2016 Coding and Reimbursement Guide

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 border.

WARNING — SERIOUS CARDIOPULMONARY REACTIONS: Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perflutren-containing microsphere administration. Most serious reactions occur within 30 minutes of administration. Assess all patients for the presence of any condition that precludes Optison administration. Always have resuscitation equipment and trained personnel readily available.

CONTRAINDICATIONS: Do not administer Optison to patients with known or suspected: (1) Right-to-left, bidirectional, or transient right-to-left cardiac shunts or (2) Hypersensitivity to perflutren, blood, blood products, or albumin. Do not administer Optison by intra-arterial injection. ADVERSE REACTIONS: The most frequently reported adverse reactions following clinical trial use of Optison were headache, nausea and/or vomiting, warm sensation or flushing, and dizziness. Postmarketing Experience: Cardiac arrests and other serious but nonfatal 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.
Table of Contents

**Introduction** ............................................................................................................................................................................. 3
Description and Indication ............................................................................................................................................................... 3
2016 Coding and Reimbursement Guide ......................................................................................................................................... 3

**Basics of Coding** ........................................................................................................................................................................ 4
Healthcare Common Procedure Coding System (HCPCS) ................................................................................................................. 4
National Drug Codes (NDCs) ......................................................................................................................................................... 4

**Basics of Coverage** ....................................................................................................................................................................... 5
Medicare ....................................................................................................................................................................................... 5
Commercial/Private Payers .......................................................................................................................................................... 5
Medicaid ....................................................................................................................................................................................... 5

**Basics of Payment** .......................................................................................................................................................................... 6
Physician Offices and Independent Diagnostic Testing Facilities (IDTFs) .................................................................................... 6
Hospital Outpatient Setting .......................................................................................................................................................... 6

**Echocardiography Enhanced by Optison - Physician Offices and IDTFs** ..................................................................................... 7
Medicare Reimbursement ........................................................................................................................................................... 7
Commercial/Private Payer Reimbursement .................................................................................................................................. 7

**Echocardiography Enhanced by Optison - Hospital Outpatient Setting** ..................................................................................... 8
Medicare Reimbursement ........................................................................................................................................................... 8
Commercial/Private Payer Reimbursement .................................................................................................................................. 8

**National Drug Codes (NDCs)** ..................................................................................................................................................... 9

**Echocardiography Coding and 2016 Medicare Reimbursement Rates** ......................................................................................... 10

**Sources** .................................................................................................................................................................................... 15

**Support for Optison** ................................................................................................................................................................. 15
Customer Service ........................................................................................................................................................................ 15
Medical Affairs ............................................................................................................................................................................ 15
Reimbursement Hotline ............................................................................................................................................................... 15

**Important Risk and Safety Information About Optison** .......................................................................................................... 16

**Full Prescribing Information** .................................................................................................................................................. 17
Introduction

Description and Indication

Optison is a sterile nonpyrogenic suspension of microspheres of human serum albumin with perflutren for contrast enhancement during the indicated 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 border.

Please refer to the Important Risk and Safety Information. Before administration of Optison, read the Full Prescribing Information.

2016 Coding and Reimbursement Guide

The 2016 Coding and Reimbursement Guide for Optison is intended to provide available current reimbursement information. In this document, coverage, coding, and payment for Optison are reviewed. In addition, the reimbursement services are described.

DISCLAIMER: All information supplied in this guide is for informational purposes only. It is intended to assist in the coding and reimbursement process. It represents no statement of guarantee by GE Healthcare. The final decision for coding of any procedure must be made by the provider of care after considering the medical necessity of the services and supplies provided as well as considering any regulations and local, state, or federal laws that may apply. All coding and reimbursement information is subject to change without notice, and specific payers may have their own coding and reimbursement requirements and policies. Please contact your local payer for interpretation of the appropriate codes to use for specific procedures.
Basics of Coding

Healthcare providers and hospitals identify diseases, procedures, drugs, devices, and other healthcare-related items provided to patients through various coding systems. Payers use the same coding systems to develop coverage policies and calculate payment for healthcare services.

