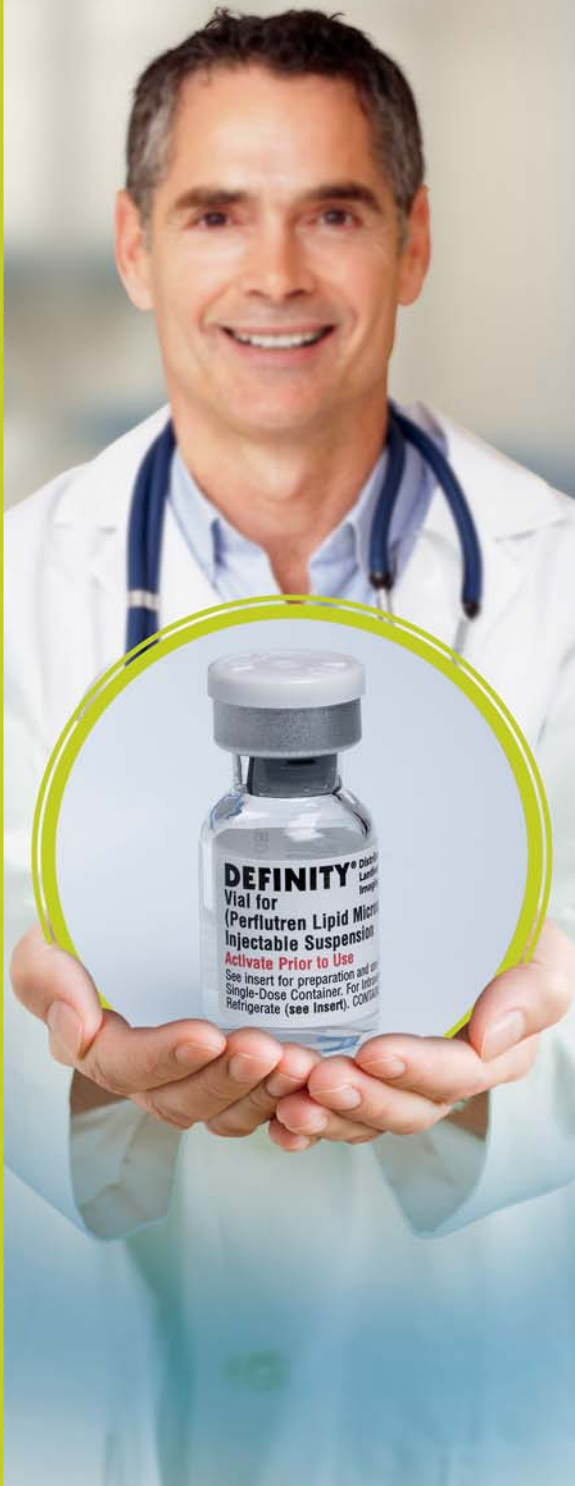


DEFINITY[®]
VIAL FOR (Perflutren Lipid Microsphere)
INJECTABLE SUSPENSION

Medicare Reimbursement Information



2017

2017 Medicare Reimbursement Information Lantheus Medical Imaging

Questions regarding reimbursement for Lantheus Medical Imaging products?

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

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1. Basic Reimbursement Background and Settings

CPT – Current Procedural Terminology

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

HCPCS - Healthcare Common Procedure Coding System

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

HCPCS code for DEFINITY®

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

C-codes

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

Q-codes

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

NDC codes – National Drug Code

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

NDC codes DEFINITY®

- NDC 1 vial 11994-011-01
- NDC 4 vial kit 11994-011-04
- NDC 16 vial kit 11994-011-16

