515188-0904 September 2004

DEFINITY®
Vial for (Perflutren Lipid Microsphere) Injectable Suspension

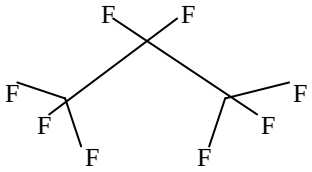
For Intravenous Use

DESCRIPTION

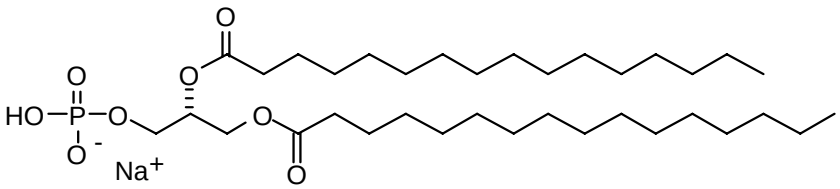
The DEFINITY® vial contains components that upon activation yield perflutren lipid microspheres, a diagnostic drug that is intended to be used for contrast enhancement during the indicated echocardiographic procedures. The vial contains a clear, colorless, sterile, non-pyrogenic, hypertonic liquid, which 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-trioxa-4-phosphapentacosan-1-aminium, 4-oxide, inner salt (abbreviated DPPC); and (R)-∝-[6-hydroxy-6-oxido-9-[(1-oxohexadecyl)oxy]-5,7,11-trioxa-2-aza-6-phosphahexacos-1-yl]- ω-methoxypoly(ox-1,2-ethanediyl), monosodium salt (abbreviated MPEG5000 DPPE).

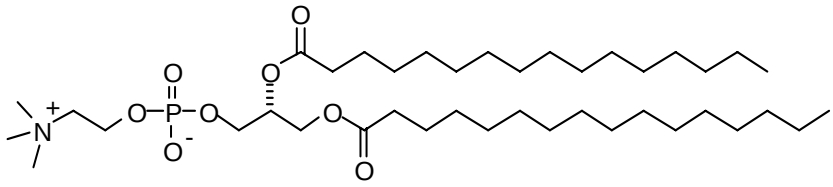
Octafluoropropane is chemically characterized as 1,1,1,2,2,3,3,3-octafluoropropane. It has a molecular weight of 188, empirical formula of C_3F_8 and has the following structural formula:



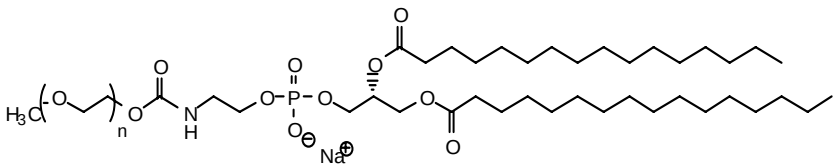
DPPA has a molecular weight of 670, empirical formula of $C_{35}H_{68}O_8PNa$, and following structural formula:



DPPC has a molecular weight of 734, empirical formula of $C_{40}H_{80}NO_8P$, and following structural formula:



MPEG5000 DPPE has an approximate molecular weight of 5750 represented by empirical formula $C_{265}H_{527}NO_{123}PNa$, 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 10^{10} perflutren lipid microspheres, and about 150 µL/mL (1.1 mg/mL) octafluoropropane. The microsphere particle size parameters are listed in Table 1 below:

Table 1: Microsphere Size Distribution

	Microsphere particle size parameters
Mean diameter range	1.1 µm – 3.3 µm
Percent less than 10 µm	98%
Maximum diameter	20 µm

See DEFINITY® Activation, Preparation, and Handling Instructions.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

After activation of DEFINITY® and intravenous injection, the physical acoustic properties of activated DEFINITY® (see DESCRIPTION) provide contrast enhancement of the endocardial borders during echocardiography. The perflutren lipid microspheres exhibit lower acoustic impedance than blood and enhance the intrinsic backscatter of blood.

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.

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 μL/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.

PHARMACOKINETICS

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

Octafluoropropane (OFP) Protein Binding

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

Metabolism

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

Elimination

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

SPECIAL POPULATIONS

The pharmacokinetics of octafluoropropane gas (OFP) were 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.

Microspheres may obstruct the vasculature of some patients. See WARNINGS for use in subjects with cardiac shunts and pulmonary hypertension.

The pharmacokinetics of activated DEFINITY® has not been studied in subjects with hepatic diseases or congestive heart failure.

Gender:

The effects of activated DEFINITY® appeared to be similar in men and women.

Age/Race:

The effects of age and race on the pharmacokinetics of activated DEFINITY® have not been studied.

