Questions regarding reimbursement for Lantheus Medical Imaging products?

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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 1 vial 11994-011-01
- 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

**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.

<table>
<thead>
<tr>
<th>Medicare Hospital Inpatients</th>
<th>Medicare Hospital Outpatients</th>
<th>Physician Offices and IDTFs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital reimbursement is based on Diagnostically Related Group (DRG) payment. There is no additional payment for drugs or imaging procedures.</td>
<td>Contrast agent payments are packaged with the procedure payment and are therefore not paid separately. Reimbursement rates are established based on past cost analysis by Medicare.</td>
<td>Contrast agents are paid in addition to and separately from procedure. Contrast agents reimbursed based on Medicare’s Average Selling Price listings.</td>
</tr>
</tbody>
</table>
2. DEFINITY® Hospital Outpatient Setting and APC Payments

In the Medicare Hospital Outpatient setting echo contrast agents are reimbursed, however, the contrast payment is packaged with the imaging procedure payment.

<table>
<thead>
<tr>
<th>Procedure Description</th>
<th>Payment</th>
</tr>
</thead>
<tbody>
<tr>
<td>93306 TTE complete with Doppler and color flow without contrast</td>
<td>$449.50</td>
</tr>
<tr>
<td>C8929 TTE complete with Doppler and color flow with contrast</td>
<td>$656.63</td>
</tr>
</tbody>
</table>

In the example above the payment for contrast is packaged with C8929. The payment for C8929 is $207.13 higher than for CPT 93306 TTE “without contrast” in order to cover the higher cost of performing a contrast echo.

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

When billing for echo procedures, report either 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 payment amounts. The JW modifier is not used for HOPPS packaged contrast agents.

For complete code descriptors see page 8
THE CERTIFICATIONS ON THE REVERSE APPLY TO THIS BILL AND ARE MADE A PART HEREOF.  

C-code must be billed in order to obtain reimbursement for the contrast agent combined with the echo procedure.  Q9957 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>Echo without contrast¹</th>
<th>Echo with contrast²</th>
</tr>
</thead>
<tbody>
<tr>
<td>93303 Transthoracic echocardiography for congenital cardiac anomalies; complete</td>
<td>C8921 Transsthoracic echocardiography with contrast, or without contrast followed by with contrast, for congenital cardiac anomalies; complete</td>
</tr>
<tr>
<td>93304 Transthoracic echocardiography for congenital cardiac anomalies; follow-up or limited study</td>
<td>C8922 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 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 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 Echocardiography, transthoracic, real-time, with image documentation (2D), includes M-mode recording, when performed, complete, without spectral or color Doppler echocardiography</td>
<td>C8923 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 Echocardiography, transthoracic, real-time, with image documentation (2D), includes M-mode recording, when performed, follow-up or limited study</td>
<td>C8924 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 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 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 Transesophageal echocardiography for congenital cardiac anomalies; including probe placement image acquisition, interpretation and report</td>
<td>C8926 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 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 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 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 pharmaco logically induced stress, with interpretation and report</td>
<td>C8928 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 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 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 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, 93038, 93312, 93314, 93315, 93317, 93350, 93351, 93555) Report 0399T once.</td>
<td>NA</td>
</tr>
<tr>
<td>NA</td>
<td>0439T 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, 93038 93350, 93351)</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 Q4 2016⁴ - $51.82 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 that⁶:

“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)”.