**Current Procedural Terminology (CPT®) Codes**
CPT codes describe the service and/or procedure being performed, not the outcomes achieved. Comparable procedures using different technologies are normally billed under the same CPT codes, unless there is a major distinction in the procedural technique associated with the products. The physician component of a CPT code is universal for all payers.

**Healthcare Common Procedure Coding System (HCPCS)**
The HCPCS is a standardized coding system used primarily to identify products, supplies, and services not included in the CPT codes such as ambulance services and durable medical equipment, prosthetics, orthotics, and supplies.

- **C-codes** are created by Medicare and used only for hospital outpatients
- **Q-codes** are created by Medicare to identify items not assigned a CPT code. Many drugs, supplies, and biologicals are assigned Q-codes (eg, Optison)

**National Drug Codes (NDCs)**
NDCs are unique 10-digit numeric codes, composed of three segments, used to identify drugs. The first segment identifies the labeler (manufacturer), the second segment identifies the product, and the third identifies the packaging. Some payers require 11-digit numeric codes.
Basics of Coverage

The existence of CPT and HCPCS codes does not guarantee coverage. All payers have their own unique policies and guidelines. The policy may even differ within one payer (e.g., BCBS has multiple plans; each plan may have a different policy or guideline). It is important that you review and adhere to each relevant payer policy.

Medicare
For procedures and products covered under Medicare Part B, coverage decisions are typically made through local coverage determinations (LCDs). These LCDs are specific to the jurisdiction of a Medicare Administrative Contractor (MAC), meaning that the coverage policy or guideline would only apply to that MAC’s jurisdiction. Therefore, coverage policies may vary by MAC.

Medicare may also create National Coverage Determinations (NCDs) to which all MACs must adhere.

Commercial/Private Payers
Each private payer determines its own coverage policies. Private payers may implement restrictions and/or specific criteria. Coverage may also vary based on the patient’s benefits or on the negotiated contract between the providers and the payer. Some payers have formal, published policies, but the lack of a published policy does not indicate noncoverage.

Medicaid
Each Medicaid program is administered by its particular state. That state determines its own specific coverage policies or guidelines. Some state Medicaid programs follow Medicare’s policies, while others create their own. Some programs may implement restrictions and/or specific criteria. Medicaid coverage may also vary by provider type, setting of care, and the type of Medicaid plan the patient has (e.g., fee-for-service, managed Medicaid).
Basics of Payment

Payment is the amount that a payer renders to a healthcare entity for covered therapies and services. The payment methodology and amount vary based on where the care is provided.

The Centers for Medicare & Medicaid Services (CMS) sets a reimbursement amount for procedures, drugs, and/or supplies to allow for a uniform method of payment. The rates are set nationally, but adjustments are made to reflect the geographic differences in costs.

**Physician Offices and Independent Diagnostic Testing Facilities (IDTFs)**
Reimbursement for physician offices and IDTFs is based on the CPT code(s) used to report the service(s) provided. Medicare assigns each CPT code Relative Value Units (RVUs), which take into account the physician’s work, practice (overhead) expenses, and malpractice expenses associated with a procedure. The RVUs are then converted to a standard payment rate per procedure and are adjusted geographically.

Contrast agents are reimbursed in addition to the echocardiography procedure in this setting of care.

**Hospital Outpatient Setting**
In the hospital outpatient setting, the CPT codes are grouped into clinically homogeneous Ambulatory Payment Classifications (APCs) (Medicare only). Under APCs, hospitals are paid per encounter, and reimbursement is determined by the services and procedures provided as reported by CPT code.

Contrast agents are not reimbursed in addition to the echocardiography procedure in this setting of care.

**Note:** Private payers may or may not recognize Q-codes. Private payer reimbursement structure differs from payer to payer.
Echocardiography Enhanced by Optison — Physician Offices and IDTFs

Medicare Reimbursement
In the physician office/IDTF setting, both the product and the echocardiogram enhanced by Optison may be reimbursed by Medicare.

