Medicare Reimbursement Information

Please see Indications and Important Safety Information on page 11 and the full Prescribing Information, including boxed WARNING regarding serious cardiopulmonary reactions on pages 12-14.
Questions regarding reimbursement for Lantheus Medical Imaging products?

Call Randy VanCoughnett at 978-436-7995 or email randy.vancoughnett@lantheus.com.

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**TABLE OF CONTENTS**

1. Basic Reimbursement Background and Settings ................................................... 4-5
2. **DEFINITY®** Hospital Outpatient Setting and Ambulatory Payment Classification (APC) Payments ................................................................. 6
3. Hospital Outpatient Claim Form Contrast Echo Example ........................................ 7
5. **DEFINITY®** Non Hospital Setting ........................................................................ 9
6. Echo National Average Payments for Physician Office and Independent Diagnostic Testing Facility (IDTF) ................................................................. 10
7. Indications, Contraindications and Important Safety Information ............................ 11
8. Full Prescribing Information ................................................................................. 12-14
1. Basic Reimbursement Background and Settings

CPT – Current Procedural Terminology

• American Medical Association’s five digit numeric codes used to report medical procedures and services.

HCPCS - Healthcare Common Procedure Coding System

• Level I HCPCS codes are American Medical Association’s Current Procedural Terminology (CPT).
• Level II HCPCS codes are alphanumeric five digit codes primarily used to identify contrast agents, radiopharmaceuticals, supplies and devices.

HCPCS code for DEFINITY®

• Q9957 Injection, perflutren lipid microspheres, per mL.
• There are two units per vial of DEFINITY®.

C-codes

• Unique, temporary HCPCS codes created by Medicare and used only for hospital outpatients. This is often done when no other appropriate code exists.

Q-codes

• Temporary codes created by Medicare to identify items not assigned a CPT code. Many drugs, supplies and biologicals are assigned Q codes.

NDC codes – National Drug Code

• A unique numeric code to identify drugs. The first segment of numbers identifies the labeler or manufacturer, the second segment identifies the product and the third identifies the package.

NDC codes DEFINITY®

• NDC 4 vial kit 11994-011-04
• NDC 16 vial kit 11994-011-16
Echocardiography codes\textsuperscript{1,2}

- **CPT 93306 – TTE “rest” echo complete**
  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.

- **HCPCS C8929 TTE “rest” echo complete with contrast**
  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.

- **HCPCS C8929 - CMS “short descriptor”\textsuperscript{2}**
  TTE w or w/o fol wcon, Doppler

\textit{JW modifier} - The JW modifier is not required for packaged drugs such as DEFINITY\textsuperscript{®} for Medicare Hospital Outpatients.

Lantheus Medical Imaging, Inc. cannot guarantee coverage or payment for products or procedures. Payer policies can vary widely. For more specific information contact the payer directly in order to obtain up to date coverage, coding and payment information.

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**Medicare Hospital Inpatients**

Hospital reimbursement is based on Diagnostically Related Group (DRG) payment.

There is no additional payment for drugs or imaging procedures.

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**Medicare Hospital Outpatients**

Payment for non pass-through contrast agents is packaged with the imaging procedure payment.

When separate payment is made for a pass-through drug an APC offset is subtracted from the final payment so as to not pay twice for the pass-through drug.

Reimbursement for hospital outpatient procedures is based on past cost analysis by Medicare.

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**Physician Offices and IDTFs**

Contrast agents are paid in addition to and separately from procedure.

Contrast agents reimbursed based on Medicare’s Average Selling Price listings.
In the Medicare Hospital Outpatient setting echo contrast agents are reimbursed, however, the contrast payment is packaged with the imaging procedure payment.

C8929, with contrast, is reimbursed $194.26 higher than 93306, without contrast, due to the higher cost to perform a contrast echo.

Hospitals must bill for the appropriate C-code when reporting an echo with DEFINITY® in order to receive the packaged payment for DEFINITY®. If a C-code is not billed there will be no payment for contrast. Q9957 is not paid as a separate item.

