

NEW ZEALAND DATA SHEET

1 PRODUCT NAME

DEFINITY® (perflutren lipid microsphere) dispersion for injection. Octafluoropropane and perfluoropropane are synonyms for perflutren.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

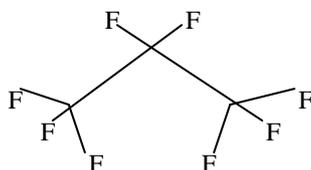
The perflutren lipid microspheres are composed of perflutren encapsulated in an outer lipid shell consisting of (R) - hexadecanoic acid, 1 -[(phosphonoxy)methyl]-1,2-ethanediyl ester, monosodium salt (abbreviated DPPA); (R) - 4-hydroxy-N,N,N-trimethyl-10-oxo-7-[(1-oxohexadecyl)oxy]-3,4,9-trioxa-4-phosphapentacosan-1-aminium,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

The CAS number of DEFINITY® is [76-19-7]. The physical and chemical characteristics of perflutren gas are provided in Table 1.

Table 1 Physical and Chemical Characteristics of Perflutren

Physical/Chemical Property	Characteristic
Appearance	Colorless gas
Boiling point (1 atmosphere)	-36.7°C
Freezing Point (1 atmosphere)	-183°C
Density, Liquid (20°C)	1.350 g/mL

Perflutren 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:



Prior to Vialmix™ activation, the DEFINITY® vial contains 6.52 mg/mL perflutren 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.

NEW ZEALAND DATA SHEET

After activating the contents of the vial in a Vialmix™, each mL of the milky white suspension contains a maximum of 1.2×10^{10} perflutren lipid microspheres, and about 1.1 mg/mL perflutren. 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 µm — 3.3 µm
Percent less than 10 µm	98%
Maximum diameter	20 µm

3 PHARMACEUTICAL FORM

DEFINITY® contains a clear, colourless, sterile, nonpyrogenic, hypertonic liquid, which upon activation with the aid of a Vialmix™, provides a homogeneous, opaque, milky white injectable suspension of perflutren lipid microspheres.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

DEFINITY® is indicated for use in patients in contrast-enhanced diagnostic ultrasound imaging to improve characterization of focal lesions of the liver and kidney.

DEFINITY® is indicated for use in patients with suboptimal echocardiograms to provide opacification of cardiac chambers, improvement of left ventricular endocardial border delineation and assessment of regional wall motion at both rest and stress.

4.2 Dose and method of 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.

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

Abdominal Ultrasound of the Liver and Kidney

Bolus intravenous injection using non-linear contrast imaging technique:

NEW ZEALAND DATA SHEET

The recommended dose for DEFINITY® is multiple injections of 0.1-0.4mL, followed by a 3-5 mL 0.9% sodium chloride solution for injection. The total dose of DEFINITY® should not exceed 1.6 mL.

Bolus intravenous injection using fundamental imaging technique:

The recommended dose for DEFINITY® is 10 µL/kg of the product by slow bolus intravenous injection, followed by a 10 mL 0.9% sodium chloride solution for injection.

Echocardiography

Bolus intravenous injection using non-linear contrast imaging technique:

The recommended dose for DEFINITY® is multiple injections of 0.1-0.4 mL, followed by a 3-5 mL 0.9% sodium chloride solution for injection to maintain optimal contrast enhancement. The total dose of DEFINITY® should not exceed 1.6 mL.

Bolus intravenous injection using fundamental imaging technique:

The recommended dose for DEFINITY® is 10 µL/kg of the product by slow bolus intravenous injection, followed by a 10mL 0.9% sodium chloride solution for injections. If necessary, a second 10 µL/kg dose followed by a second 10 mL 0.9% sodium chloride solution for injection may be administered 5 minutes after the first injection to prolong contrast enhancement.

Intravenous infusion using non-linear contrast of fundamental imaging technique:

The recommended dose for DEFINITY® is via an intravenous infusion of 1.3 mL added to 50 mL of 0.9% sodium chloride solution for injection. 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.

DEFINITY® should not be used in patients below 18 years until efficacy and safety in these groups have been established.

Instructions for Use

- a. Allow the vial to warm to room temperature before starting the activation procedure.
- b. 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.

- c. 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

NEW ZEALAND DATA SHEET

- after the microspheres are resuspended by hand agitation. Store the activated DEFINITY® at room temperature in the original product vial.
- d. Invert the vial and withdraw the activated milky white suspension using a needleless spike (Intellipin®) or a 18- to 20-gauge syringe needle. Position the needle to withdraw the material from the middle of the liquid in the inverted vial. DO NOT INJECT AIR INTO THE DEFINITY® VIAL. *
 - e. Use the product immediately after its withdrawal from the vial; do not allow the product to stand in the syringe.

USE IN ONE PATIENT ON ONE OCCASION ONLY: DEFINITY® does not contain antimicrobial 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.