### 2017 Medicare Reimbursement Information Lantheus Medical Imaging

#### 6. 2017 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>240.10</td>
<td>93315</td>
<td>26 TEE cong. acq, inter, report</td>
<td>131.71</td>
</tr>
<tr>
<td>93303</td>
<td>TC TTE limited congenital</td>
<td>175.14</td>
<td>93317</td>
<td>26 TEE acq, inter, report only</td>
<td>95.46</td>
</tr>
<tr>
<td>93304</td>
<td>G TTE limited</td>
<td>157.55</td>
<td>93318</td>
<td>26 TEE monitoring</td>
<td>107.31</td>
</tr>
<tr>
<td>93304</td>
<td>TC TTE limited</td>
<td>120.23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>93306</td>
<td>G TTE comp, Dop, CF</td>
<td>231.48</td>
<td>93320</td>
<td>G Doppler echo</td>
<td>54.91</td>
</tr>
<tr>
<td>93306</td>
<td>TC TTE comp, Dop, CF</td>
<td>166.52</td>
<td>93320</td>
<td>TC Doppler echo</td>
<td>36.25</td>
</tr>
<tr>
<td>93306</td>
<td>26 TTE comp, Dop, CF</td>
<td>64.96</td>
<td>93321</td>
<td>G Doppler echo F/U or limited</td>
<td>27.63</td>
</tr>
<tr>
<td>93307</td>
<td>GC TTE comp, w/o Dop, CF</td>
<td>131.71</td>
<td>93321</td>
<td>TC Doppler echo F/U or limited</td>
<td>20.10</td>
</tr>
<tr>
<td>93307</td>
<td>TC TTE comp, w/o Dop, CF</td>
<td>85.77</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>93308</td>
<td>G TTE F/U or limited</td>
<td>126.69</td>
<td>93325</td>
<td>G Doppler color flow add-on</td>
<td>25.84</td>
</tr>
<tr>
<td>93308</td>
<td>TC TTE F/U or limited</td>
<td>100.49</td>
<td>93325</td>
<td>TC Doppler color flow add-on</td>
<td>22.61</td>
</tr>
<tr>
<td>93308</td>
<td>26 TTE F/U or limited</td>
<td>26.20</td>
<td>93325</td>
<td>26 Doppler color flow add-on</td>
<td>3.23</td>
</tr>
<tr>
<td>93312</td>
<td>G TEE place acq,int, rep.</td>
<td>249.79</td>
<td>93350</td>
<td>G Stress TTE only</td>
<td>244.04</td>
</tr>
<tr>
<td>93312</td>
<td>TC TEE place acq,int, rep.</td>
<td>138.17</td>
<td>93350</td>
<td>TC Stress TTE only</td>
<td>171.55</td>
</tr>
<tr>
<td>93312</td>
<td>26 TEE place acq,int, rep.</td>
<td>111.61</td>
<td>93351</td>
<td>G Stress TTE with exercise</td>
<td>274.91</td>
</tr>
<tr>
<td>93314</td>
<td>G TEE acq, inter, report</td>
<td>240.10</td>
<td>93351</td>
<td>TC Stress TTE with exercise</td>
<td>188.06</td>
</tr>
<tr>
<td>93314</td>
<td>TC TEE acq, inter, report</td>
<td>146.78</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>93314</td>
<td>26 TEE acq, inter, report</td>
<td>93.31</td>
<td>93352</td>
<td>G Use of contrast at stress</td>
<td>34.45</td>
</tr>
<tr>
<td>0399T</td>
<td>Myocardial strain imaging</td>
<td>contractor</td>
<td>0439T</td>
<td>Myocardial perfusion echo</td>
<td>contractor</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](https://www.cms.gov/apps/physician-fee-schedule/license-agreement.aspx)

For complete text for CPT code descriptors see page 8.
DEFINITY® Vial for (Perflutren Lipid Microsphere) Injectable Suspension

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.

Please see full prescribing information on pages 12-14, including boxed WARNING regarding serious cardiopulmonary reactions.
**FULL PRESCRIBING INFORMATION: CONTENTS**

1. **INDICATIONS AND USAGE**
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   2.1 Important Administration Instructions
   2.2 Dosage
   2.3 Imaging Guidelines
   2.4 DEFINITY Activation, Preparation and Handling Instructions
   3. **DOSE FORMS AND STRENGTHS**
   4. **CONTRAINDICATIONS**
   5. **WARNINGS AND PRECAUTIONS**
      5.1 Serious Cardiopulmonary Reactions
      5.2 Hypersensitivity Reactions
      5.3 Systemic Embolization
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      16.2 Storage and Handling
   17. **PATIENT COUNSELING INFORMATION**
   18. **ADDITIONAL INFORMATION**

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**DEFINITY®**

**VIAL (Perflutren Lipid Microsphere)**

**INJECTABLE SUSPENSION**


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**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.

**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 (microL)/kg of the activated product by intravenous bolus injection within 30-60 seconds, followed by a 10 mL saline flush. If necessary, a second 10 microliters (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 via an IV infusion of 1.3 mL added to 50 mL of preservative-free saline. The rate of infusion should be initiated at 4.0 mL/minute, but titrated as necessary to achieve optimal image enhancement, not to exceed 10 mL/minute.