When billing echo procedures, report the appropriate C-code for an echo with contrast or the appropriate CPT code for an echo without contrast. Do not report both. When using DEFINITY®, hospitals should report Q9957 two units per vial. It is not paid separately but this allows Medicare to collect cost and charge data in order to set future payments.

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### APCs ECHO PROCEDURES - WITHOUT CONTRAST

- **APC 5523** - $230.56
  - Level 3 Imaging Without Contrast
  - 93307 TTE complete w/o Doppler and color flow
  - 93308 TTE follow up or limited
  - (60 total imaging procedure codes in APC 5523)

- **APC 5524** - $497.49
  - Level 4 Imaging Without Contrast
  - 93303 TTE congenital, complete
  - 93304 TTE congenital follow up or limited
  - 93306 TTE complete with Doppler and color flow
  - 93312 TEE include placement, acq, inter, report
  - 93313 TEE placement only
  - 93315 TEE cong, placement, acq, inter, report
  - 93316 TEE congenital placement only
  - 93318 TEE monitor, placement, acq, inter
  - 93350 Stress TTE (w/o ECG monitoring)
  - 93351 Stress TTE (includes ECG monitoring)
  - (17 total imaging procedure codes in APC 5524)

  **0399T Myocardial strain imaging**
  - (Not assigned to an APC. No separate payment. HOPPS payment packaged)

### APCs ECHO PROCEDURES - WITH CONTRAST

- **APC 5572** - $385.88
  - Level 2 Imaging With Contrast
  - C8924 TTE follow up or limited with contrast
  - (59 total imaging with contrast codes in APC 5572)

- **APC 5573** - $691.75
  - Level 3 Imaging With Contrast
  - C8921 TTE congenital complete with contrast
  - C8922 TTE congenital follow up or limited with contrast
  - C8923 TTE complete w/o Doppler, CF with contrast
  - C8925 TEE placement, acq, inter, report with contrast
  - C8926 TEE congenital placement, image, inter, report with contrast
  - C8927 TEE monitor, placement, acq, inter, w/ contrast
  - C8928 Stress TTE (no ECG monitoring) with contrast
  - C8929 TTE comp. with Dop., color flow with contrast
  - C8930 Stress TTE (with ECG monitoring ) with contrast
  - (21 total Imaging with contrast codes in APC 5573)

  **0439T Myocardial contrast perfusion echo**
  - (Not assigned to an APC. No separate payment. HOPPS payment packaged)

For complete code descriptors see page 8
3. Claim Form

<table>
<thead>
<tr>
<th>Claim Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anytown Hospital</td>
</tr>
<tr>
<td>Patient Name: Doe, John</td>
</tr>
<tr>
<td>Birth Date: XX/XX/1940</td>
</tr>
</tbody>
</table>

### Claim Notes

- **C-code must be billed in order to obtain reimbursement for the contrast agent combined with the echo procedure.**
- **Q957 will not be paid as a separate line item.**
- **Q-code identifies which contrast agent was used.**

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**Notes:**

- TTE echo complete with contrast: C8929
- Peflutren lipid microspheres: Q9957

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**Page:** 1 of **TOTAL:**
### 4. Complete code descriptors