*NOTE: When using either a needleless spike (Intellipin®) or a 18- to 20-gauge needle, the entire contents of the vial should be removed, then small injections from the syringe should be given to a single patient.

4.3 Contraindications

Activated DEFINITY® should not be administered to patients with known hypersensitivity to perflutren or any other components of DEFINITY®.

Activated DEFINITY® is contraindicated in patients with known cardiac shunts (see PRECAUTIONS).

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

4.4 Special warnings and precautions for use

General

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.

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

Serious Cardiopulmonary Reactions:

Serious cardiopulmonary reactions, including fatalities, have occurred during or following DEFINITY® 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 failures, 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.

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

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 with potential for microsphere trapping in small arterioles (< 15µm) and in capillaries. 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. 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).

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. However, predisposing conditions may increase the risk of ventricular arrhythmias associated with QTc prolongation. DEFINITY® should be used only after careful consideration in patients with ongoing proarrhythmic conditions, previous history of symptomatic arrhythmias, family history of congenital long QT syndrome and on drugs known to cause QTc prolongation.

Congestive Heart Failure

DEFINITY® should be administered with caution in patients with congestive heart failure or arrhythmias. In clinical trials with DEFINITY® the incidence of adverse experiences has higher in patients with a history of congestive heart failure.

Paediatric Use

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

Elderly

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

4.5 Interaction with other medicines and other forms of interaction

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

NEW ZEALAND DATA SHEET

4.6 Fertility, pregnancy and lactation

Effects of Fertility

No effect on male or female fertility was found when rats were treated with DEFINITY® at up to 5 mL/kg/day IV (35x the maximal human dose based on body surface area).

Pregnancy Category B1

There was no evidence for a direct fetotoxic or teratogenic effect of DEFINITY® in rats or rabbits given 1 mL/kg/day IV (7x and 18x the maximal human dose based on body surface area, respectively). 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.

Use in Lactation

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.

4.7 Effects on ability to drive and use machines

The effects on ability to drive and use machines for activated DEFINITY® have not been studied.

4.8 Undesirable effects

The reported adverse effects following the use of DEFINITY® in pivotal and supportive trials (total of 2,526 patients) have generally been mild to moderate in intensity, occur within minutes after administration and usually resolve without therapeutic intervention within 15 minutes. The most frequently reported adverse reactions are: headache (2.0%), flushing (1.0%) and back pain (0.9%).

Table 3 New-Onset AEs Occurring in At Least 0.5% of DMP 115-treated Subjects in all Patient Studies, Regardless of Indication

Preferred Term	All AEs		Treatment- Related AEs	
Total Subjects Treated	2526		2526	
Total Subjects with AEs	646	(25.6%)	193	(7.6%)
Fatigue	150	(5.9%)	4	(0.2%)
Headache	88	(3.5%)	50	(2.0%)
Dyspnoea	81	(3.2%)	3	(0.1%)
Chest pain	61	(2.4%)	8	(0.3%)
Flushing	41	(1.6%)	25	(1.0%)
Back pain	35	(1.4%)	23	(0.9%)
Nausea	35	(1.4%)	19	(0.8%)
Dizziness	25	(1.0%)	12	(0.5%)
Dysgeusia	21	(0.8%)	21	(0.8%)
Chest discomfort	18	(0.7%)	2	(<0.1%)

NEW ZEALAND DATA SHEET

Pain NOS	15	(0.6%)	3	(0.1%)
Abdominal pain NOS	14	(0.6%)	3	(0.1%)
Hypertension NOS	14	(0.6%)	2	(<0.1%)
Diarrhoea NOS	13	(0.5%)	4	(0.2%)
Hypotension NOS	13	(0.5%)	4	(0.2%)
Injection site pain	12	(0.5%)	9	(0.4%)

In addition, the following adverse events were reported with the following frequencies:

Table 4 Additional Adverse Events with Frequencies

Adverse Event	Frequency
Uncommon ($\geq 1/1,000$, $<1/100$)	Throat irritation, Pruritus, Increased Sweating
Rare ($\geq 1/1,000$, $<1,000$)	Paresthesia, Syncope, Peripheral Coldness, Cough, Dry Throat, Respiratory Distress, Dyspepsia, Erythema, Erythematous Rash, Rash, Urticaria, Arthralgia, Flank Pain, Neck Pain, Muscle Cramp, Pyrexia, Rigors, Abnormal Electrocardiogram

Post Marketing Experience:

The following adverse reactions have been identified during the post-marketing use of DEFINITY®. 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.

Allergic type symptoms (e.g. anaphylactoid like symptoms, face oedema, hypotension) have been reported rarely.

4.9 Overdose

The clinical consequences of overdosing with activated DEFINITY® are not known. Single doses of up to 100 µL/kg and multiple doses up to 150 µL/kg were tolerated well in Phase I clinical trials. Treatment of an overdose should be directed toward the support of all vital functions and prompt institution of symptomatic therapy (see CONTRAINDICATIONS and PRECAUTIONS).