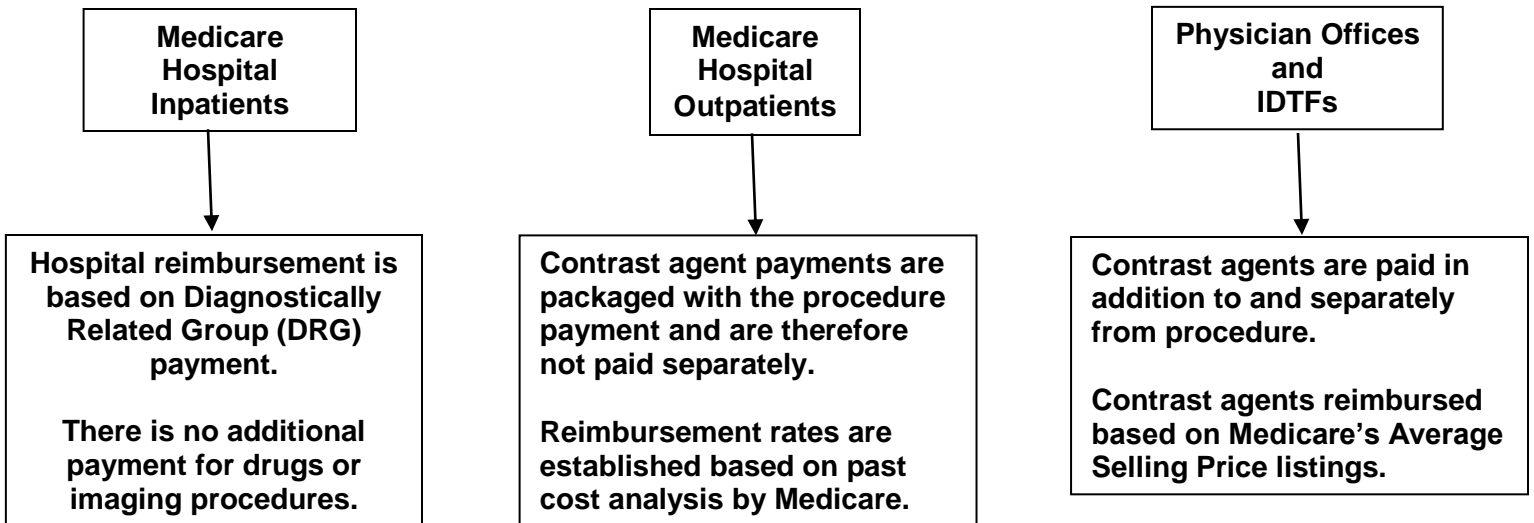
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Echocardiography codes^{1,2}

- **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”²**
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.



2017 Medicare Reimbursement Information Lantheus Medical Imaging

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.

| | |
|---|-----------------------|
| 93306 TTE complete with Doppler and color flow without contrast | \$449.50 ³ |
| C8929 TTE complete with Doppler and color flow with contrast | \$656.63 |

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.

APCs Echo Procedures - Without Contrast³

APC 5523 - \$225.81

Level 2 Diagnostic Radiology Without Contrast

93308 TTE follow up or limited
(69 additional diagnostic radiology codes in APC 5523)

APC 5524 - \$449.50

Level 4 Diagnostic Radiology Without Contrast

93303 TTE congenital, complete
93304 TTE congenital follow up or limited
93306 TTE complete with Doppler and color flow
93307 TTE complete w/o Doppler and color flow
93312 TEE include placement, acq, inter, report
93313 TEE placement only
93315 TEE cong, placement, acq, inter, report
93316 TEE congenital placement only
93318 TEE monitor, placement, acq, inter
93350 Stress TTE (w/o ECG monitoring)
93351 Stress TTE (includes ECG monitoring)
(25 additional diagnostic radiology codes in APC 5524)

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

APCs Echo Procedures - With Contrast³

APC 5572 - \$426.34

Level 2 Diagnostic Radiology With Contrast

C8924 TTE follow up or limited with contrast
(38 additional diagnostic radiology codes in APC 5572)

APC 5573 - \$656.63

Level 3 Diagnostic Radiology With Contrast

C8921 TTE congenital complete with contrast
C8923 TTE complete w/o Doppler, CF with contrast
C8922 TTE congenital follow up or limited with contrast
C8925 TEE placement, acq, inter, report with contrast
C8926 TEE congenital placement, image, inter, report
with contrast
C8927 TEE monitor, placement, acq, inter, w/ contrast
C8928 Stress TTE (no ECG monitoring) with contrast
C8929 TTE comp. with Dop., color flow with contrast
C8930 Stress TTE (with ECG monitoring) with contrast
(4 additional diagnostic radiology codes in APC 5573)