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>93303</td>
<td>Transthoracic echocardiography for congenital cardiac anomalies; complete</td>
<td>C8921</td>
<td>Transthoracic echocardiography with contrast, or without contrast followed by with contrast, for congenital cardiac anomalies; complete</td>
</tr>
<tr>
<td>93304</td>
<td>Transthoracic echocardiography for congenital cardiac anomalies; follow-up or limited study</td>
<td>C8922</td>
<td>Transthoracic echocardiography with contrast, or without contrast followed by with contrast, for congenital cardiac anomalies; f/u or limited study</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>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>
</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>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>
</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>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>
</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>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>
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<tr>
<td>93315</td>
<td>Transesophageal echocardiography for congenital cardiac anomalies; including probe placement image acquisition, interpretation and report</td>
<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>
</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>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>
</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>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>
<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>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>
</tr>
<tr>
<td>0399T</td>
<td>Myocardial strain imaging (quantitative assessment of myocardial mechanics using image-based analysis of local myocardial dynamics) (List separately in addition to code for primary procedure) Sunset 2021 (Use 0399T in conjunction with 93303, 93304, 93306, 90337, 93308, 93312, 93314, 93315, 93317, 93350, 93351, 93355) Report 0399T once.</td>
<td>NA</td>
<td>Myocardial perfusion contrast echocardiography, at rest or with stress, for assessment of myocardial ischemia or viability. (List separately in addition to code for primary procedure) Sunset January, 2022. (Use 0439T in conjunction with 93306, 90337, 93308 93350, 93351)</td>
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<tr>
<td>0439T</td>
<td></td>
<td>Four</td>
<td>Myocardial strain imaging (quantitative assessment of myocardial mechanics using image-based analysis of local myocardial dynamics) (List separately in addition to code for primary procedure) Sunset 2021 (Use 0399T in conjunction with 93303, 93304, 93306, 90337, 93308, 93312, 93314, 93315, 93317, 93350, 93351, 93355) Report 0399T once.</td>
</tr>
</tbody>
</table>
5. DEFINITY® Non Hospital Setting

HCPCS Q9957 Injection, perflutren lipid microspheres, per mL

- Q9957 HCPCS code for DEFINITY®.
- When reporting HCPCS Q9957 there are two units per vial of DEFINITY®.
- Medicare Part B payment for Q1 2018 is $48.71 per unit (updated quarterly)
- DEFINITY® is a single use vial.

DEFINITY® is reimbursed separately by Medicare Part B in the physician office setting. The payment allowance limits are updated each quarter and listed on the CMS website at http://www.cms.hhs.gov/McrPartBDrugAvgSalesPrice/

Non Medicare, private payers usually reimburse echo contrast agents separately in the physician office and IDTF setting. It is not unusual for a private payer to reimburse contrast agents at a rate that is higher than Medicare, however, providers must check their contracts and/or contact their private payers to confirm coding, coverage and payment amounts for contrast agents.

DEFINITY® is a single use vial. Medicare allows reimbursement for the amount injected plus the amount discarded for single use vials. For DEFINITY® one mL is equal to one billing unit. The vial contains more than one mL and less than two mLs, therefore there are two units per vial. When reporting drug units providers round up to the next whole unit when a unit of measure is exceeded.

Category III codes such as 0399T and 0439T are contractor priced by Medicare under the physician fee schedule. Providers should check with their local Medicare Part B contractor for payment amounts and coverage information.

The interpreting physician must perform the test that was ordered by the treating / referring physician or they must contact the treating physician to change the order. However, the interpreting physician can determine the design of the test without notifying the treating physician for such items as the use or non use of contrast.

In the Medicare Benefit Policy Manual Chapter 15 section 80.6.4 - Rules for Testing Facility Interpreting Physician to Furnish Different or Additional Tests it states that:

“Unless specified in the order, the interpreting physician may determine, without notifying the treating physician/practitioner, the parameters of the diagnostic test (e.g., number of radiographic views obtained, thickness of tomographic sections acquired, use or non-use of contrast media)”. 
### 2019 National Average Payments for Physician Office IDTF