Pediatrics:

The pharmacokinetics of activated DEFINITY® in pediatric subjects has not been studied. The safety of injecting activated DEFINITY® in neonates and infants with immature pulmonary vasculature has not been studied (see WARNINGS).

Elderly:

The pharmacokinetics of activated DEFINITY® in the elderly has not been studied.

DRUG-DRUG INTERACTIONS

Drug-drug interactions for activated DEFINITY® have not been studied.

CLINICAL TRIALS

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 μL/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 I.V. bolus doses of either saline (placebo) or activated DEFINITY® 10 μL/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 2, compared to baseline, a single bolus dose of 10 μL/kg 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 4 readers for the apical 2-chamber view.

Ventricular Chamber Enhancement: Left ventricular chamber enhancement after an activated DEFINITY® dose of 10 μL/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 42-71% 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 2
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, crossover trial, 64 patients were randomized to receive both bolus (10 µL/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.

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.

CONTRAINDICATIONS

Activated DEFINITY® should not be administered to patients with known hypersensitivity to octafluoropropane or in patients with known cardiac shunts (see WARNINGS).

Activated DEFINITY® should not be administered by direct intra-arterial injection (see WARNINGS).

WARNINGS

CARDIAC SHUNTS:

The safety of activated DEFINITY® in patients with right-to-left, bi-directional, or transient right-to-left cardiac shunts has not been studied. In these patients, phospholipid-encapsulated microspheres can bypass the pulmonary particle-filtering mechanisms and directly enter the arterial circulation. In an animal study utilizing intra-arterial administration of activated DEFINITY®, microsphere trapping was seen in small arterioles < 15 μm, especially at branch points and in capillaries at all doses tested (1-6 times the maximal human dose (MHD) based on body surface area). An animal study utilizing an intra-venous administration did not result in microvascular obstruction because of presumed filtering by the lungs. Extreme caution should be exercised when considering the administration of activated DEFINITY® in patients that may have cardiac shunts.

PULMONARY VASCULAR COMPROMISE:

The safety of activated DEFINITY® in humans with compromised pulmonary vascular beds or with small cross-sectional vascular area has not been studied. Activated DEFINITY® given at a dose of 1 mL/kg (13.5x MHD based on body surface area) increased the respiratory rate and pulmonary arterial pressure (300% and 188%, respectively) in dogs. One dog died displaying clinical signs consistent with cardiopulmonary collapse. Clinical signs consistent with cardiopulmonary collapse were also noted in rats dosed with activated DEFINITY® (multiple-dose study) and included deaths at doses >0.3 mL/kg (2.5x MHD based on body surface area). Additionally, histopathological pulmonary lesions were detected in rats at doses above 0.1 mL/kg (0.8x MHD based on body surface area).

In an animal model with artificially induced acute pulmonary hypertension, activated DEFINITY® did not alter pulmonary arterial pressures; however, this acute model does not test the effects on pulmonary occlusion of a histopathologically compromised vasculature that results from chronic disease. Therefore, activated DEFINITY® should be administered with caution to patients with chronic pulmonary vascular disorders (e.g., severe emphysema, pulmonary vasculitis or other causes of reduced pulmonary vascular cross sectional area).

PRECAUTIONS

General

The safety of microspheres in patients on mechanical ventilation has not been studied.

Diagnostic procedures that involve the use of contrast agents should be carried out under the direction of a physician with a thorough knowledge of the procedure to be performed.

Electrocardiographic (ECG) Changes: High ultrasound mechanical index values may cause microsphere cavitation or rupture and lead to ventricular arrhythmias. Additionally, end-systolic triggering with high mechanical indices has been reported to cause ventricular arrhythmias. The safety of activated DEFINITY® at mechanical indices greater than 0.8 has not been established. The safety of activated DEFINITY® with the use of end-systolic triggering has not been established.

ECG parameters for doses up to 10 μL/kg were monitored in 221 subjects at multiple time points from 1 hour to 72 hours after the first bolus injection. In the 221 subjects, QTc prolongations of >30 msec were noted in 64 (29%) subjects. Forty-six out of 64 subjects with QTc prolongations were further evaluated and 39% (18/46) showed associated cardiac rhythm changes. No malignant cardiac symptomatology or events of syncope were reported as a result of these ECG changes. The effects of concomitant drugs were not studied.

Information For Patients

Patients receiving activated DEFINITY® should be instructed to:

1. Inform your physician or health care provider if you may be pregnant, are trying to become pregnant, or are nursing.
2. Inform your physician or health care provider if you have a congenital heart defect (see CONTRAINDICATIONS and WARNINGS).

Carcinogenesis, Mutagenesis, 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 up to 1mL/kg (24x and 15x maximal human dose based on body surface area, respectively).

