

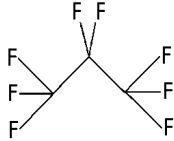


OPTISON™ (Perflutren Protein-Type A Microspheres for Injection, USP)

DESCRIPTION

OPTISON™ (Perflutren Protein-Type A Microspheres for Injection, USP) is a sterile non-pyrogenic suspension of microspheres of human serum albumin with perflutren for contrast enhancement during the indicated ultrasound imaging procedures. The vial 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 C_3F_8 , and it has the following structural formula:



Each mL of OPTISON contains 5.0-8.0x10⁶ protein-type A microspheres, 10 mg Albumin Human, USP, 0.22 ± 0.11 mg/mL perflutren, 0.2 mg N-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 microsphere particle size parameters are listed in Table 1.

Mean diameter (range)	3.0-4.5µm (max. 32.0µm)
Percent less than 10µm	95%

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 studied.

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 96% ± 23% (mean ± SD), and 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, impinging ultrasound waves are scattered and reflected at the microsphere-blood interface and ultimately may be visualized in the ultrasound image. At the frequencies used in adult echocardiography (2-5 MHz), the microspheres resonate which further increases 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

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 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 had the following characteristics: 79% men, 21% women, 64% White, 25% Black, 10% Hispanic, and 1% other race or ethnic group. The patients had a mean age of 61 years (range: 21 to 83 years), a mean weight of 196 lbs (range: 117 to 342 lbs), a mean height of 68 inches (range: 47 to 78 inches), and a mean body surface area of 2.0m² (range: 1.4 to 2.6m²). Approximately 23% of the patients had chronic pulmonary disease, and 17% had congestive and dilated cardiomyopathy with left ventricular ejection fractions (LVEFs) of between 20% and 40% (by previous echocardiography). Patients with a LVEF of less than 20% or with New York Heart Association Class IV heart failure were not included in the 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 4-chamber view and remained unchanged for the contrast imaging. Static echocardiographic 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 also assessed qualitatively (i.e., not well delineated, average delineation, good delineation, excellent delineation) before and after OPTISON administration.

In comparison to non-contrast ultrasound, OPTISON significantly increased the length of endocardial border that could be visualized both at end-systole and end-diastole (see Table 2). In these patients there was a trend towards less visualization in women. Similarly, in comparison to non-contrast ultrasound, OPTISON significantly improved the qualitative ability to delineate each of the left ventricular segments, though the effect was less for the septal segments. As assessed by videodensitometry, OPTISON increased left ventricular opacification (peak intensity) in the mid-chamber and apical views (see Table 3). In subset analysis, OPTISON tended to enhance the quality of the spectral Doppler signal of the pulmonary veins. The imaging effects of OPTISON on endocardial border delineation and left ventricular 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 anatomical structures (e.g., wall thickness), or the evaluation of myocardial perfusion were not performed.

Table 2
Left Ventricular Endocardial Border Length
Before and After OPTISON^{a, b}

OPTISON dose	Length of End-Systole (cm)		Length of End-Diastole (cm)	
	n	mean ± S.D.	n	mean
Study A (n=101)				
0 mL (baseline)	87	7.7 ± 3.0	86	9.3 ± 3.4
0.2 mL	85	11.7 ± 4.3	85	15.7 ± 3.8
0.5 mL	86	12.0 ± 4.9	91	15.8 ± 5.1
3.0 mL	87	12.3 ± 4.4	88	16.7 ± 4.0
5.0 mL	89	12.7 ± 4.9	90	16.6 ± 4.3
Study B (n=102)				
0 mL (baseline)	89	8.1 ± 3.4	89	9.6 ± 3.7
0.2 mL	90	11.3 ± 4.5	95	15.0 ± 5.3
0.5 mL	95	12.4 ± 4.9	97	16.4 ± 4.6
3.0 mL	94	12.6 ± 4.8	99	16.5 ± 4.7
5.0 mL	92	13.0 ± 4.5	95	16.2 ± 5.1

- a The difference in the number of enrolled patients and evaluated patients at each dose reflects exclusions based on withdrawal from the trial, or those with technically inadequate or missing images.
- b An intent-to-treat analysis, with non-favorable values imputed for missing patients, provided qualitatively similar results.