**TC** - Technical Component, **26** - Professional Component, **G** - Global

<table>
<thead>
<tr>
<th>CPT</th>
<th>Short Descriptor</th>
<th>Payment</th>
<th>CPT</th>
<th>Short Descriptor</th>
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<tr>
<td>93303  G TTE limited congenital</td>
<td>$ 239.66</td>
<td>93315  26 TEE cong. acq, inter, report</td>
<td>$ 131.90</td>
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<td>93303  TC TTE limited congenital</td>
<td>$ 174.43</td>
<td>93317  26 TEE acq, inter, report only</td>
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<tr>
<td>93303  26 TTE limited congenital</td>
<td>$ 65.23</td>
<td>93318  26 TEE monitoring</td>
<td>$ 107.40</td>
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<tr>
<td>93304  G TTE limited</td>
<td>$ 163.26</td>
<td>93320  G Doppler echo</td>
<td>$ 54.42</td>
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<tr>
<td>93304  TC TTE limited</td>
<td>$ 125.78</td>
<td>93320  TC Doppler echo</td>
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<td>93304  26 TTE limited</td>
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<td>93321  26 Doppler echo F/U or limited</td>
<td>$ 27.39</td>
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<tr>
<td>93306  G TTE comp, Dop, CF</td>
<td>$ 210.47</td>
<td>93321  26 Doppler echo F/U or limited</td>
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<td>93306  TC TTE comp, Dop, CF</td>
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<td>93321  TC Doppler echo F/U or limited</td>
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<td>93350  G Stress TTE only</td>
<td>$191.37</td>
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<td>93308  TC TTE F/U or limited</td>
<td>$ 73.88</td>
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<tr>
<td>93308  26 TTE F/U or limited</td>
<td>$ 26.31</td>
<td>93351  G Stress TTE with exercise</td>
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<td>93312  G TEE place acq, int, rep.</td>
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<td>93314  G TEE acq, inter, report</td>
<td>$ 242.54</td>
<td>93352  G Use of contrast at stress</td>
<td>$ 34.24</td>
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<tr>
<td>93314  TC TEE acq, inter, report</td>
<td>$ 148.48</td>
<td>0439T  Myocardial perfusion echo</td>
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<td>93314  26 TEE acq, inter, report</td>
<td>$ 94.06</td>
<td>0439T  Myocardial perfusion echo</td>
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</table>

Payment amounts vary from location to location.
See CMS physician fee schedule to confirm your local payment amounts at:

For complete text for CPT code descriptors see page 8
INDICATIONS
Activated DEFINITY® (Perflutren Lipid Microsphere) Injectable Suspension is indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

CONTRAINDICATIONS
Do not administer DEFINITY® to patients with known or suspected hypersensitivity to perflutren.

IMPORTANT SAFETY INFORMATION

**WARNING: Serious Cardiopulmonary Reactions**
Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perflutren-containing microsphere administration [see Warnings and Precautions (5.1)]. Most serious reactions occur within 30 minutes of administration.
- Assess all patients for the presence of any condition that precludes DEFINITY® administration [see Contraindications (4)].
- Always have resuscitation equipment and trained personnel readily available.

In postmarketing use, rare but serious cardiopulmonary or hypersensitivity reactions have been reported during or shortly following perflutren-containing microsphere administration [see Adverse Reactions (6)]. The risk for these reactions may be increased among patients with unstable cardiopulmonary conditions [see Adverse Reactions (6.2)]. It is not always possible to reliably establish a causal relationship to drug exposure due to the presence of underlying cardiopulmonary disease.
DEFINITY® (Perflutren Lipid Microsphere) Injectable Suspension

FOR INTRAVENOUS USE

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DEFINITY safely and effectively. See full prescribing information for DEFINITY.

DEFINITY (Perflutren Lipid Microsphere) Injectable Suspension, for intravenous use

Initial U.S. Approval: 2001

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

See full prescribing information for complete boxed warning

Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perflutren-containing microsphere administration (5.1). Most serious reactions occur within 30 minutes of administration.

- Assess all patients for the presence of any condition that precludes DEFINITY administration (4).
- Always have resuscitation equipment and trained personnel readily available.

RECENT MAJOR CHANGES

Contraindications (4) 01/2017

Warnings and Precautions (5.3) 01/2017

INDICATIONS AND USAGE

DEFINITY is an ultrasound contrast agent indicated for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

- DOSAGE AND ADMINISTRATION

DEFINITY may be injected by either an intravenous (IV) bolus or infusion. The maximum dose is either two bolus doses or one single intravenous infusion.

