Medicare
Reimbursement Information
2020
Questions regarding reimbursement for Lantheus Medical Imaging products?

Call Randy VanCoughnett at 978-436-7995 or email randy.vancoughnett@lantheus.com.
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 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 codes1,2

- **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”**  
  TTE w or w/o fol wcon, Doppler

**JW modifier** - The JW modifier is not required for packaged drugs such as DEFINITY® 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.
2. **DEFINITY® Hospital Outpatient Setting and APC Payments**

In the Medicare Hospital Outpatient setting DEFINITY® is reimbursed, however, the payment is packaged with the imaging procedure payment.

<table>
<thead>
<tr>
<th>Procedure Code</th>
<th>Description</th>
<th>Payment</th>
</tr>
</thead>
<tbody>
<tr>
<td>93306</td>
<td>TTE complete with Doppler and color flow without contrast</td>
<td>$481.53</td>
</tr>
<tr>
<td>C8929</td>
<td>TTE complete with Doppler and color flow with contrast</td>
<td>$680.74</td>
</tr>
</tbody>
</table>

C8929, with contrast, is reimbursed $199.21 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.

### APCs ECHO PROCEDURES - WITHOUT CONTRAST

<table>
<thead>
<tr>
<th>APC</th>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5523</td>
<td>Level 3</td>
<td>Imaging Without Contrast</td>
</tr>
<tr>
<td>5524</td>
<td>Level 4</td>
<td>Imaging Without Contrast</td>
</tr>
</tbody>
</table>

### APCs ECHO PROCEDURES - WITH CONTRAST

<table>
<thead>
<tr>
<th>APC</th>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5572</td>
<td>Level 2</td>
<td>Imaging With Contrast</td>
</tr>
<tr>
<td>5573</td>
<td>Level 3</td>
<td>Imaging With Contrast</td>
</tr>
</tbody>
</table>

For complete code descriptors see page 8
C-code must be billed in order to obtain reimbursement for the contrast agent combined with the echo procedure. Q9929 will not be paid as a separate line item.
### 4. Complete code descriptors.