Pregnancy Category B

Reproduction toxicity studies have been performed in rats and rabbits at up to 3mL/kg and, 1mL/kg (24x and 15x maximal human dose based on body surface area for rats and rabbits, respectively). The studies revealed no evidence of an effect of activated DEFINITY® treatment on the developing fetus. Adequate and well-controlled studies in pregnant women have not been conducted. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Studies to detect if activated DEFINITY® is excreted in human milk have not been conducted. Because many drugs are excreted in human milk, caution should be exercised when activated DEFINITY® is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of activated DEFINITY® have not been established in the pediatric population (see WARNINGS).

ADVERSE REACTIONS

A total of 1716 subjects were evaluated in 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 treatment-related adverse reaction (Table 3). There were 8 deaths that were attributed to underlying disorders. There were 26 serious adverse events and 15 (0.9%) subjects discontinued because of an adverse event.

Deaths and serious adverse events: Among the 1716 activated DEFINITY® patients, 19 (1.1%) suffered serious cardiopulmonary adverse events including eight deaths. The deaths occurred several days after activated DEFINITY® administration and appear to be related to the course of underlying disease. Of the 11 other serious adverse events, which appeared within days of the drug administration (2-15 days), all appeared to be a progression underlying cardiac and non-cardiac disease.

Discontinuations: There were 10 discontinuations reported with a mean age of 41.5 years. Nine of these patients were discontinued after the first injection. One patient experienced a hypersensitivity reaction with urticaria and pruritus and all the other patients experienced dizziness, chest pain, dyspnea or back pain. Adverse events appeared within minutes (1 – 15 min) of the drug administration and were of moderate intensity resolving usually without treatment within minutes or hours after onset.

For all adverse events, 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. As shown in Table 3, the most common adverse events were reported in the Central and peripheral nervous system (3.1%), Body as a Whole (2.4%) and Gastrointestinal system (1.8%). The most common events were headache (2.3%), back and renal pain (1.2%), flushing (1.1%) and nausea (1.0%).

Table 3. Treatment-Related, New-Onset Adverse Experiences Occurring in ≥0.5% of All Activated DEFINITY®-Treated Subjects

	All activated DEFINITY® (N=1716)	
Total Number of Treatment-Related A.E.'s	269	
Total Number of Subjects with a Treatment-Related A.E.	144	(8.4%)
WHOART body system WHOART 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®

A.E.=Adverse Experience

n=Number of subjects reporting at least one A.E.

Other treatment-related adverse experiences 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, monocytosis 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 and abnormal urine
Miscellaneous: Lymphadenopathy

OVERDOSAGE

The clinical consequences of overdosing with activated DEFINITY® are not known. Treatment of an overdose should be directed toward the support of all vital functions and prompt institution of symptomatic therapy (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

DOSAGE AND ADMINISTRATION

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 Bristol-Myers Squibb Medical Imaging, Inc., 331 Treble Cove Road, North Billerica, MA 01862. For customer orders call 1-800-299-3431.

DEFINITY® may be injected by either an intravenous bolus or infusion.

Bolus: The recommended dose for activated DEFINITY® is 10 microliters (μL)/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 (μL)/kg dose followed by a second 10 mL saline flush may be administered 30 minutes after the first injection to prolong contrast enhancement.

Infusion: The recommended 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.

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.

Imaging: After baseline non-contrast echocardiography is completed, the mechanical index for the ultrasound device should be set at 0.8 or below (see PRECAUTIONS: General). Then inject activated DEFINITY® (as described above) and begin ultrasound imaging immediately. The activated DEFINITY® echocardiogram images should be evaluated in combination with the non-contrast echocardiogram images.

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™ Users Guide.

   WARNING: 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.

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

4. Invert the vial and withdraw the activated milky white suspension using the Intellipin™ (Dispensing Pin) or 18 to 20 gauge syringe needle. Withdraw the material from the middle of the liquid in the inverted vial. DO NOT INJECT AIR INTO THE DEFINITY® VIAL.

5. Use the product immediately after its withdrawal from the vial; do not allow the product to stand in the syringe.

FOR SINGLE USE ONLY: DEFINITY® does not contain bacterial preservative. Bacterial contamination with the risk of post-administration 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.

HOW SUPPLIED

DEFINITY® is supplied as a single use 2-mL clear glass vial containing clear liquid. Each package (clear plastic clamshell) contains four (4) single-use vials.

STORAGE

Store between 2-8°C (36°-46°F) in a refrigerator.

CAUTION: Federal law prohibits dispensing without prescription.

Distributed By
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For ordering, tel. toll free: 800-225-1572
All Other Business: 800-362-2668
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call 978-667-9531)