Perflutren Protein-Type A Microspheres Injectable Suspension, USP

**WARNING: SERIOUS CARDIOPULMONARY REACTIONS**

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

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

**DESCRIPTION**

OPTISON™ (Perflutren Protein-Type A Microspheres Injectable Suspension, USP) is a sterile non-pyrogenic suspension of microspheres of human serum albumin for contrast enhancement during the indicated ultrasonic imaging procedures. The oil contains a clear liquid lower layer and a white upper layer that, after resuspension by gentle mixing, provides a homogeneous, opaque, milky-white suspension for intravenous injection.

Perflutren is chemically characterized as 1,1,1,2,2,3,3,3-perflutren with a molecular weight of 188, an empirical formula of C32H62N6O22P, and it has the following structural formula:

$$\text{CH}_3\text{C}_2\text{H}_5\text{O}_2\text{P}(\text{O})\text{C}_2\text{H}_5$$

Each mL of OPTISON contains 5.0-8.0 x 10^4 protein-type A microspheres, 10 mg Albumin Human, USP, 0.26 ± 0.11 mg/mL perflutren, 0.2 mg Na-acetyltryptophan, and 0.12 mg caprylic acid in 0.9% aqueous sodium chloride. The headspace of the vial is filled with perflutren gas. The pH is adjusted to 6.4-7.4. The protein in the microsphere shell makes up approximately 5-7% (w/w) of the total protein in the liquid.

The efficacy of OPTISON was evaluated in two identical multicenter, dose escalation, randomized, cross-over studies. The study test drugs were four doses of OPTISON (0.2, 0.5, 3.0 and 5.0 mL) and two doses of ALBUNEX™ (0.08 and 0.22 mL/kg). The two test drugs were administered to the patients in a random sequence, with two to ten days between each drug. After non-contrast imaging, the test doses were administered in ascending order with at least ten minutes between each dose. Ultrasound settings were optimized for the baseline (non-contrast) apical four-chamber view and remained unchanged for the contrast imaging. Static echographic images and video-tape segments were interpreted by a reader who was blinded to the patient’s clinical history and to the identity and dose of the test drug. The primary efficacy endpoint was left ventricular endocardial border delineation, assessed before and after OPTISON administration, by the measurement of visualized endocardial border length. The six segments of the left ventricular endocardial border were scored for contrast enhancement during the indicated apical imaging. The test doses were administered single blind and the image analysis was performed blind and without knowledge of the patient’s clinical history. The imaging effects of OPTISON on endocardial border delineation and left ventricular apical opacification tended to be qualitatively similar in patients with and without pulmonary disease or dilated cardiomyopathy.

In these studies, quantitative measures of left ventricular function (e.g., ejection fraction), quantitative measurements of anatomic structures (e.g., wall thickness), or the evaluation of myocardial perfusion were not performed.

**CLINICAL PHARMACOLOGY**

**General**

The OPTISON microspheres create an echogenic contrast effect in the blood.

**Pharmacokinetics**

Studies in humans have evaluated the pharmacokinetics of the perflutren component of the OPTISON microspheres. After injection of OPTISON, diffusion of the perflutren gas out of the microspheres is limited by the low partition coefficient of the gas in blood that contributes to the persistence of the microspheres. The diffusion rate has not been determined.

In an anesthetized dog model, the acoustic properties of OPTISON were established at 0.6 mechanical index and 2.5 MHz frequency.

Neither the pharmacokinetics of the intact microspheres or of the human albumin component have been evaluated in humans.

**Metabolism**

Perflutren is a stable gas that is not metabolized. The human albumin component of the microsphere is expected to be handled by the normal metabolic routes for human albumin.

**Perflutren Elimination**

Following a single intravenous dose of 20 mL OPTISON to 10 healthy volunteers (5 men and 5 women), most of the perflutren was eliminated through the lungs within 10 minutes. The recovery was 99.7±23% (mean ± SD). The pulmonary elimination half-life was 1.3 ± 0.69 minutes (mean ± SD). The perflutren concentration in expired air peaked approximately 30-40 seconds after administration.

**Perflutren Protein Binding**

The binding of perflutren to plasma proteins or its partitioning into blood cells have not been studied. However, perflutren protein binding is expected to be minimal due to the low partition coefficient of the gas in blood.

**Special Populations**

The pharmacokinetics of OPTISON have not been studied in patients with hepatic or respiratory diseases.

**Gender, Age, Race**

The effects of gender, age, or race on the pharmacokinetics of OPTISON have not been studied.

**Drug-Drug Interactions**

Drug-drug interactions for OPTISON have not been studied.

**Pediatrics**

The pharmacokinetics of OPTISON in pediatric patients have not been studied.