**Without contrast left column, with contrast right column**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Add-on 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; follow-up 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>
</tr>
<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>93356</td>
<td>Myocardial strain imaging using speckle tracking-derived assessment of myocardial mechanics (List separately in addition to codes for echocardiography imaging) Add code. Use in conjunction with 93303, 93304, 93306, 90337, 93308, 93350, 93351. Report once per session.</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>
</tr>
<tr>
<td>NA</td>
<td></td>
<td>0439T</td>
<td></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 2020 - $48.20 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/](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 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)**.”
## 6. 2020 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>
<th>Payment</th>
</tr>
</thead>
<tbody>
<tr>
<td>93303</td>
<td>G TTE limited congenital</td>
<td>$237.47</td>
<td>93315</td>
<td>26 TEE cong. acq, inter, report</td>
<td>$132.45</td>
</tr>
<tr>
<td>93303</td>
<td>TC TTE limited congenital</td>
<td>$172.15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>93303</td>
<td>26 TTE limited congenital</td>
<td>$65.32</td>
<td>93317</td>
<td>26 TEE acq, inter, report only</td>
<td>$94.19</td>
</tr>
<tr>
<td>93304</td>
<td>G TTE limited</td>
<td>$163.12</td>
<td>93318</td>
<td>26 TEE monitoring</td>
<td>$107.19</td>
</tr>
<tr>
<td>93304</td>
<td>TC TTE limited</td>
<td>$125.59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>93304</td>
<td>26 TTE limited</td>
<td>$37.53</td>
<td>93320</td>
<td>G Doppler echo</td>
<td>$54.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>93320</td>
<td>TC Doppler echo</td>
<td>$35.73</td>
</tr>
<tr>
<td>93306</td>
<td>G TTE comp, Dop, CF</td>
<td>$211.49</td>
<td>93321</td>
<td>G Doppler echo F/U or limited</td>
<td>$27.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>93321</td>
<td>TC Doppler echo F/U or limited</td>
<td>$19.49</td>
</tr>
<tr>
<td>93307</td>
<td>G TTE comp, w/o Dop, CF</td>
<td>$144.00</td>
<td>93325</td>
<td>G Doppler color flow add-on</td>
<td>$25.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>93325</td>
<td>TC Doppler color flow add-on</td>
<td>$22.01</td>
</tr>
<tr>
<td>93308</td>
<td>G TTE F/U or limited</td>
<td>$100.69</td>
<td>93325</td>
<td>26 Doppler color flow add-on</td>
<td>$3.25</td>
</tr>
<tr>
<td>93308</td>
<td>TC TTE F/U or limited</td>
<td>$74.34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>93308</td>
<td>26 TTE F/U or limited</td>
<td>$26.35</td>
<td>93350</td>
<td>G Stress TTE only</td>
<td>$193.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>93350</td>
<td>TC Stress TTE only</td>
<td>$120.54</td>
</tr>
<tr>
<td>93312</td>
<td>G TEE place acq, int, rep.</td>
<td>$251.18</td>
<td>93350</td>
<td>26 Stress TTE only</td>
<td>$72.90</td>
</tr>
<tr>
<td>93312</td>
<td>TC TEE place acq, int, rep.</td>
<td>$138.58</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>93312</td>
<td>26 TEE place acq, int, rep.</td>
<td>$112.60</td>
<td>93351</td>
<td>G Stress TTE with exercise</td>
<td>$239.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>93351</td>
<td>TC Stress TTE with exercise</td>
<td>$151.94</td>
</tr>
<tr>
<td>93314</td>
<td>G TEE acq, inter, report</td>
<td>$241.08</td>
<td>93351</td>
<td>26 Stress TTE with exercise</td>
<td>$87.34</td>
</tr>
<tr>
<td>93314</td>
<td>TC TEE acq, inter, report</td>
<td>$147.60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>93314</td>
<td>26 TEE acq, inter, report</td>
<td>$93.47</td>
<td>93352</td>
<td>G Use of contrast at stress</td>
<td>$34.29</td>
</tr>
<tr>
<td>93356</td>
<td>G Myocardial strain image - F</td>
<td>$12.27</td>
<td>0439T</td>
<td>Myocardial perfusion echo</td>
<td>$12.77</td>
</tr>
<tr>
<td>93356</td>
<td>G Myocardial strain image - NF</td>
<td>$40.78</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Payment amounts vary from location to location. See CMS physician fee schedule to confirm your local payment amounts at: https://www.cms.gov/apps/physician-fee-schedule/license-agreement.aspx

F – Facility, NF – Non-Facility

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

Initial U.S. Approval: 2001

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

See full prescribing information for complete boxed warning.

Serious cardiopulmonary reactions, including fatalities, have occurred commonly 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.

FULL PRESCRIBING INFORMATION: CONTENTS

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Important Administration Instructions
2.2 Dosage
2.3 Imaging Guidelines
2.4 DEFINITY Activation, Preparation and Handling Instructions
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Serious Cardiopulmonary Reactions
5.2 Hypersensitivity Reactions
5.3 Systemic Embolization
5.4 Ventricular Arrhythmia Related to High Mechanical Index
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 USE IN SPECIFIC POPULATIONS
8 PATIENT COUNSELING INFORMATION
9 DRUG INTERACTIONS
9.1 Drugs That May Alter the Echocardiographic Image
9.2 Drugs That May Alter the Ultrasound Image
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility
14 CLINICAL STUDIES
14.1 Echocardiography
14.2 Pulmonary Hemodynamic Effects
15 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
16.2 Storage and Handling
17 PATIENT COUNSELING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

1 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.

2 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 microL/kg of the activated product by intravenous bolus injection within 30 to 60 seconds, followed by a 10 mL saline flush. If necessary, a second microL/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 a 10 microL/kg/h rate of infusion septicemia can occur following the puncture of the elastomer septum. It is essential to follow directions for activation of DEFINITY carefully and to adhere to strict aseptic procedures during preparation.

3 DOSAGE FORMS AND STRENGTHS

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.

CONTRAINDICATIONS

Do not administer DEFINITY to patients with known or suspected:

Hypersensitivity to perflutren.