Reimbursement for Optison is based on Medicare’s Average Sales Price (ASP) plus 6%. **Note: The ASP rates change on a quarterly basis.**

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
<th>Payment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q9956</td>
<td>Injection, octafluoropropane microspheres, per mL</td>
<td>ASP + 6%</td>
</tr>
</tbody>
</table>

To report the echocardiography performed, use the appropriate CPT code. The code listed below is a sample of the available codes. Please see page 10-14 for a full list of available echocardiography codes.

**Medicare 2016 National Average – Echocardiogram* Coding and Reimbursement (sample)**

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>93350</td>
<td>Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed, during rest and cardiovascular stress test using treadmill, bicycle exercise and/or pharmacologically induced stress, with interpretation and report</td>
</tr>
</tbody>
</table>

Commercial/Private Payer Reimbursement
Payment for Optison may be based on a percentage markup of the ASP, similar to Medicare, or a percentage markup or markdown of the average wholesale price (AWP), or the wholesale acquisition cost (WAC). Echocardiogram payment varies from payer to payer. Please refer to specific payer policies or contact payer for appropriate codes and payments for specific procedures.

*Optison is not FDA-approved for stress echocardiography.
Echocardiography Enhanced by Optison — Hospital Outpatient Setting

Medicare Reimbursement
Optison is not eligible for separate payment under the Medicare Hospital Outpatient Prospective Payment System (OPPS). Rather, payment for Optison is packaged with the payment for the echocardiogram; there is no additional payment for the contrast agent. Hospitals should still bill for Q9956. This allows the CMS to obtain cost and charge data in order to set future payments.

When billing for echocardiographic procedures, hospitals must report either the appropriate C-code for an echocardiogram with contrast or the appropriate CPT code for an echocardiogram without contrast. Do not report both. C-codes are for Medicare hospital outpatient services only.

To report the type of echocardiographic procedure performed, use the appropriate CPT code. The codes listed below are samples of the available codes. Please see page 10-14 for a full list of available echocardiography codes.

<table>
<thead>
<tr>
<th>Code</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q9956</td>
<td>Injection, octafluoropropane microspheres, per mL</td>
</tr>
<tr>
<td>93350</td>
<td>Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed, during rest and cardiovascular stress test using treadmill, bicycle exercise, and/or pharmacologically induced stress, with interpretation and report</td>
</tr>
<tr>
<td>C8928</td>
<td>Transthoracic echocardiography with contrast, or without contrast followed by with contrast, real-time with image documentation (2D), includes M-mode recording, when performed, during rest and cardiovascular stress test using treadmill, bicycle exercise, and/or pharmacologically induced stress, with interpretation and report</td>
</tr>
</tbody>
</table>

Commercial/Private Payer Reimbursement
Private payers may or may not recognize C-codes. Please refer to specific payer policies or contact payer for appropriate codes and payments for specific procedures.

*Optison is not FDA-approved for stress echocardiography.
National Drug Codes (NDCs)

NDCs are unique 10-digit codes, composed of three segments, used to identify drugs. The first segment identifies the labeler (manufacturer), the second segment identifies the product, and the third identifies the packaging.

Some payers require physicians to report 11-digit NDCs when reporting a drug on a claim form.

Converting the 10-digit NDC for Optison to an 11-digit NDC requires the inclusion of a leading zero in the labeler code section of the NDC (the first section).

<table>
<thead>
<tr>
<th></th>
<th>10-digit NDCs</th>
<th>11-digit NDCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual vial</td>
<td>0407-2707-01</td>
<td>00407-2707-01</td>
</tr>
<tr>
<td>5-vial pack</td>
<td>0407-2707-03</td>
<td>00407-2707-03</td>
</tr>
<tr>
<td>18-vial pack</td>
<td>0407-2707-18</td>
<td>00407-2707-18</td>
</tr>
</tbody>
</table>
Echocardiography Coding and 2016 Medicare Reimbursement Rates*

Hospitals are instructed by Medicare to bill for any type of echocardiography with contrast using the applicable HCPCS C-code(s). Hospitals that perform echocardiograms without contrast should use the existing CPT codes.

