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DEFINITY®

(Perflutren) (Lipid-Encapsulated Perfluoropropane Microbubbles, Injectable)

Injectable Suspension

The format and contents of this leaflet was determined, checked and approved by the Israeli Ministry of Health 06/2010

WARNING: serious Cardiopulmonary Reactions

Serious cardiopulmonary reactions, including fatalities, have occurred during or within 30 minutes following perflutren-containing microsphere administration.

- Assess all patients for the presence of any condition that precludes DEFINITY® administration (see **CONTRAINDICATIONS**).
- In patients with pulmonary hypertension or unstable cardiopulmonary conditions, monitor vital sign measurements, electrocardiography and cutaneous oxygen saturation during and for at least 30 minutes after DEFINITY® administration (see **WARNINGS**).
- Always have resuscitation equipment and trained personnel readily available.

THERAPEUTIC CLASSIFICATION

Contrast Enhancing Imaging Agent for Echocardiography and Diagnostic Ultrasound of Liver and Kidney.

ACTION AND CLINICAL PHARMACOLOGY

DEFINITY® (perflutren injectable suspension) is an ultrasound contrast imaging agent that is designed to improve echocardiographic and radiologic ultrasound image quality by enhancing the echogenicity of the organs/tissues of interest. DEFINITY® is a sterile, non-pyrogenic suspension of phospholipid-encapsulated perfluoropropane microbubbles that is activated by shaking with the aid of the VIALMIX®, and is used for contrast enhancement during cardiac and abdominal ultrasound imaging procedures.

DEFINITY® microbubbles exhibit lower acoustic impedance than blood. Ultrasound waves are scattered and reflected at the microbubble-blood interface and are ultimately visualized in the ultrasound image. At the frequencies used in diagnostic ultrasound (1-7.5 MHz), the microbubbles resonate, further increasing the extent of ultrasound scattering and reflection.

Pharmacokinetics

The pharmacokinetics of the perfluoropropane (PFP) component of activated DEFINITY® was studied in 12 normal and 12 chronic obstructive pulmonary disease (COPD) patients following a 50 µl/kg dose. PFP was rapidly cleared from the systemic circulation (via the lungs). PFP was not detectable after 10 minutes in most subjects, either in the blood or expired air. In all subjects, maximal concentrations of PFP were achieved at approximately 1.0 to 2.0 minutes after the start of injection.

Doppler ultrasound measurements were performed with DEFINITY® in conjunction with the pharmacokinetic evaluation of PFP. Doppler signal intensity corresponded well with measured and extrapolated PFP concentrations in blood. The time to maximum Doppler signal intensity t_{max} was shown to be similar to the PFP blood t_{max} (1.13 versus 1.77 minutes). The observed 99% drop in Doppler signal intensity within 10 minutes ($t_{½}$ approximately 5 minutes) was in agreement with the decline in measurable blood levels of PFP. Human pharmacokinetic data on the fate of intact or degassed microbubbles is not available.

Metabolism

PFP is a stable gas that is not metabolized. The three lipid components of DEFINITY® (DPPA, DPPC and DPPE) are naturally occurring in man as blood lipids. The amount of these lipids in a dose of DEFINITY® represent ~1% (DPPE), ~0.02% (DPPC) and ~0.002% (DPPA) of the naturally occurring levels in plasma and are expected to follow similar metabolic pathways as reported for endogenous phospholipids.

INDICATIONS AND CLINICAL USE

Echocardiography

DEFINITY® (perflutren injectable suspension) is indicated for contrast-enhanced ultrasound imaging of cardiac structures (ventricular chambers and endocardial borders) and function (regional wall motion) in adult patients with suboptimal echocardiograms.

The safety and efficacy of DEFINITY® with exercise stress or pharmacologic stress testing have not been established.

Abdominal Ultrasound

DEFINITY® is also indicated for contrast-enhanced ultrasound imaging of the liver and kidneys in adult patients to improve the evaluation of pathology.