WARNINGS AND PRECAUTIONS

Serious cardiopulmonary reactions, including fatalities, have occurred commonly 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 (see Warnings and Precautions (5.1)).
• Always have resuscitation equipment and trained personnel readily available.

FULL PRESCRIBING 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 Warnings and Precautions (5.1)).
• Always have resuscitation equipment and trained personnel readily available.

2.4 DEFINITY Activation, Preparation and Handling Instructions

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.

CONTRAINDICATIONS

Do not administer DEFINITY to patients with known or suspected:

Hypersensitivity to perflutren.

WARNINGS AND PRECAUTIONS

Serious cardiopulmonary reactions, including fatalities, have occurred commonly 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 (see Warnings and Precautions (5.1)).
• Always have resuscitation equipment and trained personnel readily available.

FULL PRESCRIBING 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 Warnings and Precautions (5.1)).
• Always have resuscitation equipment and trained personnel readily available.

2.4 DEFINITY Activation, Preparation and Handling Instructions

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.

3.1 VIALMIX (as described above) and begin ultrasound imaging immediately.

In a crossover trial of 64 patients randomized to both bolus and infusion, the duration of clinically useful contrast enhancement for fundamental imaging was approximately 3.4 minutes after a 10 microL/kg bolus and was approximately 7.1 minutes during the continuous infusion of 1.3 mL activated DEFINITY in 50 mL saline at a rate of 4 mL/min.

2.4 DEFINITY Activation, Preparation and Handling Instructions

1. Allow the vial to warm to room temperature before starting the activation procedure.
2. Activate DEFINITY by shaking the vial for 45 seconds using a VIALMIX.

Note: illustrations of this procedure are contained in the VIALMIX User’s Guide.

Do not use this drug unless it has completed a full 45 second activation cycle in the VIALMIX. DEFINITY will not be properly activated unless the full 45 second activation cycle is complete. Do not re-inject the vial if VIALMIX did not complete a full 45-second cycle. Do not re-activate a successfully activated DEFINITY vial (see step 3).

3. Immediately after activation in the VIALMIX, activated DEFINITY appears as a milky white suspension and may be used immediately after activation. If the product is not used within 5 minutes of VIALMIX activation, the microspheres should be resuspended by 10 seconds of hand agitation by inverting the vial before the product is withdrawn in a syringe. The activated DEFINITY may be used for up to 12 hours from the time of VIALMIX but only after the microspheres are resuspended by hand agitation. Store the activated DEFINITY at room temperature in the original product vial.

4. Invert the vial and withdraw the activated milky white suspension using the IntelliVUE® VMS (Vented Vial Adapter 13mm), or 18 to 20 gauge syringe needle. Withdraw the material from the middle of the liquid in the inverted vial. Do not inject air into the DEFINITY Vial.

5. Use the product immediately after its withdrawal from the vial; do not allow the product to stand in the syringe. For single use only: DEFINITY does not contain bacterial preservative. Bacterial contamination with the risk of post-administration septicaemia can occur following the puncture of the elastomeric septum. It is essential to follow directions for activation of DEFINITY carefully and to adhere to strict aseptic procedures during preparation.

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.

Prior to activation, the headspace of each vial contains 6.52 mg/mL octafluoronaproxone and the clear liquid contains 0.75mg/mL of a lipid blend. After activation, each vial contains a maximum of 1.2 X 10^11 perflutren lipid microspheres, and about 150 microL/mL octafluoronaproxone (see Description (11)).

4 CONTRAINDICATIONS

Do not administer DEFINITY to patients with known or suspected:

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

5 WARNINGS AND PRECAUTIONS

5.1 Serious Cardiopulmonary Reactions

Serious cardiopulmonary reactions including fatalities have occurred uncommonly during or shortly following perflutren-containing microsphere administration, typically within 30 minutes of administration. The risk for these reactions may be increased among patients with unstable cardiopulmonary conditions (acute respiratory failure, acute coronary ischemia, acute cor pulmonale, pulmonary hypertension, or unstable or congestive heart failure, or serious ventricular arrhythmias). Always have cardiopulmonary resuscitation personnel and equipment readily available prior to DEFINITY administration and monitor all patients for acute reactions.