*Optison is not FDA-approved for stress echocardiography.
<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Code Description</th>
<th>Medicare National Average Payment Hospital Outpatient FY2016/APC</th>
<th>Medicare National Average Payment Physician/IDTF FY2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>93303</td>
<td>Transthoracic echocardiography for congenital cardiac anomalies; complete</td>
<td>$699/5534</td>
<td>$241</td>
</tr>
<tr>
<td>93304</td>
<td>Transthoracic echocardiography for congenital cardiac anomalies; follow-up or limited study</td>
<td>$417/5533</td>
<td>$157</td>
</tr>
<tr>
<td>93306</td>
<td>Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed, complete, with spectral Doppler echocardiography, and with color flow Doppler echocardiography</td>
<td>$417/5533</td>
<td>$230</td>
</tr>
<tr>
<td>93307</td>
<td>Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed, complete, without spectral or color Doppler echocardiography</td>
<td>$417/5533</td>
<td>$131</td>
</tr>
<tr>
<td>93308</td>
<td>Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed, follow-up or limited study</td>
<td>$154/5532</td>
<td>$126</td>
</tr>
<tr>
<td>93312</td>
<td>Echocardiography, transesophageal, real-time with image documentation (2D) (with or without M-mode recording); including probe placement, image acquisition, interpretation and report</td>
<td>$699/5534</td>
<td>$311</td>
</tr>
<tr>
<td>93313</td>
<td>Echocardiography, transesophageal, real-time with image documentation (2D) (with or without M-mode recording); placement of transesophageal probe only</td>
<td>$699/5534</td>
<td>$23</td>
</tr>
<tr>
<td>CPT Code</td>
<td>Code Description</td>
<td>Medicare National Average Payment Hospital Outpatient FY2016/APC</td>
<td>Medicare National Average Payment Physician/IDTF FY2016</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------</td>
<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>93315</td>
<td>Transesophageal echocardiography for congenital cardiac anomalies; including probe placement, image acquisition, interpretation and report</td>
<td>$699/5534</td>
<td>Carrier Priced</td>
</tr>
<tr>
<td>93318</td>
<td>Echocardiography, transesophageal (TEE) for monitoring purposes, including probe placement, real time 2-dimensional image acquisition and interpretation leading to ongoing (continuous) assessment of (dynamically changing) cardiac pumping function and to therapeutic measures on an immediate time basis</td>
<td>$699/5534</td>
<td>Carrier Priced</td>
</tr>
<tr>
<td>93350</td>
<td>Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed, during rest and cardiovascular stress test using treadmill, bicycle exercise and/or pharmacologically induced stress, with interpretation and report</td>
<td>$417/5533</td>
<td>$243</td>
</tr>
<tr>
<td>93351</td>
<td>Echocardiography, transthoracic, real-time with image documentation (2D), includes M-mode recording, when performed, during rest and cardiovascular stress test using treadmill, bicycle exercise and/or pharmacologically induced stress, with interpretation and report; including performance of continuous electrocardiographic monitoring, with supervision by a physician or other qualified health care professional</td>
<td>$417/5533</td>
<td>$273</td>
</tr>
<tr>
<td>HCPCS Code</td>
<td>Description</td>
<td>Medicare National Average Payment Hospital Outpatient FY2016/APC</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>C8921</td>