CONTRAINDICATIONS

Do not administer DEFINITY® (perflutren injectable suspension) to patients with known or suspected:

- Right-to-left, bi-directional, or transient right-to-left cardiac shunts (see **WARNINGS**),
- Hypersensitivity to DEFINITY® or its components (See **WARNINGS** - Hypersensitivity Reactions and **ADVERSE REACTIONS** - Post Market Adverse Drug Reactions).

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

Gas Contrast Agents, for use in diagnostic ultrasound examinations, should not be administered within 24 hours prior to extracorporeal shock wave lithotripsy.

WARNINGS

Serious Cardiopulmonary Reactions:

Serious cardiopulmonary reactions, including fatalities, have occurred during or following perflutren-containing microsphere administration. The risk for these reactions may be increased among patients with pulmonary hypertension or unstable cardiopulmonary conditions (acute myocardial infarction, acute coronary artery syndromes, worsening or unstable congestive heart failure, serious ventricular arrhythmias or respiratory failure, including patients receiving mechanical ventilation). In these patients, monitor vital signs, electrocardiography, and cutaneous oxygen saturation during and for at least 30 minutes after DEFINITY® administration. In the absence of these underlying conditions, observe patients closely during and following DEFINITY® administration.

In postmarketing use, uncommon but serious reactions observed during or shortly following perflutren-containing microsphere administration included fatal cardiac or respiratory arrest, loss of consciousness, convulsions, symptomatic arrhythmias (atrial fibrillation, supraventricular tachycardia, ventricular tachycardia or fibrillation), hypotension, respiratory distress or cardiac ischemia (see **ADVERSE REACTIONS**).

Always have cardiopulmonary resuscitation personnel and equipment readily available prior to DEFINITY® administration and monitor all patients for acute reactions.

Serious immediate hypersensitivity reactions which could be life threatening have been rarely reported within minutes of the administration of DEFINITY®, therefore, patients should be closely monitored. These reactions include anaphylactoid / anaphylactic reactions, shock, bronchospasm, tongue / throat swelling, decreased O2 saturation, loss of consciousness. Therefore, emergency supplies and equipment, and personnel experienced with resuscitative measures should always be available.

In dogs, activated DEFINITY® given at a dose of 1mL/kg (13.5 x maximum human dose based on body surface area) increased the respiratory rate and pulmonary pressure (300% and 188% respectively). One dog died displaying signs consistent with cardiopulmonary collapse. In dogs with artifically induced acute pulmonary hypertension, DEFINITY® (tested up to 200 µl/kg) did not alter hemodynamics (includes pulmonary arterial pressure).

Systemic Embolization of DEFINITY® in Patients with Cardiac Shunts:

The safety of DEFINITY® in patients with right-to-left, bi-directional or transient right-to-left cardiac shunts has not been studied. In these patients, encapsulated microspheres can bypass the pulmonary particle-filtering mechanisms and directly enter the arterial circulation resulting in microvascular occlusion and ischemia. In an animal study utilizing intra-arterial administration of activated DEFINITY®, microspheres trapping was seen in small arterioles < 15 µm, especially at branch points and in capillaries at all doses tested (1-6x the maximal human dose based on body surface area). An animal study utilizing an intravenous administration did not result in microvascular obstruction because of presumed filtering by the lungs. Do not administer DEFINITY® by intra-arterial injection (see **CONTRAINDICATIONS**).

PRECAUTIONS

General Precaution

Diagnostic procedures that involve the use of intravenous contrast-enhancing agents containing microbubbles of gas should be carried out under the direction of a physician with a prerequisite training and a thorough knowledge of the procedure to be performed in appropriate facilities for conducting diagnostic imaging. The recommended dose and mode of administration and procedures of activation of DEFINITY® (perflutren injectable suspension) should be strictly adhered to.

DEFINITY® should be administered with caution in patients with a history of drug allergies, asthma or hay fever, and multiple allergies.

The safety of microbubbles in patients on mechanical ventilation has not been established.