The reported reactions include: 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, loss of consciousness, and convulsions (see Adverse Reactions (6)).
5.2 Hypersensitivity Reactions

In postmarketing use, serious hypersensitivity reactions were observed during or shortly following perfluor-containing microsphere administration including:

- Shock, bronchospasm, throat tightness, angioedema, edema (pharyngeal, palatal, mouth, peripheral, localized), swelling (face, eye, lip, tongue, upper airway), facial hypoesthesia, rash, urticaria, pruritus, flushing, and erythema have occurred in patients with no prior exposure to perfluor-containing microsphere products [see Adverse Reactions (6)]. Always have cardiopulmonary resuscitation personnel and equipment readily available prior to DEFINITY administration and monitor all patients for hypersensitivity reactions.

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 was not studied for intravenous administration; do not administer DEFINITY by intra-arterial injection [see Doseage and Administration (2.1)].

5.4 Ventricular Arrhythmia Related to High 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. DEFINITY is not recommended for use at mechanical indices greater than 0.8 [see Doseage and Administration (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 DEFINITY. In this group, 1063 (61.9%) were male and 653 (38.1%) were female, 1328 (77.4%) were White, 126 (7.4%) were Black, 74 (4.3%) were Hispanic, and 56 (3.3%) were classified as other or racial ethnic groups. The mean age was 60.1 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.

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 these reactions are unlikely to occur at a rate greater than 0.3% when DEFINITY is used according to recommendations.

The following adverse reactions have been identified during the post-marketing use of perfluor-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. Fatial 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 serious reactions may be increased among patients with unstable cardiopulmonary conditions (acute myocardial infarction, acute coronary artery syndromes, congestive heart failure, cardiac arrest), serious ventricular arrhythmias [see Warnings and Precautions (5.1, 5.2)].

Reported reactions included:

- Cardiac:
  - Fatality: 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:
  - Anaphylaxis: Anaphylactic shock, bronchospasm, throat tightness, angioedema, edema (pharyngeal, palatal, mouth, peripheral, localized), swelling (face, eye, lip, tongue, upper airway), facial hypoesthesia, rash, urticaria, pruritus, flushing, erythema.
- Neurologic:
  - Coma, loss of consciousness, convulsion, seizure, transient ischemic attack, agitation, tremor, vision blurred, dizziness, headache, fatigue.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from case reports with DEFINITY use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. DEFINITY has a very short half-life; therefore, administration of DEFINITY to a pregnant woman is not expected to result in clinically relevant fetal exposure. No adverse developmental outcomes were observed in animal reproduction studies with administration of active DEFINITY in pregnant rats and rabbits during organogenesis at doses up to 8 and 16 times, respectively, the maximum human dose based on body surface area (see Data).

All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

DEFINITY was administered intravenously to rats at doses of 0.1, 0.3, and 1.0 mL/kg (approximately 0.8, 2.4, and 8 times the recommended maximum human dose based on body surface area); DEFINITY doses were administered daily from day 6 to day 17 of gestation. DEFINITY was administered intravenously to rabbits at doses of 0.1, 0.3, and 1.0 mL/kg (approximately, 1.6, 4.8, and 16 times the recommended maximum human dose based on body surface area); DEF

8.2 Lactation

Breastfeeding

There are no data on the presence of DEFINITY in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for DEFINITY and any potential adverse effects on the breastfed infant from DEFINITY or from the underlying maternal condition.

8.3 Pediatric Use

DEFINITY has not been established in the pediatric population. The safety and effectiveness of DEFINITY in neonates and infants with immature pulmonary vasculature has not been studied. The pharmacokinetics of activated DEFINITY in pediatric subjects has not been studied.

8.5 Geriatric Use

In clinical trials, the overall incidence of adverse reactions was similar for the <65 year age group and the ≥65 year age group. Of the total number of subjects in clinical trials of DEFINITY, 144 (33%) were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified aging as a factor affecting the response to DEFINITY doses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

11 DESCRIPTION

DEFINITY (Perflutren Lipid Microsphere) Injectable Suspension is an ultrasound contrast agent. The DEFINITY vial contains components that upon activation yield perfluor lipid microspheres. The vials contain a clear, colorless, sterile, non-pyrogenic, hypotonic liquid, which upon activation with the aid of a VALIMIX, provides a homogeneous, opaque, milky white injectable suspension of perfluor lipid microspheres. The suspension of activated DEFINITY is administered by intravenous injection.