**WARNINGS AND PRECAUTIONS**

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.

**CONTRAINDICATIONS**

- Hypersensitivity to perflutren.

**ADVERSE REACTIONS**

DEFINITY is supplied as a single use 2-mL clear glass vial containing perflutren. The VIALMIX apparatus should be ordered from Lantheus Medical Imaging, 331 Treble Cove Road, North Billerica, MA, 01862. For customer orders call 1-800-299-3431.

DEFINITY may be injected by either an intravenous (IV) bolus or infusion. Do not administer DEFINITY by intra-arterial injection [see Warnings and Precautions (5.3)].

- The maximum dose is either two bolus doses or one single intravenous infusion.
- The safety of bolus and infusion dosing in combination or in sequence, has not been studied.

**DOSAGE**

**Bolus**

The recommended bolus dose for activated DEFINITY is 10 microliters (microL)/kg of the activated product by intravenous bolus injection within 30-60 seconds, followed by a 10 mL saline flush. If necessary, a second 10 microliters (microL)/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 initiated at 4.0 mL/minute, but titrated as necessary to achieve optimal image enhancement, not to exceed 10 mL/minute.

**Imaging Guidelines**

After baseline non-contrast echocardiography is completed, set the mechanical index for the ultrasound device at 0.8 or below [see Warnings and Precautions (5.4)]. Then inject activated DEFINITY (as described above) and begin ultrasound imaging immediately. Evaluate the activated DEFINITY echocardiogram images in combination with the non-contrast echocardiogram images.

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 completed. Do not reactivate the vial if VIALMIX did not complete a full 45 second cycle. Do not reinsert a successfully activated DEFINITY vial (see step 3). Do not use a VIALMIX that is not functioning properly. Refer to the VIALMIX User’s Guide for “VIALMIX calibration and replacement procedures” to ensure that a properly functioning VIALMIX is used.

3. Immediately after activation in the VIALMIX, activated DEFINITY must be used immediately following activation and may be used immediately after activation. If the product is not used within 5 minutes of VIALMIX activation, the microspheres should be re suspensd 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 Intellipin (Dispensing Pin), the PINSYNC (Vented Vial Adaptor 13mm), or 18 to 20 gauge syringe, and 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 sepsis 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.

**3. DOSE FORMS AND STRENGTHS**

DEFINITY is supplied as a single use 2-mL clear glass vial containing perflutren. The VIALMIX apparatus should be ordered from Lantheus Medical Imaging, 331 Treble Cove Road, North Billerica, MA, 01862. For customer orders call 1-800-299-3431.

**4. CONTRAINDICATIONS**

- Do not administer DEFINITY to patients with known or suspected:
  - Hypersensitivity to perflutren [see Warnings and Precautions (5)].

**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 myocardial infarction, acute coronary artery syndromes, worsening or unstable 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, syncope-like events, hypotension, paroxysmal atrial fibrillation, atrial flutter, bradycardia, cardiopulmonary arrest, ventricular fibrillation, ventricular tachycardia, 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 perflutren-containing microsphere administration including:

- Shock, hypotension, syncope-like events, hypotension, angioedema, edema (pharyngeal, palatal, mouth, peripheral, localized), swelling (face, eye, lip, tongue, upper airway), facial hypotonia, rash, urticaria, pruritus, flushing, and erythema occurred in patients with no prior exposure to perflutren-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.
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 of more than 0.3% when DEFINITY is used in according to recommendations. The following adverse reactions have been identified during the post-marketing use of perflutren-containing microsphere products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Fatal 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, worsening or unstable congestive 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), hypotension, hypoxemia, hypoxia, chest pain, respiratory distress, stridor, wheezing.

Hypersensitivity:
- Anaphylactic reaction, anaphylactic shock, bronchospasm, throat tightening, 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

Pregnancy Category B

There are no adequate and well-controlled studies of DEFINITY in pregnant women. Reproduction studies performed in rats and rabbits at doses up to 24 and 15 times the human dose based on body surface area (in rats and rabbits respectively) revealed no evidence of impairment of 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.

8.3 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)). Because many drugs are excreted in human milk, caution should be exercised when DEFINITY is administered to a nursing mother.