The recommended bolus dose for activated DEFINITY is 10 microliters (μL/kg) of the activated product by intravenous bolus injection between 30-60 seconds, followed by a 10 mL saline flush. If necessary, a second 10 microliters (μL/kg) dose followed by a second 10 mL saline flush may be administered 30 minutes after the first injection to prolong contrast enhancement.

The recommended infusion dose for activated DEFINITY is via an IV infusion of 1.3 mL added to 50 mL of preservative-free saline. The recommended infusion rate is 4.0 mL/minute. The second 10 microliters (μL/kg) dose followed by a second 10 mL saline flush may be administered 30 minutes after the first injection to prolong contrast enhancement.

Infusion

The recommended infusion dose for activated DEFINITY is via an IV infusion of 1.3 mL added to 50 mL of preservative-free saline. The rate of infusion should be initialized at 4.0 mL/minute and titrated as necessary to achieve optimal image enhancement, not to exceed 10 mL/minute.

DOSAGE FORMS AND STRENGTHS

DEFINITY is supplied as a single use 2-mL clear glass vial containing a clear liquid in packages of four (4) and sixteen (16) single-use vials.

CONTRAINDICATIONS

Do not administer DEFINITY to patients with known or suspected:

Hypersensitivity to perflutren (see Warnings and Precautions (5.1)).

WARNINGS AND PRECAUTIONS

Serious cardiopulmonary reactions, including fatalities, have occurred uncommonly during or following perflutren-containing microsphere administration (5.1).

Serious acute hypersensitivity reactions have occurred in patients with no prior exposure to perflutren-containing microsphere products (5.1, 5.2).

Always have cardiopulmonary resuscitation personnel and equipment readily available prior to DEFINITY administration and monitor all patients for acute reactions (5.1, 5.2).

ADVERSE REACTIONS

The most common adverse reactions (≤5%) are headache, back/renal pain, flushing, nausea, chest pain, injection site reactions, and dizziness (8).

To report SUSPECTED ADVERSE REACTIONS, contact Lantheus Medical Imaging, Inc. 1-800-362-2668 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for Patient Counseling Information.
5.3 Systemic Embolization

When administering DEFINITY to patients with a cardiac shunt, the microspheres can bypass filtering by the lung and enter the arterial circulation. Assess patients with shunts for embolic phenomena following DEFINITY administration. DEFINITY is only for intravenous administration; do not administer DEFINITY by intra-arterial injection [see Dosage and Administration (2.1)].

5.4 Ventricular Arrhythmia Related to High Mechanical Index

High ultrasound mechanical index values may cause myocardial cavitation or rupture and lead to ventricular arrhythmias. Additionally, end-systolic triggering with high mechanical indices has been reported to cause ventricular arrhythmias. DEFINITY is not recommended for use at mechanical indices greater than 0.8 [see Dosage and Administration (2.2)].

6. ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Serious Cardiopulmonary Reactions [see Warnings and Precautions (5.1)]
- Hypersensitivity Reactions [see Warnings and Precautions (5.2)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 1716 subjects were evaluated in pre-market clinical trials of activated DEFINITY. In this group, 1063 (81.9%) were male and 653 (38.1%) were female, 1328 (77.4%) were White, 258 (15.0%) were Black, 74 (4.3%) were Hispanic, and 56 (3.3%) were classified as other racial or ethnic groups. The mean age was 56.1 years (range 18 to 93). Of these, 144 (8.4%) had at least one adverse reaction (Table 1). There were 26 serious adverse events and 15 (0.9%) subjects discontinued because of an adverse event.

Serious Adverse Reactions

Among the 1716 study patients, 19 (1.1%) suffered serious cardiopulmonary adverse reactions.

For all adverse reactions, the overall incidence of adverse experiences was similar for the <65 year age group and the >65 year age group, similar in males and in females, similar among all racial or ethnic groups, and similar for bolus and infusion dosing. Table 1 summarizes the most common adverse reactions.