The perfluor lipid microspheres are composed of octafluoropropane encapsulated in an outer lipid shell consisting of (R)-hexa decanoic acid 1,2-ethanediyl ester, 5,7,11-trioxa-2-aza-6-phosphahexacos-1-yl, monosodium salt (abbreviated DPPA); (R)-4-hydroxy-N,N,N-trimethyl-10-oxo-7-[1-(oxohexadecyl)-oxy]-5,7,9,11-tetraoxa-4-phos phapentacosan-1-aminium, 4-oxide, inner salt (abbreviated DPPC); and (R)=5-[6-hydroxy-6-oxido-9-[1-(oxohexadecyl)-oxy]-5,7,9,11-tetraoxa-2-aza-6-phosphapentacosan-1-yl]-methylphosphol[oxyl-1,2-ethanediyl], monosodium salt (abbreviated MPEG5000 DPPE). Octafluoropropane is chemically characterized as 1,1,1,2,2,3,3,3-octafluoropropane. It has a molecular weight of 188, empirical formula of C8H4O3PNa, and has the following structural formula:

\[ \text{C}_{8}\text{H}_{4}\text{O}_{3}\text{PNa} \]

DPPA has a molecular weight of 670, empirical formula of C12H24O4PNa, and has the following structural formula:

\[ \text{C}_{12}\text{H}_{24}\text{O}_{4}\text{PNa} \]

DPPC has a molecular weight of 734, empirical formula of C18H34NO2P, and has the following structural formula:

\[ \text{C}_{18}\text{H}_{34}\text{NO}_{2}\text{P} \]

MPEG5000 DPPE has an approximate molecular weight of 5750 represented by empirical formula C32H55NO4PNa, contains <100ppm Ca2+ and Mg2+ and the following structural formula:

\[ \text{C}_{32}\text{H}_{55}\text{NO}_{4}\text{PNa} \]

Prior to VALIMIX activation, the DEFINITY vial contains 6.52 mg/mL octafluoropropane in the headspace which was required to be confirmed by positive IR spectroscopic tests in every vial. Each mL of the clear liquid contains 0.75 mg lipid blend (consisting of 0.045 mg DPPA, 0.401 mg DPPC, and 0.304 mg MPEG5000 DPPE), 103.5 mg propylene glycol, 126.2 mg glycine, 2.34 mg sodium phosphate monobasic monohydrate, 2.16 mg sodium phosphate dibasic heptahydrate, and 4.87 mg sodium chloride in Water for Injection. The pH is 6.2-6.8.
After activating the contents of the vial in a VIALMIX, each mL of the milky white suspension contains a maximum of 1.2 X 10^{10} perflutren lipid microspheres, and about 150 microL/mL (1.1 mg/mL) octafluoropropane. The microsphere particle size parameters are listed in Table 2 below:

<table>
<thead>
<tr>
<th>Microsphere particle size parameters</th>
<th>Mean diameter range</th>
<th>Percent less than 10 µm</th>
<th>Maximum diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.1 µm – 3.3 µm</td>
<td>98%</td>
<td>20 µm</td>
</tr>
</tbody>
</table>

**12.1 Mechanism of Action**
Perflu t linid 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 evaluated 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.

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

**Distribution**
OFP gas binding to plasma proteins or partitioning into blood cells has not been studied. However, OFP protein binding is expected to be minimal due to its low partition coefficient into whole blood.

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

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

**Special Populations**
The pharmacokinetics of octafluoropropane gas (OFP) was evaluated in subjects (n=11) with chronic obstructive pulmonary disease (COPD). The mean half-life of OFP in blood was 1.9 minutes. The total lung clearance of OFP was similar to that in healthy subjects.

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 mutagenesis assay, 3) in vivo mammalian lymphocyte chromosome aberration assay, and 4) in vivo rat micronucleus assay.

