DEFINITY® (Perfluoron Lipid Microsphere) INJECTABLE SUSPENSION

RECOMMENDATIONS FOR USE: DEFINITY RT is a strontium contrast agent indicated for use in patients with subclinical echocardiography to identify the left ventricular chamber and to improve the definition of the left ventricular endocardial border.

DOSE AND ADMINISTRATION: DEFINITY RT may be expected to elicit an intraluminal or intravascular reaction. The maximum dose is 2 hours, which is an intraluminal or intravascular reaction. The recommended bolus dose for activated DEFINITY RT is 10 microliters (ml) per kilogram (kg) body weight by an intravenous bolus injection within 60 to 60 seconds, followed by a 10 ml, 9.0% Sodium Chloride Injection, USP (Rs), saline, pseudonemon, or a similar solution. Alternatively, DEFINITY RT may be administered 30 minutes after a 10 ml, 9.0% Sodium Chloride Injection, USP (Rs), saline, pseudonemon, or a similar solution, for an intraarterial administration.

The recommended infusion dose for activated DEFINITY RT is a volumetric infusion of 1.3 ml/kg of body weight by an intravenous continuous infusion. The recommended infusion rate for activated DEFINITY RT is 10 ml/kg of body weight by an intravenous continuous infusion. The recommended maximum dose for activated DEFINITY RT is 10 ml/kg of body weight by an intravenous continuous infusion.

DOSE FORMS AND STRENGTHS: DEFINITY RT is supplied as a single-use unit. 2 ml RFD-tagged glass vial containing colorless, odorless, clear to transparent (viscous solution) of packaged (20) of single units.

CONTRAINDICATIONS: Do not administer DEFINITY RT to patients with known or suspected hypersensitivity to perfluoron lipid microspheres or its components.

WARNINGS AND PRECAUTIONS: Serious cardiorespiratory reactions, including fatalities, have occurred during or following perfusion of microsphere administration. Serious acute hypersensitivity reactions have occurred in patients with prior allergic reaction(s) to polyethylene glycol (PEG) (5.1).

ADVERSE REACTIONS: The most common adverse reactions (≥5%) are headache, back/renal pain, flushing, nausea, chest pain, injection site reactions, and dizziness (6).

PREGNANCY: Available data from case reports with DEFINITY use in pregnant women have not established a causal relationship for any adverse reactions. For all adverse reactions, the overall incidence of adverse experiences was approximately 8%. For all adverse reactions, the incidence of adverse experiences was approximately 8%.

R habilization: The following serious adverse reactions are described elsewhere in the labeling: Serious respiratory reactions. Hypersensitivity reactions. General adverse reactions. Neurologic reactions. Cardiovascular reactions. Hematologic reactions. Gastrointestinal reactions. Ocular reactions. For all serious adverse reactions, the overall incidence of adverse experiences was approximately 8%.

Table 1: New-Onset Adverse Reactions Occurring In ≥5% of ALL DEFINITY®-Treated Subjects

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>3.1</td>
</tr>
<tr>
<td>Hematologic</td>
<td>1.6</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1.4</td>
</tr>
<tr>
<td>Skin</td>
<td>1.2</td>
</tr>
<tr>
<td>Other</td>
<td>1.1</td>
</tr>
</tbody>
</table>

For all adverse reactions, the overall incidence of adverse experiences was approximately 8%. For all adverse reactions, the overall incidence of adverse experiences was approximately 8%.
**8.2. Lactation**

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

**8.4. Pediatric Use**

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

**8.5. Geriatric Use**

In clinical trials, the overall incidence of adverse reactions was similar for the ≤55 year age group and the >55 year age group. Of the total number of subjects in clinical trials of DEFINITY 144 (36%) were ≥65 and over. The overall differences in safety or effectiveness were observed between these subjects and younger participants, and other reported clinical experience has not identified differences in response to DEFINITY between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**9. DESCRIPTION**

DEFINITY RT (Perflutren Lipid Microspheres) Injectable Suspension is an ultrasonic contrast agent. The DEFINITY RT vial contains components that upon activation and dilution yield perflutren lipid microspheres. The unopened vial contains a colorless, uniformly clear to translucent (hazy), viscous, sterile, non-pyrogenic solution, which upon activation with the aid of a VALMIK R Ferd with or without 0.9% Sodium Chloride Injection, USP, provides a homogenous, if not fully aerosolized, in order to obtain a mean size of 2.1 µm. A solution may be used for the preparation of DEFINITY RT for injection.

