for dobutamine stress echocardiography. Echocardiography 2002;19:483-8.

Wei et. al., 2008
Wei K, Mulvagh SL, Carson L, et al. The safety of Definity and Optison for ultrasound image enhancement: a retrospective analysis of 78,383 administered contrast doses. J Am Soc Echocardiogr 2008;11:1202 -6.

Yu et. al., 2000
Yu EH, Sloggett CE, Iwanochko RM, Rakowski H, Siu SC. Feasibility and accuracy of left ventricular volumes and ejection fraction determination by fundamental, tissue harmonic, and intravenous contrast imaging in difficult-to-image patients. J Am Soc Echocardiogr 2000;13:216-24.

Yu et. al., 2003
Yu EH, Skyba DM, Sloggett CE, Jamorski M, Iwanochko RM, Dias BF, et al. Determination of left ventricular ejection fraction using intravenous contrast and a semiautomated border detection algorithm. J Am Soc Echocardiogr 2003;16:22-8.

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Appendix A

Information for Healthcare Professionals: 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, UPDATED 7/17/2008]: FDA is issuing this alert to update healthcare professionals about changes that were made to the *Boxed Warning, Warnings,* and *Contraindications* sections of the prescribing information for micro-bubble contrast agents in May and June, 2008. The revised *Boxed Warning* and *Warnings* continue to highlight the risk of serious cardiopulmonary reactions during or within 30 minutes following the administration of these products and recommend that high risk patients with pulmonary hypertension or unstable cardiopulmonary conditions be closely monitored during and for at least 30 minutes post administration of these contrast agents. Concurrent with these labeling changes, FDA required that manufacturers of micro-bubble contrast agents conduct clinical studies to more thoroughly assess the risks for serious cardiopulmonary reactions.

Several of the *Contraindications* that were added to the labeling in October, 2007 were removed because FDA determined that, in some patients, the benefits from the diagnostic information that could be obtained through the use of Definity or Optison may outweigh the risk for serious cardiopulmonary reactions, even among some patients at particularly high risk for these reactions. The *Contraindications* that were removed include: worsening or clinically unstable congestive heart failure, acute myocardial infarction or acute coronary syndromes, serious ventricular arrhythmias or high risk of arrhythmias due to prolongation of the QT interval, respiratory failure, severe emphysema, pulmonary emboli or other conditions that cause pulmonary hypertension.

These changes reflect conclusions of FDA reviews related to information received following the addition of new contraindications and warnings to the labeling for these products in October 2007.

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.

Adverse reactions or quality problems experienced with the use of this Product may be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail or by fax, using the contact information at the bottom of this sheet.

Considerations

The revised labeling for this class of products includes the following information and recommendations for physicians who administer micro-bubble contrast agents to improve the quality of echocardiograms:

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- Serious cardiopulmonary reactions, including fatalities, have occurred during or within 30 minutes following administration of a micro-bubble contrast agent.
- Patients with pulmonary hypertension or unstable cardiopulmonary conditions should have their vital signs and cutaneous oxygen saturation monitored during and for at least 30 minutes following the administration of a micro-bubble contrast agent.

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 a condition that has caused high blood pressure in the blood vessels going to your lungs
    - have ever had a reaction to a drug given to you during an echocardiogram

Data Summary

Changes to the labeling for Definity and Optison were made in October 2007 following the receipt of postmarket reports of serious adverse events as well as new animal data that suggested the products may cause transient but marked pulmonary hypertension. The labeling changes included addition of a boxed warning to highlight a risk for serious cardiopulmonary reactions, a recommendation to monitor all patients for at least 30 minutes following administration of the products, and new contraindications for use of the products in patients with certain cardiopulmonary conditions.

Following the labeling changes, the FDA was informed by physicians that the diagnostic information that could be provided by using Definity or Optison may, in certain situations, justify the risk for serious cardiopulmonary reactions, even in those patients at high risk for these reactions and in some patients for whom the use of these products was contraindicated. FDA reviewed published reports of hemodynamic measurements from patients undergoing heart surgery and/or congestive heart failure evaluation that suggested that these products might not carry as great a risk for pulmonary hypertension as was previously thought.