Impairment of male or female fertility was not observed in rats and rabbits treated with activated DEFINITY at 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 (61.8%) were male and 95 (38.2%) were female; 183 (73.3%) 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:

A two-open baseline controlled, unpaired blinded image evaluation studies and two identical placebo-controlled, unpaired blinded image evaluation studies. Subjects were eligible for these studies if they had two or more (of six) non-evaluable segments in either the apical 2- or 4-chamber view in non-contrast fundamental echocardiography.

In the baseline controlled studies, a total of 126 (67 in study A and 59 in study B) subjects received a bolus dose of 10 microL/kg activated DEFINITY. The outcome measures in these studies included the blinded assessment of ejection fraction (EF), end-systolic and end-diastolic left ventricular volume and 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 a 2:1 ratio to receive two IV bolus doses of either saline (placebo) or activated DEFINITY 10 microL/kg (17 placebo vs. 33 activated DEFINITY patients and 24 placebo vs. 49 activated DEFINITY patients, respectively). The outcome measure for assessing the effectiveness of activated DEFINITY was the blinded assessment of improvement in ventricular chamber enhancement (measured by videodensitometry at end-diastole and end-systole). Endocardial Border Length
As shown in Table 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 border length from baseline at end-diastole 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.

**Wall Motion**
In a retrospective analysis, in a subset of subjects (n=12 to 47, depending on reader) having at least 2 adjacent segments non-evaluable on non-contrast imaging, activated DEFINITY converted a baseline non-evaluable image to an evaluable image in 58 to 91% of the patients, depending on the reader. In the converted images, the accuracy of wall motion (i.e., normal versus abnormal) improved in 42 to 71% of the patients, depending on the reader, however, improvement in the specific diagnostic accuracy (e.g., hypokinetic, akinetic etc.) was not accomplished. Also, in 13 to 37% of the patients, depending on the reader, activated DEFINITY was found to obscure the wall motion rendering the image non-evaluable.

**Ejection Fraction**
In the 2 baseline controlled studies, ejection fraction results were evaluated in comparison to MRI. The results were evaluated by 3 blinded, independent radiologists. In these studies, although there was a statistically significant increase in ventricular chamber enhancement, activated DEFINITY did not significantly improve the assessment of ejection fraction compared to the baseline images.

**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 (1994-011-01)
- Four (4) 2mL vials per kit - NDC (1994-011-04)
- Sixteen (16) 2mL vials per kit - NDC (1994-011-18)

16.2 Storage and Handling
Store between 2-8°C (36º-46ºF).

**PATIENT COUNSELING INFORMATION**
Advise patients to inform their healthcare provider if they develop any symptoms of hypersensitivity after DEFINITY administration, including rash, wheezing, or shortness of breath.

**2020 Medicare Reimbursement Information**

**Endocardial Border Length – Blinded Read**

<table>
<thead>
<tr>
<th>Study/View</th>
<th>Mean(SD) at End-Diastole</th>
<th>Mean(SD) at End-Systole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apical 2-chamber</td>
<td>8.93(3.4)</td>
<td>7.13(3.3)</td>
</tr>
<tr>
<td>Baseline</td>
<td>6.50(2.6)</td>
<td>5.51(2.4)</td>
</tr>
<tr>
<td>Post-DEFINITY</td>
<td>6.42(2.6)</td>
<td>5.51(2.4)</td>
</tr>
<tr>
<td>Avanced 4-chamber</td>
<td>8.10(3.3)</td>
<td>6.70(3.2)</td>
</tr>
<tr>
<td>Baseline</td>
<td>6.10(3.3)</td>
<td>5.10(3.2)</td>
</tr>
<tr>
<td>Post-DEFINITY</td>
<td>5.30(3.3)</td>
<td>4.50(3.2)</td>
</tr>
</tbody>
</table>

**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**

**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) and elevated (> 35 mmHg, < 75 mmHg) 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 ECUs 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.
1. American Medical Association CPT

2. American Medical Association HCPCS Level II Professional


Questions regarding reimbursement for Lantheus Medical Imaging products?

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