8.4 Pediatric Use

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

The safety and injectability 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, 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>Body system</th>
<th>Total Number of Subjects with an Adverse Reaction</th>
<th>Body system</th>
<th>Total Number of Subjects with an Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEFINITY (N=1716)</td>
<td></td>
<td>DEFINITY (N=1716)</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>(%)</td>
<td>n</td>
<td>(%)</td>
</tr>
<tr>
<td>Body system preferred term</td>
<td></td>
<td>Body system preferred term</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>(%)</td>
<td>n</td>
<td>(%)</td>
</tr>
<tr>
<td>Application Site Disorders</td>
<td>11 (0.6)</td>
<td>Injection Site Reactions</td>
<td>11 (0.6)</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>41 (2.4)</td>
<td>Body as a Whole</td>
<td>20 (1.2)</td>
</tr>
<tr>
<td>Back/renal pain</td>
<td>13 (0.8)</td>
<td>Back/renal pain</td>
<td>12 (0.7)</td>
</tr>
<tr>
<td>Central and peripheral nervous system disorders</td>
<td>54 (3.1)</td>
<td>Central and peripheral nervous system disorders</td>
<td>40 (2.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (0.6)</td>
<td>Headache</td>
<td>11 (0.6)</td>
</tr>
<tr>
<td>Gastrointestinal system</td>
<td>31 (1.8)</td>
<td>Gastrointestinal system</td>
<td>31 (1.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>17 (1.0)</td>
<td>Gastrointestinal system</td>
<td>31 (1.8)</td>
</tr>
<tr>
<td>Vascular (extracardiac) disorders</td>
<td>19 (1.1)</td>
<td>Nausea</td>
<td>17 (1.0)</td>
</tr>
<tr>
<td>Urinary</td>
<td>19 (1.1)</td>
<td>Vascular (extracardiac) disorders</td>
<td>19 (1.1)</td>
</tr>
</tbody>
</table>

N=Sample size 1716 subjects who received activated DEFINITY

n=Number of subjects reporting at least one Adverse Reaction

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

Body as a Whole: Fatigue, fever, hot flushes, pain, rigors, and syncope

Cardiovascular: Abnormal ECGs, bradycardia, tachycardia, palpitation, hypertension and hypotension

Digestive: Dyspepsia, dry mouth, tongue disorder, toothache, abdominal pain, diarrhea and vomiting

Hematologic: Granulocytosis, leukocytosis, leukenopenia, and eosinophilia

Musculoskeletal: Arthralgia

Nervous System: Leg cramps, hypertonias, vertigo and paresthesia

Platelet, Bleeding, and Clotting: Hematoma

Respiratory: Coughing, hypoxia, pharyngitis, rhinitis and dyspnea

Special Senses: Decreased hearing, conjunctivitis, abnormal vision and taste perversion

Skin: Pruritus, rash, erythematosus rash, urticaria, increased sweating, and dry skin

Urine: Albuminuria

11 DESCRIPTION

DEFINITY (Perflutren Lipid Microsphere) Injectable Suspension is an ultrasound contrast agent. The DEFINITY vial contains components that upon activation yield perflutren liquid microspheres. The vial contains a clear, colorless, non-pyrogenic, hyperonic liquid, which upon activation with the aid of a VIALMIX, provides a homogeneous, opaque, milky injectable suspension. These acoustic properties of activated DEFINITY provide contrast enhancement of the left ventricular chamber and aid delineation of the myocardium.

To a known degree, the drug has been shown to be effective for these uses and for the other labeled indications.

DEFINITY is administered by intravenous injection. It has been used for the enhancement of the left ventricular chamber and aid delineation of the myocardium.

DEFINITY is a clear, colorless, sterile, non-pyrogenic, hypertonic liquid, that upon activation yield perflutren lipid microspheres. The vial contains a clear, colorless, sterile, non-pyrogenic, hypertonic liquid, that upon activation yield perflutren lipid microspheres. The suspension of activated DEFINITY is a suspension of perflutren lipid microspheres. The concentrated suspension contains 0.75 mg lipid blend (consisting of 0.045 mg DPPA, 0.401 mg DPPE, 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.