**Pharmacodynamics**

The general acoustic properties of OPTISON are similar to those of ALBUNEX™. The acoustic impedance of the OPTISON microspheres is much lower than that of the blood. Therefore, imaging ultrasound waves are scattered and reflected at the microsphere-blood interface and ultimately may be visualized in the ultrasound image. At the frequencies used for adult echocardiography (2-5 MHz), the microspheres resonate which further enhances the extent of ultrasound scattering and reflection.

As assessed by the unblinded investigators in clinical studies, the median duration of OPTISON contrast enhancement for each of the four doses of OPTISON 0.2, 0.5, 3.0, and 5.0 mL were approximately one, two, four, and five minutes, respectively (see CLINICAL TRIALS section).

**CLINICAL TRIALS**

**Echocardiography**

The efficacy of OPTISON was evaluated in two identical multicenter, dose escalation, randomized, cross-over studies of OPTISON and ALBUNEX™. The test drugs were administered single blind and the image analysis was double blind. Eligible patients were undergoing routine echocardiography and all patients were required to have at least two of the six segments of the left ventricular endocardial border that were not well delineated in the apical 4-chamber view. In these studies, the 203 patients (Study A: n=101, Study B: n=102) received at least one dose of study drug according to the following characteristics: 79% men, 21% women, 53.5 ± 20.7 years, 25% Black, 10% Hispanic, and 1% other race or ethnic group. The patients had an age range of 6 years (range 21 to 83 years), and at least one of the following: 108% of the patients had chronic pulmonary disease, 17% had congestive and dilated cardiomyopathy with left ventricular ejection fractions (LVEFs) of between 20% and 40%; 16% previously echocardiographed. Patients with a LVEF of less than 20% or with New York Heart Association Class IV heart failure were not included in the studies.

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**Pulmonary Hemodynamic Effects:**

The effect of OPTISON on pulmonary hemodynamics was studied in a prospective, open-label study of 30 patients for pulmonary artery catheterization, including 19 with an elevated baseline pulmonary artery occlusion pressure (PAOP) >15 mmHg and 11 with a normal PAOP <13 mmHg. Systemic hemodynamic parameters and ECGs were also evaluated. No clinically important pulmonary hemodynamic, systemic hemodynamic, or ECG abnormalities were observed. This study did not assess the effect of OPTISON on visualization of cardiac or pulmonary structures.

**INDICATIONS**

OPTISON™ is indicated for use in patients with suboptimal echocardiographs to opacify the left ventricle and to improve the delineation of the left ventricular endocardial border.

**CONTRAINDICATIONS**

Do not administer OPTISON to patients with known or suspected:

- Right-to-left, bi-directional, or transient right-to-left cardiac shunts.
- Hypersensitivity to perflutren, blood, blood products or albumin (see WARNINGS).

**WARNINGS**

**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 acute coronary syndromes, acutely complicated conditions (acute myocardial infarction, acute coronary artery syndromes, worsening or unstable congestive heart failure, or serious ventricular arrhythmias). The reported reactions to perflutren-containing microspheres include fatal cardiac or respiratory arrest, shock, syncope, symptomatic arrhythmias (atrial fibrillation, tachycardia, bradycardia, supraventricular tachycardia, ventricular fibrillation, ventricular tachycardia), hypotension, hypoxemia, dyspnea, hypoxia, chest pain, respiratory distress, stridor, wheezing, loss of consciousness and convulsions (see ADVERSE REACTIONS).
Always have cardiopulmonary resuscitation personnel and equipment readily available prior to OPTISON administration and monitor all patients for acute reactions.

Anaphylactic Reactions
In postmarketing use, uncommon but serious anaphylactic reactions were observed during or shortly following perfluorcarbon-containing microspheres. Symptoms included shock, hypersensitivity, bronchospasm, throat tightness, angioedema, edema (laryngeal, palatal, mouth, peripheral, localized, swallowing, nose, eye, tongue, upper airway), facial hyposthesia, rash, urticaria, pruritus, flushing, and erythema and have occurred in patients with no prior exposure to perfluorcarbon-containing products (see ADVERSE REACTIONS).

Systemic Embolization of OPTISON in Patients with Cardiac Shunts
In patients with right-to-left, left-to-right, or transient right-to-left cardiac shunts perfluorcarbon-containing microspheres can bypass the pulmonary particle-filtering mechanisms and directly enter the arterial circulation resulting in vascular occlusion and ischemia. Do not administer OPTISON by intra-arterial injection (see CONTRAINDICATIONS).

High Ultrasound Mechanical Index
High ultrasound mechanical index values may cause microsphere cavitation and rupture or lead to ventricular arrhythmias. Accordingly, exact monitoring with high mechanical indices has been reported to cause ventricular arrhythmias. The safety of OPTISON at mechanical indices greater than 0.8 has not been evaluated. The safety of OPTISON with the use of end-systolic triggering has not been evaluated.