The suspension of activated DEFINITY RT is administered intravenous injection.

- **Perflutren lipid microspheres** are comprised of octafluoropropane encapsulated in an outer lipid shell consisting of (R)-hexadecanoic acid, 1-phosphatic acid, 3,4,9-trioxa-4-phosphapentacosan-1-aminium, 4-oxide, inner salt (abbreviated DPPA); (R) - 4-hydroxy-N,N,N-trimethyl-10-oxo-7-[1-oxohexadecyl]oxy-1-[(phosphonoxy)methyl]-1,2-ethanediyl ester, monosodium salt (abbreviated DPPC); and (R) - hexadecanoic acid, 1-phosphatic acid, 3,4,9-trioxa-4-phosphapentacosan-1-aminium, 4-oxide, inner salt (abbreviated DPPC), and (R) - hexadecanoic acid, 1-phosphatic acid, 3,4,9-trioxa-4-phosphapentacosan-1-aminium, 4-oxide, inner salt (abbreviated DPPC) as well as (R) - hexadecanoic acid, 1-phosphatic acid, 3,4,9-trioxa-4-phosphapentacosan-1-aminium, 4-oxide, inner salt (abbreviated DPPC).

**10. CLINICAL PHARMACOLOGY**

**10.1. Microsphere particle size parameters** are listed in Table 2 below:

<table>
<thead>
<tr>
<th>Table 2: Microsphere Size Distribution</th>
<th>Micromeritic size parameters</th>
<th>Mean diameter (µm)</th>
<th>Percent less than 10µm</th>
<th>98% Maximum diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.1 µm – 3.3 µm</td>
<td></td>
<td></td>
<td>25 µm</td>
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</tbody>
</table>

**12.3. Pharmacokinetics**

Hepatic clearance and biliary excretion of DEFINITY RT is negligible. The pharmacokinetics of activated DEFINITY RT are not available for the intact or deaggregated microparticles. The calculated mean terminal elimination half-life of DEFINITY RT in plasma is approximately 1.3 minutes.

**12.3.1. Distribution**

The pharmacokinetics of activated DEFINITY RT have not been studied in subjects with hepatic 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 mutation assay** (Ames assay).
- **2) chromosomal aberration assay** (in 19 Chinese lymphocyte cultures).
- **3) micronucleus assay** (in 4 mouse micronucleus assays).

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 248 subjects were evaluated in clinical trials (238 received activated DEFINITY and 41 placebo). In this group, 104 (61.6%) were male and 95 (58.4%) were female. 183 (73.5%) were White, 38 (15.3%) were Black, 21 (8.2%) were Hispanic, and 7 (2.8%) were classified as other racial or ethnic groups. The mean age was 50.3 years (range 18–87).

Activated DEFINITY was evaluated in four controlled clinical trials. Two open-label baseline controlled, unblinded imaging evaluation studies and four placebo-controlled, unblinded blinded image evaluation studies.

Since subjects were eligible for these studies if they had two or more of the non-evaluable segments in the apical 2–4 or apical 4–6 view of the right ventricle, the study population was representative.

The baseline controlled studies, a total of 136 (67 in study 4 and 69 in study 5) subjects were evaluated. Also, in 13 to 37% of the patients, depending on the reader, activated DEFINITY converted a baseline non-evaluable image to an evaluable one. Also, in 13 to 37% of the patients, depending on the reader, activated DEFINITY converted a baseline non-evaluable image to an evaluable one.

In a retrospective analysis, in a subset of subjects (n=12 to 47, depending on reader) a change in border length from baseline at end-systole was statistically significant for 3 out of 4 readers for the apical 2-chamber view and for 2 out of 4 readers for the apical 4-chamber view.

**14.2. Pulmonary Hemodynamic Effects**

The impact of DEFINITY on pulmonary hemodynamics was explored in a prospective, open-label study of patients with normal pulmonary arterial pressure undergoing right heart catheterization. Patients with pulmonary arterial pressure systolic pressure greater than 50 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.