<td>Transthoracic echocardiography with contrast, or without contrast followed by with contrast, for congenital cardiac anomalies; complete</td>
<td>$671/5562</td>
<td></td>
</tr>
<tr>
<td>C8922</td>
<td>Transthoracic echocardiography with contrast, or without contrast followed by with contrast, for congenital cardiac anomalies; follow-up or limited study</td>
<td>$454/5561</td>
<td></td>
</tr>
<tr>
<td>C8923</td>
<td>Transthoracic echocardiography with contrast, or without contrast followed by with contrast, real-time with image documentation (2D), includes M-mode recording, when performed, complete, without spectral or color doppler echocardiography</td>
<td>$454/5561</td>
<td></td>
</tr>
<tr>
<td>C8924</td>
<td>Transthoracic echocardiography with contrast, or without contrast followed by with contrast, real-time with image documentation (2D), includes M-mode recording, when performed, follow-up or limited study</td>
<td>$454/5561</td>
<td></td>
</tr>
<tr>
<td>C8925</td>
<td>Transesophageal echocardiography (TEE) with contrast, or without contrast followed by with contrast, real time with image documentation (2D) (with or without M-mode recording); including probe placement, image acquisition, interpretation and report</td>
<td>$671/5562</td>
<td></td>
</tr>
<tr>
<td>C8926</td>
<td>Transesophageal echocardiography (TEE) with contrast, or without contrast followed by with contrast, for congenital cardiac anomalies; including probe placement, image acquisition, interpretation and report</td>
<td>$671/5562</td>
<td></td>
</tr>
<tr>
<td>HCPCS Code</td>
<td>Description</td>
<td>Medicare National Average Payment Hospital Outpatient FY2016/APC</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>C8927</td>
<td>Transesophageal echocardiography (TEE) with contrast, or without contrast followed by with contrast, for monitoring purposes, including probe placement, real time 2-dimensional image acquisition and interpretation leading to ongoing (continuous) assessment of (dynamically changing) cardiac pumping function and to therapeutic measures on an immediate time basis</td>
<td>$671/5562</td>
<td></td>
</tr>
<tr>
<td>C8928</td>
<td>Transthoracic echocardiography with contrast, or without contrast followed by with contrast, real-time with image documentation (2D), includes M-mode recording, when performed, during rest and cardiovascular stress test using treadmill, bicycle exercise and/or pharmacologically induced stress, with interpretation and report</td>
<td>$671/5562</td>
<td></td>
</tr>
<tr>
<td>C8929</td>
<td>Transthoracic echocardiography with contrast, or without contrast followed by with contrast, real-time with image documentation (2D), includes M-mode recording, when performed, complete, with spectral doppler echocardiography, and with color flow doppler echocardiography</td>
<td>$671/5562</td>
<td></td>
</tr>
<tr>
<td>C8930</td>
<td>Transthoracic echocardiography, with contrast, or without contrast followed by with contrast, real-time with image documentation (2D), includes M-mode recording, when performed, during rest and cardiovascular stress test using treadmill, bicycle exercise and/or pharmacologically induced stress, with interpretation and report; including performance of continuous electrocardiographic monitoring, with physician supervision</td>
<td>$671/5562</td>
<td></td>
</tr>
</tbody>
</table>
Sources