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

For complete code descriptors see page 8

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|--------------------|--|--------------------|--|--------------------|-------------|--------------------------------|--|--------------------|--|---------------------------------|--|---------------------------------|--|----------------------------|-----------------|----|--|----|--|--------------------------------------|--|--|--|----|--|
| 1 Anytown Hospital | | | | | | | | | | 2 | | | | | | | | | | 3a PAT. CNTL. # | | 4 TYPE OF BILL | | | |
| 100 Main St | | | | | | | | | | | | | | | | | | | | b. MED. REC. # | | | | | |
| Anytown Anystate | | | | | | | | | | | | | | | | | | | | 5 FED. TAX NO. | | 6 STATEMENT COVERS PERIOD FROM THROUGH | | 7 | |
| 8 PATIENT NAME | | | | | a Doe, John | | | | | 9 PATIENT ADDRESS | | | | | a 123 Maple Ave | | | | | | | | | | |
| b | | | | | | | | | | | | | | | | | | | | | | | | | |
| 10 BIRTHDATE | | 11 SEX | | 12 DATE | | ADMISSION 13 HR 14 TYPE 15 SRC | | 16 DHR | | 17 STAT | | 18 | | 19 | | 20 | | 21 | | CONDITION CODES 22 23 24 25 26 27 28 | | 29 ACDT STATE | | 30 | |
| xx/xx/1940 | | | | | | | | | | | | | | | | | | | | | | | | | |
| 31 OCCURRENCE CODE | | 32 OCCURRENCE DATE | | 33 OCCURRENCE CODE | | 34 OCCURRENCE DATE | | 35 OCCURRENCE CODE | | 36 OCCURRENCE SPAN FROM THROUGH | | 37 OCCURRENCE SPAN FROM THROUGH | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | |
| 38 | | | | | | | | | | 39 VALUE CODES CODE AMOUNT | | 40 VALUE CODES CODE AMOUNT | | 41 VALUE CODES CODE AMOUNT | | | | | | | | | | | |
| | | | | | | | | | | a | | b | | c | | d | | | | | | | | | |
| | | | | | | | | | | b | | c | | d | | | | | | | | | | | |
| | | | | | | | | | | c | | d | | | | | | | | | | | | | |
| | | | | | | | | | | d | | | | | | | | | | | | | | | |

| 42 REV. CD. | 43 DESCRIPTION | 44 HCPCS / RATE / HIPPS CODE | 45 SERV. DATE | 46 SERV. UNITS | 47 TOTAL CHARGES | 48 NON-COVERED CHARGES | 49 |
|-------------|---------------------------------|------------------------------|---------------|----------------|------------------|------------------------|----|
| 1 | TTE echo complete with contrast | C8929 | 01/05/2017 | 1 | xx xx | | 1 |
| 2 | peflutren lipid microspheres | Q9957 | 01/05/2017 | 2 | xx xx | | 2 |
| 3 | | | | | | | 3 |
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| 22 | | | | | | | 22 |
| 23 | | | | | | | 23 |

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

Q-code identifies which contrast agent was used.

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|----------------------------------|--|-------------------------|--|------------------|--|------------------|--|--------------|--|----------------------------|--|------------|--|--------|------------------------|--------|--|--------|--|------------------|--|--------------|--|-------------------|------------------------|--------------------|--|--------|--|
| 50 PAYER NAME | | | | | | | | | | 51 HEALTH PLAN ID | | | | | | | | | | 52 REL. INFO | | 53 ASG. BEN. | | 54 PRIOR PAYMENTS | | 55 EST. AMOUNT DUE | | 56 NPI | |
| A Medicare | | | | | | | | | | | | | | | | | | | | | | | | | | 57 OTHER PRV ID | | | |
| B | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| C | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 58 INSURED'S NAME | | | | | | | | | | 59 P.REL | | | | | 60 INSURED'S UNIQUE ID | | | | | 61 GROUP NAME | | | | | 62 INSURANCE GROUP NO. | | | | |
| A | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| B | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| C | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 63 TREATMENT AUTHORIZATION CODES | | | | | | | | | | 64 DOCUMENT CONTROL NUMBER | | | | | | | | | | 65 EMPLOYER NAME | | | | | | | | | |
| A | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| B | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| C | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 66 DX | | 67 | | A | | B | | C | | D | | E | | F | | G | | H | | 68 | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 69 ADMIT DX | | 70 PATIENT REASON DX | | a | | b | | c | | 71 PPS CODE | | 72 ECI | | | | | | | | 73 | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 74 PRINCIPAL PROCEDURE CODE | | 75 OTHER PROCEDURE CODE | | 76 ATTENDING NPI | | 77 OPERATING NPI | | 78 OTHER NPI | | 79 OTHER NPI | | 80 REMARKS | | 81CC a | | 81CC b | | 81CC c | | 81CC d | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
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2017 Medicare Reimbursement Information Lantheus Medical Imaging