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

NEW ZEALAND DATA SHEET

When used in conjunction with diagnostic ultrasound, DEFINITY® provides opacification of cardiac chambers, improvement in delineation of endocardial borders and assessment of regional myocardial wall motion. DEFINITY® provides contrast enhancement in ultrasound studies of the liver and kidney and enhancement of Doppler ultrasound assessment of the vasculature of the liver and kidney.

The ultrasound echoes from blood and biological soft tissues such as fat and muscles are generated at interfaces due to small differences in the ultrasonic properties of the tissues. The ultrasonic properties of DEFINITY® are very different from those of soft tissue and will generate strong echoes.

Upon activation, DEFINITY® consists of lipid encapsulated perflutren microspheres. Microspheres in the 1 to < 10 µm diameter size range contribute to the contrast effect by generating strongly enhanced echoes.

As DEFINITY® consists of microspheres that are stable and small enough for transpulmonary passage, enhanced echo signals in the left heart, systemic circulation and abdominal organs are obtained.

A strict dose/response relationship cannot be defined, although higher doses have been shown to produce a contrast effect of longer duration. In a crossover study the duration of clinically useful contrast enhancement for fundamental imaging was approximately 3.4 minutes after a 10 µL/kg bolus and approximately 7.1 minutes after a continuous infusion of 1.3 mL activated DEFINITY® in 50 mLs saline at a rate of 4 mL/min.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of perflutren gas were evaluated in normal healthy subjects and subjects with chronic obstructive pulmonary disease (COPD) following intravenous administration of a 50 µL/kg dose of DEFINITY®. Perflutren is a stable gas that is not metabolized.

The perflutren component of DEFINITY® was rapidly cleared from the systemic circulation via the lungs. In most subjects after 4-5 minutes, Perflutren was undetectable in blood and in expired air. Perflutren concentration in blood were shown to decline in a mono-exponential fashion with a mean half-life of 1.3 minutes in healthy subjects and 1.9 minutes in COPD subjects. The systemic clearance of Perflutren was similar in healthy and COPD subjects. Total lung clearance (CL_{lung}) of Perflutren was shown to be no different in healthy subjects compared to COPD subjects. CL_{lung} was found to be statistically significantly reduced (51%) in females compared to males (all subjects). These results suggest that overall Perflutren systemic elimination is rapid and is not statistically significantly reduced in COPD patients compared to healthy subjects.

Doppler ultrasound measurements were performed with DEFINITY® in conjunction with the pharmacokinetic evaluation of perflutren. Doppler signal intensity corresponded well with measured and extrapolated perflutren concentrations in blood. The time to maximum Doppler signal intensity t_{max} was shown to be similar to the perflutren blood t_{max} (1.13 versus 1.77 minutes). The observed 99% drop in Doppler signal intensity within 10 minutes ($t_{1/2}$ approximately 2 minutes) was in agreement with the decline in measurable blood levels of perflutren.

Human pharmacokinetic information is not available for lipid microspheres. The naturally occurring phospholipids in DEFINITY® are distributed in the endogenous lipid pools in the body (for example, liver) whereas the synthetic component (MPEG5000) has been shown to be excreted in the urine in nonclinical studies. All lipids are metabolized to free fatty acids.

5.3 Preclinical safety data

Carcinogenesis

Studies with activated DEFINITY® have not been performed to evaluate carcinogenic potential.

Mutagenesis

No evidence of genotoxicity was 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 Fertility

No effect on male or female fertility was found when rats were treated with DEFINITY® at up to 5 mL/kg/day IV (35x the maximal human dose based on body surface area).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colfosceril palmitate
Dibasic sodium phosphate monohydrate
Glycerol
Sodium dipalmitoylphosphatidate
N-(Methoxy-PEG-5000 carbamoyl)-
dipalmitoylphosphatidylethanolamine sodium
Monobasic sodium phosphate monohydrate
Propylene glycol
Sodium chloride
Water for injection

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months from date of manufacture

6.4 Special precautions for storage

Store at 2-8°C (Refrigerate. Do not freeze.)

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

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

NEW ZEALAND DATA SHEET

DEFINITY® IS INTENDED FOR ADMINISTRATION ONLY AFTER ACTIVATION IN THE VIALMIX™ APPARATUS.

- 6.6 Special precautions for disposal <and other handling>
Any unused medicine or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

General Sales Medicine

8 SPONSOR

Global Medical Solutions (NZ) Limited
6/517 Mt Wellington HWY
Auckland 1060
NEW ZEALAND

9 DATE OF FIRST APPROVAL

6/12/2007

10 DATE OF REVISION OF THE TEXT

30/06/2019

SUMMARY TABLE OF CHANGES

Data sheet has been updated to SmPC format