A specific analysis correlating the mechanical index values (0.3 to 1.9) used in clinical trials with DEFINITY® with the observed cardiac disturbances is not available. The safety of DEFINITY® at mechanical indices greater than 0.8 has not been established. Users of diagnostic ultrasound devices should employ exposures, in any relevant mode, which are As Low As Reasonably Achievable (ALARA).

High Ultrasound Mechanical Index: High Ultrasound Mechanical Index (MI) values may cause microspheres cavitation or rupture and in combination with end systolic triggering may induce premature ventricular contractions (PVC). In addition, end-systolic triggering with high MI has been reported to cause ventricular arrhythmias following administration of a microsphere product. In clinical trials with DEFINITY®, the majority of patients were imaged at or below a mechanical index of 0.8. The safety of DEFINITY® at MI values greater than 0.8 or with the use of high mechanical index end-systolic triggering has not been evaluated.

A total of 1716 patients received DEFINITY® in clinical trials. The incidence of treatment-related cardiovascular events was < 0.5% and included: abnormal ECGs, bradycardia, tachycardia, palpitation, hypertension, and hypotension. Two patients had treatment-related cardiac adverse events and associated QTc changes (1 increase and 1 decrease) of ≥ 30 msec from baseline.

QTc Interval Prolongation: In 610 subjects (568 received DEFINITY® and 42 received placebo), ECG parameters after doses up to 40 FL/kg were recorded for up to 72 hours after the first bolus injection. QTc prolongation of ≈30 msec was noted in 70 (12.3%) DEFINITY® treated subjects and in 12 (28.6%) placebo treated subjects. QTc prolongation of >60 msec was noted in 20 (3.5%) DEFINITY® treated subjects and 2 (4.8%) placebo treated subjects.

Use in Pregnancy and Lactation: Results of reproduction toxicity studies in rats and rabbits revealed that DEFINITY® in doses up to 1.0 mL/kg (24x and 15x maximal human dose based on body surface area for rats and rabbits, respectively) did not adversely affect fetal growth, survival or morphological development. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, DEFINITY® should be used in pregnancy only if potential benefit to the mother justifies the potential risk to the fetus.

It is not known whether DEFINITY® is excreted in human milk; therefore, caution should be exercised when DEFINITY® is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in the pediatric population below the age of 16 have not been established.

Drug Interactions: Drug-drug interactions with DEFINITY® have not been studied.

Information For Patients: To assure safe and effective use of DEFINITY®, patients should be advised of the following information and instructions when appropriate:

- to inform their physician if they have a congenital heart defect, or recent worsening of heart or lung conditions
- have had prior reactions to DEFINITY®
- that DEFINITY® may add to the QTc prolonging effects of other drugs such as cisapride, erythromycin, some antipsychotics, and tricyclic antidepressants
- to inform their physician if they are currently receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents
- to inform their physician of any family history of QTc prolongation or proarrhythmic conditions such as recent hypokalemia, significant bradycardia, acute myocardial ischemia, clinically relevant heart failure with reduced left-ventricular ejection fraction or previous history of symptomatic arrhythmias
- to inform their physician if they are or may be pregnant or nursing
- to inform their physician of any medications they take
- to contact their physician if they experience palpitations or fainting spells after injection of DEFINITY®.

ADVERSE REACTIONS

A total of 1716 patients were evaluated in pre-market clinical trials of activated DEFINITY® (perflutren injectable suspension). 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 (range 18 to 93). Of these, 144 (8.4%) patients had at least one treatment-related adverse reaction (Table 1).

Deaths and serious adverse events: Among the 1716 DEFINITY® patients studied, serious adverse events were reported in 30 patients, which included 8 deaths. None of the serious adverse events were considered related to DEFINITY® administration. The 8 deaths occurred several days after DEFINITY® administration and were attributed to underlying disorders. The other serious adverse events reported were attributed to progression or treatment of underlying disorders. However, a role for DEFINITY® in the initiation or course of these adverse events cannot be ruled out.

Discontinuations: There were 15 discontinuations reported with a mean age of 41.5 years. Nine of these patients were discontinued after the first injection. One experienced a hypersensitivity reaction with urticaria and pruritis 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.