PRECAUTIONS

General
This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. Accordingly, exact monitoring with high mechanical indices has been reported to cause ventricular arrhythmias. The safety of OPTISON at mechanical indices greater than 0.8 has not been evaluated. The safety of OPTISON with the use of end-systolic triggering has not been evaluated.

In these patients, 47 (16.8%) reported at least one adverse event. Of these one event was serious and required hospitalization. One subject with a history of epilepsy was seizure free for 1 year after receiving OPTISON. One subject had a positive skin test and was not given a repeat dose of OPTISON.

In postmarketing use, uncommon but serious anaphylactoid reactions were observed during or shortly following injection of OPTISON™. In the clinical dose ranging studies of 40 normal volunteers, doses higher than those recommended in the DOSAGE AND ADMINISTRATION section tended to be associated with an increased frequency of reported adverse events.

In a prospective, post-marketing safety surveillance study of OPTISON used in routine clinical practice, a total of 1039 subjects received OPTISON. Of these patients, 648 (62.4%) were male and 391 (37.6%) were female with a mean age of 51 years (SD 16). The racial distributions were 864 (83.2%) White, 143 (13.2%) Black, 18 (1.7%) Asian, and 16 (1.5%) other racial or ethnic groups. Overall, 175 patients (16.8%) reported at least one adverse event. No serious adverse reactions, including deaths, were reported in this study, suggesting that these reactions are unlikely to occur at a rate of more than 0.1% when OPTISON is used according to recommendations. The following adverse reactions have been identified during the postmarketing use of OPTISON. 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.

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 arrest, hypotension, supraventricular and ventricular arrhythmias, respiratory distress or decreased oxygenation. Reports also identified neurologic reactions (loss of consciousness or convulsions) as well as anaphylactoid reactions (see WARNINGS).

DOSAGE AND ADMINISTRATION
The recommended dose of OPTISON is 0.5 mL injected into a peripheral vein. This may be repeated for further contrast enhancement as needed. See individualization of dose below.

The injection rate should not exceed 1 mL per second.

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2. Follow the OPTISON injection with a flush of 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP.

3. The maximum total dose should not exceed 5.0 mL in any 10 minute period.

4. The maximum total dose should not exceed 8.7 mL in any one patient study.

Individualization of Dose
Image quality in cardiac ultrasound is a function of the acoustic window which is influenced by many variables including body habitus, intervening lung tissue, echogenic contrast agent, and acoustic factors. Other variables may influence the ultrasound contrast effect.

If the contrast enhancement is inadequate after the dose of 0.5 mL, additional doses in increments of 0.5 mL up to 5.0 mL cumulative within a 10 minute period may be injected up to a maximum total dose of 8 mL in any one patient study.

DIRECTIONS FOR HANDLING
OPTISON does not contain preservatives. Bacterial contamination with the risk of post-infusion septicemia can occur if the container has been damaged or following puncture of the rubber cap. A single vial must not be used for more than one patient. Discard unused product properly.

DO NOT USE if the container has been damaged or the protective seal and/or rubber cap have been entered.

DO NOT USE if the upper end of the vial is bent. This indicates that the microspheres may have been damaged and may result in poor or no echocardiography.

DO NOT INJECT air into the vial.

1. Invert the OPTISON vial and gently rotate to resuspend the microspheres. This process will allow the product to come to room temperature before use.

2. Inspect the vial for complete resuspension. Failure to adequately resuspend OPTISON may cause an under delivery of the microspheres, and may result in inadequate contrast.

3. Do not use OPTISON if, after resuspension, the solution appears to be clear rather than opaque milky-white.

4. Ventr the OPTISON vial with a sterile vent spike or with a sterile 18 gauge needle before withdrawing the OPTISON suspension into the injection syringe.

INJECTION PROCEDURE
The time from resuspension of the OPTISON to injection must not exceed one minute. If one minute is exceeded, resuspend the microspheres in the syringe and repeat the resuspension and injection process if necessary.

Injection: provide intravenous access in a peripheral vein with a 20 gauge or larger angiocatheter. Suggested methods of administration include: a short extension tubing, heparin lock, or intravenous line, all with a 1:500000 dilution.

For short extension tubing or heparin lock: fill syringe with 0.9% Sodium Chloride Injection, USP, and flush the line for potency before and after the injection of OPTISON.

For a continuous intravenous line: open an intravenous line with 0.9% Sodium Chloride Injection, USP for 5% Dextrose Injection, USP at a slow infusion rate to maintain vascular patency. The line should be flushed immediately after injection of OPTISON.

DO NOT ASPIRATE blood back into the OPTISON/suspension syringe before administration; this may promote the formation of a blood clot within the syringe.

HOW SUPPLIED
OPTISON® (Perflutren Protein-Type A Microspheres) Injectable Suspension, USP is available in a carton of five 3 mL vials in single use 3 mL vials.