Table 3
Intensity of Left Ventricular Opacification^{a, b, c}
Before and After OPTISON^{a, b, c}

OPTISON dose	Mid-Chamber		Apex	
	Intensity of End-Diastole	Intensity of End-Systole	Intensity of End-Diastole	Intensity of End-Systole
Study A (n = 101)				
0 mL (baseline)	91 39.5 ± 16.9	91 40.0 ± 18.1	91 46.7 ± 19.7	91 46.9 ± 20.1
0.2 mL	91 56.7 ± 26.2	91 55.4 ± 26.6	91 63.2 ± 28.9	91 61.1 ± 28.5
0.5 mL	91 57.3 ± 26.8	90 57.4 ± 26.7	91 67.0 ± 30.1	90 64.1 ± 30.2
3.0 mL	90 53.9 ± 22.5	90 55.8 ± 24.3	90 66.1 ± 28.2	90 61.8 ± 26.8
5.0 mL	89 54.7 ± 24.0	89 57.9 ± 28.3	89 69.1 ± 30.4	89 63.7 ± 28.9
Study B (n = 102)				
0 mL (baseline)	95 40.4 ± 17.4	95 40.9 ± 17.5	95 43.7 ± 19.9	95 45.0 ± 19.6
0.2 mL	97 52.5 ± 21.0	97 51.5 ± 20.6	97 58.4 ± 22.2	97 56.0 ± 22.2
0.5 mL	97 53.3 ± 20.7	96 53.6 ± 21.0	97 64.4 ± 25.3	96 61.6 ± 26.7
3.0 mL	99 51.2 ± 23.6	99 55.6 ± 24.5	99 65.4 ± 26.3	99 62.7 ± 25.7
5.0 mL	95 51.8 ± 23.8	95 55.6 ± 24.8	95 65.2 ± 28.1	95 62.8 ± 28.1

- a Intensity measured by videodensitometry in arbitrary gray scale units (0-255).
- b The differences in the number of enrolled patients and evaluated patients at each dose reflects exclusions based on withdrawal from the trial, or those with technically inadequate or missing images.
- c An intent-to-treat analysis, with non-favorable values imputed for missing patients, provided qualitatively similar results.

INDICATIONS

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

CONTRAINDICATIONS

Do not administer OPTISON to patients with known or suspected hypersensitivity to blood, blood products, or albumin.

WARNINGS

Cardiac Shunts: The safety of OPTISON in patients with right-to-left, bidirectional or transient right-to-left cardiac shunts has not been studied. In these patients, microspheres can bypass filtering by the lung and directly enter the arterial circulation. Extreme caution should be exercised when considering the administration of OPTISON to patients with congenital heart defects.

The potential toxicity of microspheres in patients with small pulmonary vascular beds or with small cross-sectional vascular surface area has not been studied. OPTISON should be administered with caution to patients with severe emphysema, pulmonary vasculitis or a history of pulmonary emboli.

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 disease. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral disease or CJD have ever been identified for albumin.



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PRECAUTIONS

General

OPTISON should be administered with caution to patients with confirmed or suspected severe liver disease or respiratory distress syndrome. The safety of microspheres in patients on mechanical ventilation has not been studied.

Whenever protein-containing materials such as OPTISON are used in humans, hypersensitivity reactions may occur. In clinical studies of OPTISON, one patient had acute nausea, flushing, dizziness, tachycardia and fever that required treatment with antihistamines. Epinephrine, antihistamines, and corticosteroids should be available for immediate treatment of the patient's symptoms.

Diagnostic echocardiography procedures that involve the use of OPTISON should be carried out under the direction of a licensed practitioner having a thorough knowledge of the procedure and the safe use of the product.

Laboratory Tests

Immunologic tests of serum immunoglobulins, cytokines, and complement were monitored in a 3 week study of 20 healthy volunteers and 30 patients who received OPTISON or a 1% albumin control. Clinically relevant changes in the measured parameters were not noted. In another study 5 subjects received a skin test with OPTISON one year after receiving OPTISON. One subject had a positive skin test and was not given a repeat dose of OPTISON.

Information for Patients

Patients receiving OPTISON:

1. Inform your physician or health care provider if you may be pregnant or are nursing an infant.
2. Inform your physician if you ever have had allergic or hypersensitivity reaction to blood, blood products, or albumin.
3. Inform your physician or health care provider if you have a congenital heart defect.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Animal studies were not carried out to determine the carcinogenic potential of OPTISON.

The result of the following genotoxicity studies with OPTISON were negative: 1) Salmonella/Escherichia coli reverse mutation assay, 2) *in vitro* mammalian chromosome aberration assay using Chinese hamster ovary cells (CHO) with and without metabolic activation, 3) CHO/HGPRT forward mutation assay, and 4) *in vivo* mammalian micronucleus assay.

Pregnancy Category C

OPTISON administered intravenously to rats during organogenesis at doses of 0.25, 5.0 and 10.0 mL/kg/day was fetotoxic at 0.25 and 5.0 mL/kg (approximately 0.2 and 5 times the recommended maximum human dose, respectively, based on body surface area). Fetotoxicity was characterized by an increased incidence of reversible delayed pelvic ossification, the incidence of which was not related to dose. Signs of maternal toxicity at 5 mL/kg included respiratory and motor signs. Maternal death occurred at 10 mL/kg. A no observable adverse effect level (NOAEL) for fetotoxicity was not determined. Teratogenic effects were not observed at doses up to 10 mL/kg/day. The NOAEL for maternal toxicity was 0.25 mL/kg.