Subanalyses by age, gender and race were performed. The overall incidence of AEs was similar for the <65 year age group and the ≥65 year age group, similar in males and in females, and similar among all racial or ethnic groups.

The most frequent adverse events were reported for the Central and Peripheral Nervous System (3.1%), Body as a Whole (2.4%) and Gastrointestinal System (1.8%).

The most frequently occurring treatment-related adverse experiences (AEs) were headache (2.3%), back/renal pain (1.2%), flushing (1.1%), and nausea (1.0%).

The incidence of all treatment-related new-onset adverse experiences occurring in ≥ 0.5% of all patients in DEFINITY® studies are summarized in Table 1.

Table 1
Treatment-Related, New-Onset Adverse Experiences in Clinical Trials Occurring in ≥ 0.5% of All Subjects

	PLACEBO		DEFINITY®	
	n	(%)	n	(%)
Total Number of Subjects	183		1716	
Total Number of Subjects with an AE	13	(7.1)	144	(8.4)
Application Site Disorders	2	(1.1)	11	(0.6)
Injection Site Reactions	2	(1.1)	11	(0.6)
Body as a Whole - General Disorders	1	(0.5)	41	(2.4)
Back Pain	0	(0.0)	20	(1.2)
Chest Pain	0	(0.0)	13	(0.8)
Central and Peripheral Nervous System Disorders	5	(2.7)	54	(3.1)
Headache	4	(2.2)	40	(2.3)
Dizziness	1	(0.5)	11	(0.6)
Gastrointestinal System	2	(1.1)	31	(1.8)
Nausea	1	(0.5)	17	(1.0)
Vascular (extracardiac) disorders	1	(0.5)	19	(1.1)
Flushing	1	(0.5)	19	(1.1)

AE = Adverse Event n = number of subjects

Although headache was the most frequently reported adverse experience, its incidence was similar to placebo.

Data from clinical trials presented in the safety tablehas shown that DEFINITY®, administered intravenously in the recommended dose as a bolus injection or as an infusion, was safe and well tolerated.

Other treatment-related adverse experiences that occurred in < 0.5% of the DEFINITY®-dosed patients 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
Laboratory Abnormalities: Increased bilirubin, AST/SGOT, SGPT/ALT, creatine phosphokinase, LDH, creatinine, glucose and non-protein nitrogen
Miscellaneous: Lymphadenopathy

Post Market Adverse Drug Reactions: The following adverse reactions have been identified during the post-approval 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 cardiac arrests and other serious but non-fatal adverse reactions were uncommonly reported. Most of these uncommon reactions included cardiopulmonary symptoms and signs such as cardiac or respiratory arrest, hypotension, supraventricular and ventricular arrhythmias, respiratory distress or decreased oxygenation (see **WARNINGS**).

Allergic type reactions (e.g. anaphylactoid like reactions) have been reported rarely as part of ongoing post-marketing surveillance (See **Warnings**). Central nervous system reactions, including loss of consciousness, seizures, and / or seizure like reactions have also been reported rarely which may or may not be associated with immediate hypersensitivity reactions.

REPORTING OF SUSPECTED ADVERSE REACTIONS

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

SYMPTOMS AND TREATMENT OF OVERDOSAGE

During clinical trials there was no incidence of an overdose with DEFINITY® (perflutren injectable suspension). Should an overdose be suspected, supportive measures should be taken in response to symptoms.

DOSAGE AND ADMINISTRATION

For Single Use Only
DEFINITY® (perflutren injectable suspension) contains no 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 preparation of DEFINITY® carefully and to adhere to strict aseptic procedures during preparation.

The DEFINITY® vial must be activated prior to use with a mechanical shaking device (VIALMIX®). Upon activation, DEFINITY® appears as a milky white suspension. The activated product has an initial concentration of perflutren of 150±100 µl/mL.