Following the review of the published reports and consideration of what we heard from physicians, FDA determined that the labeling for these products should be changed to reflect our current thinking. Coincident with the changes to be made to the *Boxed Warning, Warnings* and *Contraindications* in May and June, 2008, FDA exercised its authority under the Food and Drug Administration Amendments Act of 2007 to require the manufacturers of micro-bubble contrast agents to conduct new clinical studies to more thoroughly assess the risks for serious cardiopulmonary reactions. Two of the studies will obtain pulmonary hemodynamic data from patients receiving the products; the other two studies will use existing patient databases to assess the risks for use of the products among critically ill patients.

Since the time the Information for Healthcare Professionals sheet was posted in October 2007, FDA has received postmarket reports of five deaths following the administration of Definity;

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no deaths were reported for Optison. All patients who died following the administration of Definity had severe underlying medical conditions. Three of the deaths were associated with cardiac arrest that occurred within 30 minutes following Definity administration. Most patients had multiple co-morbidities.

Also following the 2007 posting, FDA received approximately 60 reports of serious non-fatal reactions following Definity administration. The reported reactions generally occurred in a pattern similar to those previously reported. There were no additional reports of serious non-fatal reactions following Optison administration.

The revised labeling for the micro-bubble contrast agents emphasizes the need for intensive monitoring of patients with pulmonary hypertension or unstable cardiopulmonary conditions during and following administration of the products and continues to emphasize the need to observe all patients closely during and following administration of Definity or Optison. Below is a summary of the labeling changes made in May and June, 2008:

Boxed Warning *and* ***Warnings*** *specifically recommend intensive monitoring for patients with pulmonary hypertension or unstable cardiopulmonary conditions and close observation of patients without these underlying conditions.*

Boxed Warning identifies a risk for serious cardiopulmonary reactions and the ***Warnings*** section also identifies a risk for serious cardiopulmonary reactions that have occurred during or within 30 minutes following administration of the products. Patients with pulmonary hypertension or unstable cardiopulmonary conditions should be monitored with vital sign measurements, electrocardiography and cutaneous oxygen saturation during and for at least 30 minutes after administration of the products. All other patients should be observed closely during and following administration of the products. Resuscitation equipment and trained personnel should always be readily available during the drug administration and monitoring period.

Contraindications currently state that the products are contraindicated among patients with either known hypersensitivity to the products or have fixed right-to-left, bi-directional cardiac shunts or transient right-to-left shunts. The ***Contraindications*** section also notes that the products are not for intra-arterial injection.

The following *Contraindications* were removed from the labeling:

- worsening or clinically unstable congestive heart failure,
- acute myocardial infarction or acute coronary syndromes,
- serious ventricular arrhythmias or high risk for arrhythmias due to prolongation of the QT interval,
- respiratory failure,
- severe emphysema,
- pulmonary emboli or other conditions that cause pulmonary hypertension.

Micro-bubble ultrasound contrast agents are a sterile suspension of perflutren gas microspheres that are indicated for use in certain 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.

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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 but resumed marketing in 2007. Definity has been marketed since FDA approval in 2001.

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Appendix B

OPTISON Product Label

OPTISON™

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

WARNING: Serious Cardiopulmonary Reactions

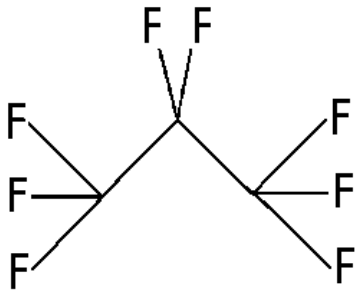
Serious cardiopulmonary reactions, including fatalities, have occurred during or following perflutren-containing microsphere administration.

- **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:



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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.

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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 t he 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

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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.

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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.

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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.

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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.

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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

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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.

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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 n ormal 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

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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.

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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.

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Rx ONLY

GE Healthcare

Distributed by
GE Healthcare Inc.
Princeton, NJ 08540

Manufactured by
Mallinckrodt Inc.
St. Louis, MO 63042

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