4. Complete code descriptors. Without contrast left column, with contrast right column

| | Echo without contrast ¹ | | | Echo with contrast ² |
|-------|--|---|-------|---|
| 93303 | Transthoracic echocardiography for congenital cardiac anomalies; complete | ↔ | C8921 | Transthoracic echocardiography with contrast, or without contrast followed by with contrast, for congenital cardiac anomalies; complete |
| 93304 | Transthoracic echocardiography for congenital cardiac anomalies; follow-up or limited study | ↔ | C8922 | Transthoracic echocardiography with contrast, or without contrast followed by with contrast, for congenital cardiac anomalies; f/u or limited study |
| 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 | ↔ | 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 |
| 93307 | Echocardiography, transthoracic, real-time, with image documentation (2D), includes M-mode recording, when performed, complete, without spectral or color Doppler echocardiography | ↔ | 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 |
| 93308 | Echocardiography, transthoracic, real-time, with image documentation (2D), includes M-mode recording, when performed, follow-up or limited study | ↔ | 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 |
| 93312 | Echocardiography, transesophageal, real-time with image documentation (2D) (with or without M-mode recording); including probe placement, image acquisition, interpretation and report | ↔ | 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 |
| 93315 | Transesophageal echocardiography for congenital cardiac anomalies; including probe placement image acquisition, interpretation and report | ↔ | 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 |
| 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 | ↔ | 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 |
| 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 pharmacologically induced stress, with interpretation and report | ↔ | 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 |
| 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. | ↔ | 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 |
| 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, 93308, 93312, 93314, 93315, 93317, 93350, 93351, 93555) Report 0399T once. | | NA | |
| NA | | | 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, 93308 93350, 93351) |

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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)”.

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6. 2017 National Average Payments for Physician Office IDTF⁵

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

| CPT | | Short Descriptor | Payment | | CPT | | Short Descriptor | Payment |
|-------|----|---------------------------|------------|--|-------|----|------------------------------|------------|
| 93303 | G | TTE limited congenital | 240.10 | | 93315 | 26 | TEE cong. acq, inter, report | 131.71 |
| 93303 | TC | TTE limited congenital | 175.14 | | | | | |
| 93303 | 26 | TTE limited congenital | 64.96 | | 93317 | 26 | TEE acq, inter, report only | 95.46 |
| | | | | | | | | |
| 93304 | G | TTE limited | 157.55 | | 93318 | 26 | TEE monitoring | 107.31 |
| 93304 | TC | TTE limited | 120.23 | | | | | |
| 93304 | 26 | TTE limited | 37.32 | | 93320 | G | Doppler echo | 54.91 |
| | | | | | 93320 | TC | Doppler echo | 36.25 |
| 93306 | G | TTE comp, Dop, CF | 231.48 | | 93320 | 26 | Doppler echo | 18.66 |
| 93306 | TC | TTE comp, Dop, CF | 166.52 | | | | | |
| 93306 | 26 | TTE comp, Dop, CF | 64.96 | | 93321 | G | Doppler echo F/U or limited | 27.63 |
| | | | | | 93321 | TC | Doppler echo F/U or limited | 20.10 |
| 93307 | G | TTE comp, w/o Dop, CF | 131.71 | | 93321 | 26 | Doppler echo F/U or limited | 7.54 |
| 93307 | TC | TTE comp, w/o Dop, CF | 85.77 | | | | | |
| 93307 | 26 | TTE comp, w/o Dop, CF | 45.94 | | 93325 | G | Doppler color flow add-on | 25.84 |
| | | | | | 93325 | TC | Doppler color flow add-on | 22.61 |
| 93308 | G | TTE F/U or limited | 126.69 | | 93325 | 26 | Doppler color flow add-on | 3.23 |
| 93308 | TC | TTE F/U or limited | 100.49 | | | | | |
| 93308 | 26 | TTE F/U or limited | 26.20 | | 93350 | G | Stress TTE only | 244.04 |
| | | | | | 93350 | TC | Stress TTE only | 171.55 |
| 93312 | G | TEE place acq,int, rep. | 249.79 | | 93350 | 26 | Stress TTE only | 72.50 |
| 93312 | TC | TEE place acq,int, rep. | 138.17 | | | | | |
| 93312 | 26 | TEE place acq,int, rep. | 111.61 | | 93351 | G | Stress TTE with exercise | 274.91 |
| | | | | | 93351 | TC | Stress TTE with exercise | 188.06 |
| 93314 | G | TEE acq, inter, report | 240.10 | | 93351 | 26 | Stress TTE with exercise | 86.85 |
| 93314 | TC | TEE acq, inter, report | 146.78 | | | | | |
| 93314 | 26 | TEE acq, inter, report | 93.31 | | 93352 | G | Use of contrast at stress | 34.45 |
| 0399T | | Myocardial strain imaging | contractor | | 0439T | | Myocardial perfusion echo | contractor |