Medicare Program: Hospital Outpatient Prospective Payment and Ambulatory Surgical Center Payment Systems and Quality Reporting Programs; Short Inpatient Hospital Stays; Transition for Certain Medicare-Dependent, Small Rural Hospitals under the Hospital Inpatient Prospective Payment System; Provider Administrative Appeals and Judicial Review CMS-1633-FC; CMS-1607-F2

Addendum B – Final OPPS Payment by HCPCS Code for CY2016


Medicare Program; Revisions to Payment Policies under the Physician Fee Schedule and Other Revisions to Part B for CY 2016 CMS-1631-FC

CY 2016 PFS Final Rule Addenda (Updated November 5, 2015)

https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched/Downloads/CY2016-PFS-FC-Addenda.zip

Support for Optison

Customer Service
To place an order, call 800 292 8514.

Medical Affairs
For technical or product-related questions and/or to reach a Clinical Applications Specialist, call 800 654 0118 (option 2, then option 3).

Reimbursement Hotline
For reimbursement-related questions (eg, appropriate coding), call our hotline at 800 767 6664.
Important Risk and Safety Information About Optison™
(Perflutren Protein-Type A Microspheres Injectable Suspension, USP)

**WARNING — SERIOUS CARDIOPULMONARY REACTIONS:** Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perflutren-containing microsphere administration. Most serious reactions occur within 30 minutes of administration. Assess all patients for the presence of any condition that precludes Optison administration. Always have resuscitation equipment and trained personnel readily available.

**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. **CONTRAINDICATIONS:** Do not administer Optison to patients with known or suspected: (1) Right-to-left, bidirectional, or transient right-to-left cardiac shunts, or (2) Hypersensitivity to perflutren, blood, blood products, or albumin. Do not administer Optison by intra-arterial injection. **WARNINGS — Anaphylactoid Reactions:** In postmarketing use, uncommon but serious anaphylactoid reactions were observed during or shortly following perflutren-containing microsphere administration, including in patients with no prior exposure to perflutren-containing microsphere products. **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 and the safety of Optison with the use of end-systolic triggering have not been evaluated. **PRECAUTIONS — General:** Optison 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 and Creutzfeldt-Jakob disease (CJD), no cases of which have ever been identified for albumin. **Pregnancy:** 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. **ADVERSE REACTIONS:** The most frequently reported adverse reactions following clinical trial use of Optison were headache, nausea and/or vomiting, warm sensation or flushing, and dizziness. **Postmarketing Experience:** Cardiac arrests and other serious but nonfatal 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.

Prior to Optison administration, please read the Full Prescribing Information.
**OPTISON™**  
(Perflutren Protein-Type A Microspheres Injectable Suspension, USP)

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**WARNINGS:**  
SERIOUS CARDIOPULMONARY REACTIONS  
Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perfluorochemical microsphere administration. Most serious reactions occur within 30 minutes of administration (see WARNINGS and PRECAUTIONS).  
- Assess all patients for the presence of any condition that precludes OPTISON administration (see CONTRAINDICATIONS).  
- 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 microparticles of human serum albumin with perflutren for contrast enhancement during the ultrasonic 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. Each mL of OPTISON contains 5.0-8.0x10⁴ 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.

**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 MHz 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.

**Following a single intravenous dose of 20 mL of 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% ± 2% (mean ± S.D.) and the pulmonary elimination half-life was 3.6 ± 0.69 minutes (mean ± S.D.). The perflutren concentration in expired air peaked approximately 30-40 seconds after administration.**

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

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

**Gender, Age, Race**  
The effects of gender, age, or race on the pharmacokinetics of OPTISON have not been studied.

**Drug-Drug Interactions**  
Drug-drug interactions for OPTISON have not been studied.

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

**Pharmacodynamics**  
The general acoustic properties of OPTISON are similar to those of ALBUMIN®. The acoustic impedance of the OPTISON microsphere 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).

**Echocardiography:**  
The efficacy of OPTISON was evaluated in two identical multicenter, dose escalation, randomized, cross-over studies of OPTISON™ and ALBUMIN®. 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 delineated in the apical 4-chamber view. In these studies, the 208 patients (Study A: n=101, Study B: n=102) received at least one dose of study drug had the following characterisics: 79% men, 21% women, 64% White, 25% Black, 10% Hispanic, and 1% other race or ethnic group. The patients had a mean age of 61 years (range 21 to 83 years), a mean weight of 154 lbs (range 117 to 342 lbs), a mean height of 68 inches (range 47 to 78 inches), and a mean body surface area of 2.0m² (range 1.4 to 2.6m²). Approximately 23% of the patients had chronic pulmonary disease, and 17% had congestive and dilated cardiomyopathy with left ventricular ejection fraction (LVEF) of 20% to 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 ALBUMIN™ 8.00 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 echographic 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 endpoint area was left ventricular endocardial border delineation, assessed before and after OPTISON administration, with a video-stratified sample of 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 (assessed by videodensitometry) compared to the 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.