OPTISON administered intravenously to rabbits during organogenesis at doses of 0.25, 2.5 and 5.0 mL/kg/day was embryofetal toxic at 2.5 and 5.0 mL/kg (approximately 5 and 10 times the recommended maximum human dose, respectively, based on body surface area). Embryofetal toxicity was characterized by a decrease in fetal body weight and an increase in embryofetal death. Teratogenic effects (cleft palates and dilation of the lateral ventricles of the brain associated with skull abnormalities and compression deformities) were observed at 2.5 mL/kg but not 5 mL/kg. Neither the incidence nor the severity of embryofetal toxicity and teratogenicity exhibited a dose-dependent relationship. Maternal toxicity (significant suppression of body weight gain, abnormal stool) was observed at 2.5 and 5.0 mL/kg with the greatest effect observed at 2.5 mL/kg. The NOAEL for embryofetal and maternal toxicity was 0.25 mL/kg (approximately 0.5 times the recommended maximum human dose).

Adequate or well-controlled studies were not conducted in pregnant women. OPTISON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk caution should be exercised when OPTISON is administered to a nursing woman.

Pediatric Use

Safety and efficacy have not been established in pediatric patients, or in patients with congenital heart disease. (See Warnings).

ADVERSE REACTIONS

OPTISON was administered in clinical studies in 279 patients. Of these patients there were 192 (68.8%) men and 87 (31.2%) women. The racial demographics were 199 (71.3%) Caucasian, 52 (18.6%) Black, 24 (8.6%) Hispanic, and 4 (1.4%) other racial or ethnic groups.

In these patients, 47 (16.8%) reported at least one adverse event. Of these one event was serious and required treatment with antihistamines for hypersensitivity manifestations of dizziness, nausea, flushing and temperature elevation. Deaths were not reported during the clinical studies.

Of the reported adverse reactions following the use of OPTISON the most frequently reported were headache (5.4%), nausea and/or vomiting (4.3%), warm sensation or flushing (3.6%), and dizziness (2.5%). The most common adverse events observed in clinical studies of OPTISON are given in Table 4.

No. of Patients Exposed to OPTISON™	279
No. of Patients Reporting on Adverse Event	47 (16.8%)
Body as a Whole	38 (13.6%)
Headache	15 (5.4%)
Warm Sensation/Flushing	10 (3.6%)
Chills/fever	4 (1.4%)
Flu-like Symptoms	3 (1.1%)
Malaise/Weakness/Fatigue	3 (1.1%)
Cardiovascular System	12 (4.3%)
Dizziness	7 (2.5%)
Chest Pain	3 (1.1%)
Digestive System	12 (4.3%)
Nausea and/or Vomiting	12 (4.3%)
Nervous System	3 (1.1%)
Respiratory System	5 (1.8%)
Dyspnea	3 (1.1%)
Skin & Appendages	11 (3.9%)
Injection Site Discomfort	3 (1.1%)
Erythema	2 (0.7%)
Special Senses	9 (3.2%)
Altered Taste	5 (1.8%)

Adverse events reported in < 0.5% of subjects who received OPTISON included: arthralgia, back pain, body or muscle aches, induration, urticaria, dry mouth, eosinophilia, palpitations, paresthesia, photophobia, premature ventricular contraction, pruritus, rash, irritableness, hypersensitivity, tinnitus, tremor, visual blurring, wheezing, oxygen saturation decline due to coughing, discoloration at the Heplock site, and burning sensation in the eyes.

Overall the reported adverse events with OPTISON were similar in type and frequency to those reported in the 199 patients who received ALBUNEX®.

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.

DOSE 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.

1. The injection rate should not exceed 1 mL per second.
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, adequacy of transducer skin interface and other acoustic factors. These 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 cumulatively in a 10 minute period may be injected intravenously up to a maximum total dose of 8.7 mL in any one patient study.

DRUG HANDLING DIRECTIONS

FOR SINGLE USE ONLY.

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 white layer is absent. This indicates that the microspheres may have been damaged and may result in poor or no echo contrast.

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

DO NOT USE if after resuspending the OPTISON, the product remains clear rather than appearing opaque and milky-white.

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 by gently rotating and inverting the syringe.

Before 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 3-way stopcock.

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

For a continuous intravenous line: open an intravenous line with 0.9% Sodium Chloride Injection, USP (or 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 in the OPTISON containing syringe before administration; this may promote the formation of a blood clot within the syringe.

HOW SUPPLIED

OPTISON (Perflutren Protein-Type A Microspheres for Injection, USP) is available in a carton of five 3 mL fills in single use 3 mL vials.

NDC 0407-2707-03

STORAGE

Store OPTISON refrigerated between 2°-8°C (36°-46°F).

Caution: Do not freeze.

Rx ONLY

OPTISON™ is a trademark of Amersham plc.

ALBUNEX® is a trademark of Mallinckrodt Inc.



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