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>

For complete text for CPT code descriptors see page 8.

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7. Indications, Contraindications and Important Safety Information

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.



331 Treble Cove Road
N. Billerica, Massachusetts 01862
USA

DEFINITY®

VIAL FOR (Perflutren Lipid Microsphere)
INJECTABLE SUSPENSION

FOR INTRAVENOUS USE

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
Initial U.S. Approval: 2001

WARNING: SERIOUS CARDIOPULMONARY REACTIONS

See full prescribing information for complete boxed warning

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

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

RECENT MAJOR CHANGES

Contraindications (4) 01/2017
Warnings and Precautions (5.3) 01/2017

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

The recommended bolus dose for activated DEFINITY is 10 microliters (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.

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 during or following perflutren-containing microsphere administration. (5.1)

Serious acute hypersensitivity reactions have occurred in patients with no prior exposure to perflutren-containing microsphere products (5.2, 6).

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

ADVERSE REACTIONS

The most common adverse reactions ($\geq 0.5\%$) are headache, back/renal pain, flushing, nausea, chest pain, injection site reactions, and dizziness (6).

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

See 17 for Patient Counseling Information.

Revised: 1/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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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 *Contraindications* (4)].
- Always have resuscitation equipment and trained personnel readily available.

1 INDICATIONS AND USAGE

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.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

- DEFINITY is intended for administration only after activation in the VIALMIX apparatus. Before injection, this product must be activated and prepared according to the instructions outlined below. 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.

2.2 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.

2.3 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

- Allow the vial to warm to room temperature before starting the activation procedure.
- 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 reactivate 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 the "VIALMIX calibration and replacement procedures" to ensure that a properly functioning VIALMIX is used.

- 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.
- Invert the vial and withdraw the activated milky white suspension using the Intellipin (Dispensing Pin), the PINSYNC (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.
- 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 septicemia 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 DOSAGE FORMS AND STRENGTHS

DEFINITY is supplied as a single use 2-mL clear glass vial containing a clear liquid in packages of four (4) and sixteen (16) single-use vials. Prior to activation, the headspace of each vial contains 6.52 mg/mL octafluoropropane and the clear liquid contains 0.75mg/mL of a lipid blend. After activation, each vial contains a maximum of 1.2×10^{10} perflutren lipid microspheres, and about 150 microL/mL (1.1 mg/mL) octafluoropropane [see *Description* (11)].

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, 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 perflutren-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 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.

5.3 Systemic Embolization

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

5.4 Ventricular Arrhythmia Related to High Mechanical Index

High ultrasound mechanical index values may cause 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 Dosage 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 activated DEFINITY. In this group, 1063 (61.9%) were male and 653 (38.1%) were female, 1328 (77.4%) were White, 258 (15.0%) were Black, 74 (4.3%) were Hispanic, and 56 (3.3%) were classified as other racial or ethnic groups. The mean age was 56.1 years (range 18 to 93). Of these, 144 (8.4%) had at least one adverse reaction (Table 1). There were 26 serious adverse events and 15 (0.9%) subjects discontinued because of an adverse event.