**Pulmonary Hemodynamic Effects:**  
The effect of OPTISON on pulmonary hemodynamics was studied in a prospective, open-label study of 30 patients scheduled for pulmonary artery catheterization, involving 19 with an elevated baseline pulmonary artery systolic pressure (PASP) >25 mmHg and 11 with normal pulmonary hemodynamic parameters and ECGs were also evaluated. No clinically important pulmonary hemodynamic, systemic hemodynamic, or ECG changes were observed. This study did not assess the effect of OPTISON on visualization of cardiac or pulmonary structures.

**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.

**CONTRAINDICATIONS:**  
Do not administer OPTISON to patients with known or suspected:  
- Right-to-left, bi-directional, or transverse right-to-left cardiac shunts, 
- Hypersensitivity to perflutren, blood, blood products or albumin (see WARNINGS).

Do not administer OPTISON by intra-arterial injection.

**WARNINGS:**  
**Serious Cardiopulmonary Reactions**  
Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or shortly following perfluorochemical microsphere administration, typically within 30 minutes of administration. The risk for these reactions may be increased among patients with unstable cardiopulmonary conditions (acute myocardial infarction, acute coronary artery syndromes, worsening or unstable congestive heart failure, or severe ventricular arrhythmias).

The reported reactions to perfluoro-containing microspheres include: fatal cardiac or respiratory arrest, shock, syncope, symptomatic arrhythmias (ventricular fibrillation, tachycardia, bradycardia, supraventricular tachycardia, ventricular fibrillation, tachycardial, hypotension, hypertension, dyspnea, hypoxia, chest pain, respiratory distress, stridor, wheezing, loss of consciousness and convulsions (see ADVERSE REACTIONS).
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, proarrhythmia, photosensitivity, pruritus, premature vascular contraction, pruritus, rash, irritability, hypersensitivity, tinnitus, tremor, visual blur/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 ABLUNEX®.

In a prospective, post-marketing safety surveillance study of OPTISON used in routine clinical practice, a total of 1039 subjects received OPTISON. Of these patients, 648 (62.4%) were male and 391 (37.6%) were female with average age of 59.9 years (min, max: 20, 97). The racial distributions were 884 (85.3%) White, 141 (13.3%) Black, 18 (1.7%) Hispanic, 0 (0%) other races, and 5 (0.5%) other ethnic or ethnic groups. Overall, 175 patients (16.8%) reported at least one adverse event. No serious adverse reactions, including deaths, were reported in this study, suggesting that these reactions are unlikely to occur at a rate of more than 0.5% when OPTISON is used according to recommendations. The following adverse reactions have been identified during the postmarketing use of OPTISON. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Cardiac arrests and other serious but non-fatal adverse reactions were uncommonly reported. Most of these uncommon reactions included cardiomyopathic symptoms and signs such as cardiac arrest, hypotension, supraventricular and ventricular arrhythmias, respiratory distress or decreased oxygenation. Reports also identified neurologic reactions (loss of consciousness or convulsions) as well as anaphylactic 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, interfering 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-injection septicaemia 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 contrast.

Do not inject air into the vial.

1. Invert the OPTISON vial and gently rotate to resuspend the microspheres. This process will allow the product to come to room temperature before use.
2. Inspect the vial for complete resuspension. Failure to adequately resuspend OPTISON may cause an under delivery of the microspheres, and may result in inadequate contrast.
3. Do not use OPTISON if, after resuspension, the solution appears to be clear rather than opaque milky-white.
4. Vest 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.

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 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 Perfluoropropane Protein-Type & Microspheres Injectable Suspension, USP, is available in a carton of five (5) 3 mL vials and a carton of eighteen (18) 3 mL vials in single use 3 mL vials.

NDC 0047-2707-03 (5 vials)
NDC 0047-2707-18 (18 vials)

Storage

Store OPTISON refrigerated between 2°-8°C (36°-46°F). Caution: Do not freeze.

Re-Use


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