Bolus Administration
The recommended dose for DEFINITY® is a single dose of 10 µl/kg of the activated product by intravenous bolus injection over 30-60 seconds, followed by a 10-mL saline flush. If necessary, a second 10 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
DEFINITY® may also be administered via an I.V. infusion of 1.3 mL added to 50 mL of preservative-free saline. The rate of infusion is suggested to be initiated at 4.0 mL/minute and could be titrated as necessary to achieve optimal image enhancement but should not exceed 10 mL/min. The total dose administered per kg will range from approximately 14.4 µl/kg (90 kg person) to 21.7 µl/kg (60 kg person). Note: DEFINITY® should be used immediately after dilution with preservative-free saline.

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.

Instructions for Preparation of DEFINITY® (Perflutren Injectable Suspension):
1. Allow the vial to warm to room temperature.
2. Activate DEFINITY® by shaking the vial for 45 seconds using the VIALMIX®. Immediately after shaking, DEFINITY® appears as a milky white suspension. **The contents of the vial are not to be administered to the patient without first undergoing the mechanical activation procedure.**
3. Withdraw DEFINITY® from the vial using an 18- to 20-gauge syringe needle. The needle should be positioned to withdraw the material from the middle of the liquid in the inverted vial. **Do not inject air into the vial.**
4. If the product is allowed to sit for more than 5 minutes after VIALMIX® shaking, it should be resuspended with 10 seconds of hand agitation prior to syringe withdrawal.

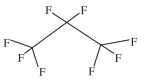
Following activation (steps 1, 2), DEFINITY® can be stored at room temperature and should be used within 12 hours of preparation.

The contents of the vial are intended only for use in the preparation of DEFINITY® and are not to be administered directly to the patient without first undergoing the preparative procedure (steps 1-4).

The contents of the vial are intended for use in a single patient.

PHARMACEUTICAL INFORMATION

Drug Substance
Common Name: Perfluoropropane
Chemical Name: 1,1,1,2,2,3,3,3-Octafluoropropane
Molecular Formula: C_3F_8
Molecular Weight: 188.02 g/mol
Structural Formula:



Description: Colourless gas

Composition
DEFINITY® (perflutren injectable suspension) comes in a 2-mL clear vial containing a 1.5 mL fill volume. Each mL of DEFINITY® contains:

Sodium Chloride, USP	4.87 mg
Propylene Glycol, USP	103.5 mg
Glycerin, USP	126.2 mg
Water for Injection, USP	QS to 1.0 mL
Lipid Blend*	0.75 mg
Sodium phosphate monobasic, monohydrate, ACS	2.34 mg
Sodium phosphate dibasic, heptahydrate, ACS	2.16 mg
Perfluoropropane Gas	perflutren 150±100 µL/mL when shaken (activated)

* The Lipid Blend is composed of the following lipids in a mole % ratio of 10:82:8: 1,2-dipalmitoyl-snglycero-3-phosphatidic acid, monosodium salt (DPPA); 1,2-dipalmitoyl-sn-glycero-3-phosphatidylcholine (DPPC); N-(methoxypolyethylene glycol 5000 carbamoyl)-1,2-dipalmitoyl-snglycero-3-phosphatidylethanolamine, monosodium salt (MPEG5000 DPPE).

Stability and Storage Recommendations
Store in a refrigerator (2-8°C) prior to activation.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used.

Following activation, DEFINITY® can be stored at room temperature and should be used within 12 hours of preparation.

The activated vials are for single use only and unused portions should be discarded.

When activated, DEFINITY® appears as a milky white suspension. If allowed to sit for more than 5 minutes after VIALMIX® shaking, it should be resuspended with 10 seconds of hand agitation prior to administration. (See **INSTRUCTIONS FOR PREPARATION OF DEFINITY®**).

AVAILABILITY OF DOSAGE FORMS

DEFINITY® (perflutren injectable suspension) is supplied as a sterile and non-pyrogenic liquid in a 2-mL glass vial.

The VIALMIX® will be provided with the initial DEFINITY® order. Product monograph available upon request.

Israeli Drug Registration Numbers: 133.15.31138.00
Manufacturer: Lantheus Medical Imaging Inc., North Billerica, MA, U.S.A.
License Holder: Ami Technologies Ltd.
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