Serious Adverse Reactions

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

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

Table 1 New-Onset Adverse Reactions Occurring in ≥0.5% of All DEFINITY-Treated Subjects

| | DEFINITY (N=1716) | |
|---|----------------------|--------|
| | n | (%) |
| Total Number of Adverse Reactions | 269 | |
| Total Number of Subjects with an Adverse Reaction | 144 | (8.4%) |
| Body system | | |
| Preferred term | n | (%) |
| Application Site Disorders | 11 | (0.6) |
| Injection Site Reactions | 11 | (0.6) |
| Body as a Whole | 41 | (2.4) |
| Back/renal pain | 20 | (1.2) |
| Chest pain | 13 | (0.8) |
| Central and peripheral nervous system disorder | 54 | (3.1) |
| Headache | 40 | (2.3) |
| Dizziness | 11 | (0.6) |
| Gastrointestinal system | 31 | (1.8) |
| Nausea | 17 | (1.0) |
| Vascular (extracardiac) disorders | 19 | (1.1) |
| Flushing | 19 | (1.1) |

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 ≤0.5% of the activated DEFINITY-dosed 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

Hematology: Granulocytosis, leukocytosis, leukopenia, and eosinophilia

Musculoskeletal: Arthralgia

Nervous System: Leg cramps, hypertonia, 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, erythematous rash, urticaria, increased sweating, and dry skin

Urinary: Albuminuria

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 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, supra-ventricular tachycardia, ventricular fibrillation, ventricular tachycardia), hypertension, hypotension, dyspnea, hypoxia, chest pain, respiratory distress, stridor, wheezing.

Hypersensitivity

Anaphylactic reaction, 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

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 impaired fertility or harm to the fetus due to DEFINITY. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 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 of injecting activated 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

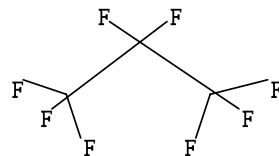
In clinical trials, the overall incidence of adverse reactions was similar for the <65 year age group and the ≥65 year age group. Of the total number of subjects in clinical trials of DEFINITY, 144 (33%) were 65 and over. No overall differences in safety or effectiveness were observed between these subjects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

11 DESCRIPTION

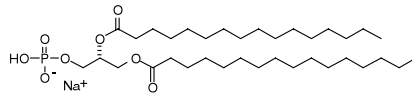
DEFINITY (Perflutren Lipid Microsphere) Injectable Suspension is an ultrasound contrast agent. The DEFINITY vial contains components that upon activation yield perflutren lipid microspheres. The vial contains a clear, colorless, sterile, non-pyrogenic, hypertonic liquid, which upon activation with the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

The perflutren lipid microspheres are composed of octafluoropropane encapsulated in an outer lipid shell consisting of (R) - hexadecanoic acid, 1-[(phosphonoxy)methyl]-1,2-ethanediyl ester, monosodium salt (abbreviated DPPA); (R) - 4-hydroxy-N,N,N-trimethyl-10-oxo-7-[(1-oxohexadecyl)oxy]-3,4,9-trioxo-4-phosphapentacosan-1-aminium, 4-oxide, inner salt (abbreviated DPPC); and (R)- α -[6-hydroxy-6-oxido-9-[(1-oxohexadecyl)oxy]-5,7,11-trioxo-2-aza-6-phosphahexacos-1-yl]- ω -methoxypoly (ox-1,2-ethanediyl), monosodium salt (abbreviated MPEG5000 DPPE).