Prior to VIALMIX activation, the DEFINITY vial contains 6.52 mg/ml octafluoropropane in the headspace. Each mL of the clear liquid contains 0.75 mg lipid blend [consisting of 0.045 mg DPPA, 0.401 mg DPPE, 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 10^6 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 2 Microsphere Size Distribution

<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>n=Sample size 1716 subjects who received activated DEFINITY</td>
<td>1.1 µm – 3.3 µm</td>
<td>98%</td>
<td>20 µm</td>
</tr>
</tbody>
</table>

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Perflutren lipid 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 0.8.

12.2 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 59 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 partitioning in blood was 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 DEFINTY 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 DEFINTY have not been performed to evaluate carcinogenic potential. Evidence of genotoxicity was not found in the following studies with activated DEFINTY: 1) bacterial mutagenesis assay (Ames assay), 2) in vitro mammalian mutagenesis assay, 3) in vivo human 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 DEFINTY 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 DEFINTY and 41 placebo). In this group, 154 (61.8%) 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 DEFINTY was evaluated in four controlled clinical trials: Two open-label 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 µg/kg activated DEFINTY. 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 DEFINTY 10 µg/kg activated DEFINTY patients, respectively. The outcome measure for assessing the effectiveness of activated DEFINTY 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 µg/kg of activated DEFINTY 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 2 out of 4 readers for the apical 2-chamber view.

Ventricular Chamber Enhancement

Left ventricular chamber enhancement after an activated DEFINTY dose of 10 µg/kg was significantly increased from baseline compared to placebo in both views at the mid-ventricular and apical levels at end-diastole. Similar results were noted at end-systole, with the exception of the 4-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><strong>Study A</strong> (N = 67)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Apical 2-chamber</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.0(3.4)</td>
<td>4.7(2.8)</td>
<td>7.1(3.3)</td>
</tr>
<tr>
<td>Post-DEFINTY</td>
<td>8.3(3.7)</td>
<td>5.2(2.6)</td>
<td>7.6(3.3)</td>
</tr>
<tr>
<td><strong>Apical 4-chamber</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.1(3.3)</td>
<td>4.3(2.6)</td>
<td>7.6(3.3)</td>
</tr>
<tr>
<td>Post-DEFINTY</td>
<td>9.1(3.3)</td>
<td>5.1(2.6)</td>
<td>8.5(3.3)</td>
</tr>
<tr>
<td><strong>Study B</strong> (N = 59)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Apical 2-chamber</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.3(2.6)</td>
<td>7.8(5.3)</td>
<td>4.1(2.4)</td>
</tr>
<tr>
<td>Post-DEFINTY</td>
<td>5.5(4.7)</td>
<td>8.0(5.3)</td>
<td>5.5(4.4)</td>
</tr>
<tr>
<td><strong>Apical 4-chamber</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>5.4(2.7)</td>
<td>9.2(5.9)</td>
<td>5.9(5.3)</td>
</tr>
<tr>
<td>Post-DEFINTY</td>
<td>7.1(3.5)</td>
<td>11.5(5.1)</td>
<td>7.3(3.5)</td>
</tr>
<tr>
<td>Activated DEFINTY Bolus Dose = 10 µg/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Significant change from baseline (paired t-test, p&lt;0.05)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In an open administration, cross over trial, 64 patients were randomized to receive both bolus (10 µg/kg) and infusion (1.3 mL activated DEFINTY in 50 mL saline at the rate of 4 mL/min) dosing of activated DEFINTY. Outcome measures for this study included clinically useful ventricular cavity enhancement and endocardial border length. Similar results were seen as described above.

Optimal activated DEFINTY doses and device settings for Harmonic imaging have not been established.

14.2 Pulmonary Hemodynamic Effects

The impact of DEFINTY 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 hemorrhagic, or ECG changes were observed. This study did not assess the effect of DEFINTY on visualization of cardiac or pulmonary structures.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DEFINTY 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 (11994-011-04)
- Sixteen (16) 2mL vials per kit - NDC (11994-011-16)

16.2 Storage and Handling

Store between 2-8°C (36°F-46°F).

17 PATIENT COUNSELING INFORMATION

Advise patients to inform their healthcare provider if they develop any symptoms of hypersensitivity after DEFINTY administration, including rash, wheezing, or shortness of breath.
2017 Medicare Reimbursement Information Lantheus Medical Imaging

1. American Medical Association CPT


Questions regarding reimbursement for Lantheus Medical Imaging products?

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