Table 1 New-Onset Adverse Reactions Occurring in ≥5% of All DEFINITY-Treated Subjects

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DEFINTY</th>
<th>(N=1716)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Adverse Reactions</td>
<td>269</td>
<td>144 (8.4%)</td>
</tr>
<tr>
<td>Total Number of Subjects with an Adverse Reaction</td>
<td>144</td>
<td></td>
</tr>
<tr>
<td>Body system</td>
<td>Preferred term</td>
<td>n (%)</td>
</tr>
<tr>
<td>Application Site Disorders</td>
<td>11 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Injection Site Reactions</td>
<td>11 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>41 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Back/renal pain</td>
<td>20 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Chest pain</td>
<td>13 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Central and peripheral nervous system disorder</td>
<td>34 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>40 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>11 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal system</td>
<td>31 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Vascular (extracardiac) disorders</td>
<td>9 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Flushing</td>
<td>19 (1.1)</td>
<td></td>
</tr>
<tr>
<td>N=Sample size 1716 subjects who received activated DEFINITY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=Number of subjects reporting at least one Adverse Reaction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other adverse reactions that occurred in ≥5% of the activated DEFINITY-dosed subjects were:

- Body as a Whole: Fatigue, fever, hot flushes, pain, rigors, and syncope
- Cardiovascular: Atrial fibrillation, tachycardia, bradycardia, tachypnea, palpitation, hypertension and hypotension
- Digestive: Dyspepsia, dry mouth, tongue disorder, toothache, abdominal pain, diarreha and vomiting
- Hematology: Granulocytopenia, leukocytosis, leucopenia, and eosinophilia
- Musculoskeletal: Arthralgia
- Nervous System: Leg cramps, hypotonia, vertigo and paresthesia
- Pulmonary, Bleeding, and Clotting: Hematoma
- Respiratory: Coughing, hypoxia, pharyngitis, rhinitis and dysphonia
- Special Senses: Decreased hearing, conjunctivitis, abnormal vision and taste perversion
- Skin: Pruritis, rash, erythematous rash, urticaria, increased sweating, and dry skin
- Urinary: Albinumuria

6.2 Postmarketing Experience

In a prospective, multicenter, open-label registry of 1053 patients receiving DEFINITY in routine clinical practice, heart rate, respiratory rate, and pulse oximetry were monitored for 30 minutes after DEFINITY administration. No deaths or serious adverse reactions were reported, suggesting that DEFINITY use was unlikely to occur at a rate of more than 0.3% when DEFINITY is used according to recommendations.

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

Cardiopulmonary and hypersensitivity reactions and other serious but non-fatal adverse reactions were uncommonly reported. These reactions typically occurred within 30 minutes of DEFINITY administration. These reactions may be increased among patients with unstable cardiopulmonary conditions (acute myocardial infarction, acute coronary artery syndromes, worsening or unstable congenital heart failure, or serious ventricular arrhythmias) [see Warnings and Precautions (5.1, 5.2)].

Reported reactions included:

- Cardiopulmonary: Fatal cardiac or respiratory arrest, shock, syncope, symptomatic arrhythmias (atrial fibrillation, tachycardia, bradycardia, supraventricular tachycardia, ventricular fibrillation, ventricular tachycardia), hypertension, hypotension, dyspnea, hypoxia, chest pain, respiratory distress, stridor, wheezing.
- Hypersensitivity: Anaphylactic reaction, anaphylactic shock, bronchospasms, throat tightening, angioedema, edema (pharyngeal, palatal, mouth, localized), swelling (face, eye, lip, tongue, upper airway), facial hypoaesthesia, rash, urticaire, pruritus, flushing, erythema.
- Neurologic: Coma, loss of consciousness, convulsion, seizures, transient ischemic attack, agitation, tremor, vision blurred, dizziness, fatigue, headache.