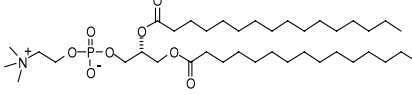
Octafluoropropane is chemically characterized as 1,1,1,2,2,3,3,3-octafluoropropane. It has a molecular weight of 188, empirical formula of C₃F₈ and has the following structural formula:



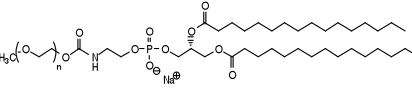
DPPA has a molecular weight of 670, empirical formula of C₂₅H₅₈O₈PNa and following structural formula:



DPPC has a molecular weight of 734, empirical formula of C₄₀H₈₀NO₈P, and following structural formula:



MPEG5000 DPPE has an approximate molecular weight of 5750 represented by empirical formula C₂₆₅H₅₂₇NO₁₂₃PNa, and the following structural formula:



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 DPPC, and 0.304 mg MPEG5000 DPPE), 103.5 mg propylene glycol, 126.2 mg glycerin, 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 10¹⁰ 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

| | Microsphere particle size parameters |
|------------------------------|--------------------------------------|
| Mean diameter range | 1.1 μ m – 3.3 μ m |
| Percent less than 10 μ m | 98% |
| Maximum diameter | 20 μ m |

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 0.7 (1.8 MHz frequency). In clinical trials, the majority of the patients were imaged at or below a mechanical index of 0.8.

12.2 Pharmacokinetics

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

Distribution

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

Metabolism

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

Elimination

OFF was not detectable after 10 minutes in most subjects either in the blood or in expired air. OFF 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 (OFF) was evaluated in subjects (n=11) with chronic obstructive pulmonary disease (COPD). The mean half-life of OFF in blood was 1.9 minutes. The total lung clearance of OFF 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 vitro* 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 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 (73.5%) were White, 38 (15.3%) were Black, 21 (8.4%) were Hispanic, and 7 (2.8%) were classified as other racial or ethnic groups. The mean age was 53.9 years (range 18 to 87).

Activated DEFINITY was evaluated in four controlled clinical trials: Two open-label baseline controlled, 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), endocardial border length (EBL) obtained by direct measurement, and qualitative assessment of wall motion.

In the two placebo-controlled studies a total of 123 subjects were randomized in 1:2 ratio to receive two IV bolus doses of either saline (placebo) or activated DEFINITY 10 microL/kg (17 placebo vs. 33 activated DEFINITY patients 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-systole was statistically significant for 3 out of 4 readers for the apical 4-chamber view and for 2 out of 4 readers for the apical 2-chamber view.

Ventricular Chamber Enhancement

Left ventricular chamber enhancement after an activated DEFINITY dose of 10 microL/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.

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 established. 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

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

| Study/View | Endocardial Border Length – Blinded Read | | | |
|--|--|------------|-------------------------|-----------|
| | Mean(SD) at End-Diastole | | Mean(SD) at End-Systole | |
| | Reader 1 | Reader 2 | Reader 1 | Reader 2 |
| Study A: (N = 67) | | | | |
| Apical 2-chamber | | | | |
| Baseline | 8.0(3.4) | 4.7(2.8) | 7.1(3.3) | 4.3(2.6) |
| Post-DEFINITY | 12.8(5.2)* | 5.8(2.6)* | 10.6(5.0)* | 4.4(2.3) |
| Apical 4-chamber | | | | |
| Baseline | 8.1(3.3) | 4.5(2.6) | 7.6(3.2) | 4.5(2.7) |
| Post-DEFINITY | 13.5(5.2)* | 6.8(3.3)* | 11.5(4.4)* | 5.3(3.1) |
| Study B: (N = 59) | | | | |
| Apical 2-chamber | | | | |
| Baseline | 4.3(2.6) | 7.8(5.3) | 4.1(2.4) | 6.5(5.1) |
| Post-DEFINITY | 5.7(4.7)* | 8.2(6.5) | 5.5(4.4)* | 6.9(6.3) |
| Apical 4-chamber | | | | |
| Baseline | 4.0(2.7) | 9.2(5.9) | 3.8(2.6) | 7.3(5.6) |
| Post-DEFINITY | 7.1(5.5)* | 11.5(7.5)* | 5.9(5.3)* | 8.7(6.3)* |
| Activated DEFINITY Bolus Dose = 10 µL/kg | | | | |
| * Significant change from baseline (paired t-test, p<0.05) | | | | |

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

Optimal activated DEFINITY doses and device settings for harmonic imaging have not been established.

14.2 Pulmonary Hemodynamic Effects

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

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

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

16.2 Storage and Handling

Store between 2-8°C (36°-46°F).

17 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.

Distributed By
Lantheus Medical Imaging
331 Treble Cove Road
N. Billerica, Massachusetts 01862 USA



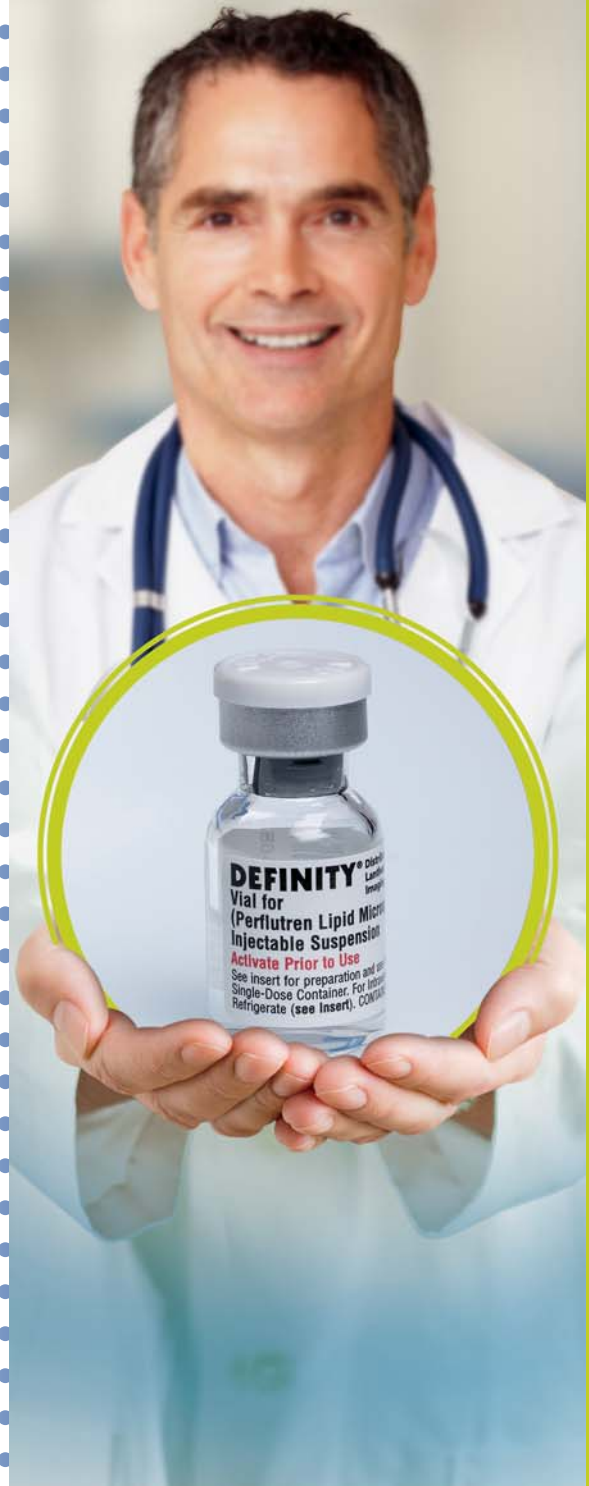
For ordering, tel. toll free: 800-299-3431
All Other Business: 800-362-2668
(For Massachusetts and International, call 978-667-9531)

2017 Medicare Reimbursement Information Lantheus Medical Imaging

1. American Medical Association CPT
2. <https://www.cms.gov/Medicare/Coding/HCPSCReleaseCodeSets/Alpha-Numeric-HCPCS-Items/2017-Alpha-Numeric-HCPCS-File.html?DLPage=1&DLEntries=10&DLSort=0&DLSortDir=descending>
3. See addendum B at <https://www.cms.gov/apps/ama/license.asp?file=/Medicare/Medicare-Fee-for-Service-Payment/HospitalOutpatientPPS/Downloads/CMS-1656-FC-2017-OPPS-FR-Addenda.zip>
4. <http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/index.html?redirect=/McrPartBDrugAvgSalesPrice/>
5. <https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched/PFS-Federal-Regulation-Notices-Items/CMS-1654-F.html?DLPage=1&DLEntries=10&DLSort=2&DLSortDir=descending>
6. <https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/bp102c15.pdf>

Questions regarding reimbursement
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