6.3 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of DEFINITY in pregnant women. Reproduction studies were performed in rats and rabbits at doses up to 20 and 15 times the human dose based on body surface area (in rats and rabbits respectively). There was no evidence of impaired fertility or harm to the fetus due to DEFINITY. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.2 Pediatric Use

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

8.3 Nursing Mothers

It is not known whether DEFINITY is excreted in human milk. Based on the rapid clearance of this drug, advise nursing mothers to pump and discard breast milk once after treatment [see Clinical Pharmacology (12.3)]. Because many drugs are excreted in human milk, caution should be exercised when DEFINITY is administered to a nursing mother.

12.1 Mechanism of Action

Perfluoripentane microspheres exhibit lower acoustic impedance than blood and enhance the intrinsic backscatter of blood. These physical acoustic properties of activated DEFINITY provide contrast enhancement of the left ventricular chamber and aid delineation of the left ventricular endocardial border during echocardiography. In animal models the acoustic properties of activated DEFINITY were established at or below a mechanical index of 0.7 (1.8 MHz frequency). In clinical trials, the majority of the patients were imaged at or below a mechanical index of 0.8.

12.2 Pharmacokinetics

Human pharmacokinetics information is not available for the intact or degassed lipid microspheres. The pharmacokinetics of octafluoropropane gas (OPF) was evaluated in healthy subjects (n=8) after the IV administration of activated DEFINITY at a 50 µmol/kg dose.

Distribution

OPF gas binding to plasma proteins or partitioning into blood cells has not been studied. However OPF is believed to be minimal due to its low partial coefficient into whole blood. Metabolism

OPF is a stable gas that is not metabolized. The phospholipid components of the microspheres are thought to be metabolized to free fatty acids. Elimination

OPF was not detectable after 10 minutes in most subjects either in the blood or in expired air. OPF concentrations in blood were shown to decline in a mono-exponential fashion with a mean half-life of 1.3 minutes in healthy subjects.

Nonclinical Toxicology

The pharmacokinetics of octafluoropropane gas (OPF) was evaluated in subjects (n=11) with chronic obstructive pulmonary disease (COPD). The mean half-life of OPF in blood was 1.9 minutes. The total lung clearance of OPF was similar to that in healthy subjects.
The pharmacokinetics of activated DEFINITY has not been studied in subjects with hepatic diseases or congestive heart failure.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Studies with activated DEFINITY have not been performed to evaluate carcinogenic potential. Evidence of genotoxicity was not found in the following studies with activated DEFINITY: 1) bacterial mutagenesis assay (Ames assay), 2) in vitro mammalian lymphocyte chromosome aberration assay, and 4) in vivo mouse lymphocyte assay. Impairment of male or female fertility was not observed in rats and rabbits treated with activated DEFINITY at doses up to 24 and 15 times the human dose based on body surface area (in rats and rabbits, respectively).

14 CLINICAL STUDIES

14.1 Echocardiography

A total of 249 subjects were evaluated in clinical trials (208 received activated DEFINITY and 41 placebo). In this group, 154 (81.8%) were male and 95 (38.2%) were female. 183 (73.5%) were White, 38 (15.3%) were Black, 21 (8.4%) were Hispanic, and 7 (2.8%) were classified as other racial or ethnic groups. The mean age was 53.9 years (range 18 to 87).

Activated DEFINITY was evaluated in four controlled clinical trials: Two open-label baseline controlled, unblinded image evaluation studies and two identical placebo-controlled, unblinded image evaluation studies. Subjects were eligible for these studies if they had two or more (of six) non-evaluable segments in either the apical 2- or 4-chamber view in non-contrast fundamental echocardiography. In the baseline controlled studies, a total of 126 (67 in study A and 59 in study B) subjects received a bolus dose of 10 microL/kg activated DEFINITY. The outcome measures in these studies included the blinded assessment of ejection fraction (EF), endocardial border length (EBL) obtained by direct measurement, and qualitative assessment of wall motion. In the two placebo-controlled studies a total of 123 subjects were randomized in 1:2 ratio to receive two IV bolus doses of either saline (placebo) or activated DEFINITY 10 microL/kg (17 placebo vs. 33 activated DEFINITY patients, respectively). The outcome measure for assessing the effectiveness of activated DEFINITY was the blinded assessment of ejection fraction (EF), endocardial border length (EBL) obtained by direct measurement, and qualitative assessment of wall motion.

Endocardial Border Length

As shown in Table 3, compared to baseline, a single bolus dose of 10 microL/kg of activated DEFINITY increased the length of endocardial border that could be measured at both end systole and end diastole. The mean change in border length from baseline at end diastole was statistically significant for all readers in the apical 4-chamber view and for 3 out of 4 readers for the apical 2-chamber view. The mean change in endocardial border length from baseline at end systole was statistically significant for 3 out of 4 readers for the apical 4-chamber view and for 2 out of 4 readers for the apical 2-chamber view.

**Table 3 MEAN (SD) ENDOCARDIAL BORDER LENGTH (CM) BY BOTH APICAL 2- AND 4-CHAMBER VIEWS AT END-SYSTOLE AND END-DIASTOLE BY STUDY, EVALUABLE SUBJECTS**

<table>
<thead>
<tr>
<th>Study/View</th>
<th>Endocardial Border Length – Blinded Read</th>
<th>Mean(SD) at End-Diastole</th>
<th>Mean(SD) at End-Systole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reader 1</td>
<td>Reader 2</td>
<td>Reader 1</td>
</tr>
<tr>
<td><strong>Study A: (N = 57)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocardial Border Length</td>
<td>12.6(3.4)*</td>
<td>12.5(3.2)*</td>
<td>13.5(3.2)*</td>
</tr>
<tr>
<td>Post-DEFINITY</td>
<td>9.4(2.8)*</td>
<td>9.7(2.3)*</td>
<td>11.4(4.4)*</td>
</tr>
<tr>
<td>Baseline</td>
<td>4.5(2.3)</td>
<td>4.5(2.3)</td>
<td>4.7(2.6)</td>
</tr>
<tr>
<td><strong>Study B: (N = 59)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocardial Border Length</td>
<td>11.8(2.6)</td>
<td>12.1(2.6)</td>
<td>11.7(2.6)</td>
</tr>
<tr>
<td>Post-DEFINITY</td>
<td>9.9(2.6)</td>
<td>10.1(2.6)</td>
<td>11.5(3.5)</td>
</tr>
<tr>
<td>Baseline</td>
<td>3.8(2.6)</td>
<td>3.8(2.6)</td>
<td>4.1(2.4)</td>
</tr>
</tbody>
</table>

14.2 Pulmonary Hemodynamic Effects

The impact of DEFINITY on pulmonary hemodynamics was explored in a prospective, open-label study of patients with normal (< 35 mmHg, 16 patients) and elevated (> 35 mmHg, > 75 mmHg, 16 patients) pulmonary artery systolic pressure undergoing right heart catheterization. Patients with pulmonary artery systolic pressure greater than 75 mmHg were excluded from this study. Systemic hemodynamic parameters and ECGs were also evaluated. No clinically important pulmonary hemodynamic, systemic hemodynamic, or ECG changes were observed. This study did not assess the effect of DEFINITY on visualization of cardiac or pulmonary structures.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DEFINITY is supplied as a single use 2-ml clear glass vial containing clear liquid in packages of four (4) and sixteen (16) single-use vials.

- One (1) 2ml vial - NDC (11994-011-01)
- Four (4) 2ml vials per kit - NDC (11984-011-04)
- Sixteen (16) 2ml vials per kit - NDC (11994-011-16)

16.2 Storage and Handling

Store between 2-8° C (36°-46° F).
1. American Medical Association CPT

2. American Medical Association HCPCS Level II Professional

3. See addendum B at https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalOutpatientPPS/Hospital-Outpatient-Regulations-and-Notices-Items/CMS-1695-FC.html?DLPage=1&DLEntries=10&DLSort=2&DLSortDir=descending


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