CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-191

Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-191

Alliance Pharmaceuticals, Inc.
Attention: Howard C. Dittrich, M.D.
Senior Vice President, Clinical Research
and Regulatory Affairs
3040 Science Park Road
San Diego, CA 92121

Dear Dr. Dittrich:

Please refer to your new drug application (NDA) dated April 5, 2002, received April 8, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Imagent®.

We acknowledge receipt of your submissions dated November 5; December 15 and 16, 1999; January 12 and 26; February 3, 4, and 28; April 5, 6, and 20; May 30; and June 9 and 16, 2000, and August 18 and 31, 2000; October 18 and 26; August 16, and December 13, 2001, February 14, 26, 28, March 5, 15, 19, April 5 and 18, 2002. We also acknowledge our meeting of March 12, and teleconference of April 1, 2002. We acknowledge your faxes of May 22, which provided data from study IMUS-012-USA; May 29, which provided edits to the label; your two faxes of May 30, 2002, the first of which outlined your commitment to evaluate Imagent® in pediatric patients, and the second which outlined your postmarketing commitment to perform a surveillance study of adverse events in at least one thousand patients receiving marked Imagent®. Additionally, we acknowledge your fax of May 31, 2002, that agreed to the labeling and clarified a previous commitment. Your submission of April 5, 2002, constituted a complete response to our action letter of February 6, 2002r.

This new drug application provides for the use of Imagent® for use in patients with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text and with the minor editorial revisions listed below. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). and include the minor editorial revisions indicated, to the submitted draft labeling (package insert). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999).

Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-191." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments and the completion dates agreed upon. Specifically, you have committed to conduct the following:

1. To conduct the subacute pulmonary hypertension study in dogs as described in the December 21, 2001, submission. The study will be implemented within 4 months of protocol agreements. The results will be submitted within 4 months of study completion. Depending upon the results of this study, a small clinical pharmacokinetics study in COPD subjects may be conducted. The need for, and design of, a clinical study will be discussed with the Agency following submission of the non-clinical study results.

2. To complete a non-clinical study to determine the fate of the activated microspheres, characterizing the length of microsphere persistence and the potential for microsphere gas exchange. Submit draft protocols within 6 months of approval with initiation of the studies within 6 months of agreement on protocol design. Submit final study reports within one year of study initiation.

3. To study the cavitation effects of Imagent® on vasculature with an animal study. If endothelial damage is seen, a subsequent study to evaluate the long term effects will be conducted. Submit draft protocols within 6 months of approval with initiation of the studies within 6 months of agreement on protocol design. Submit final study reports within 6 months of study completion.

4. To test (b)(4) throughout the expiration dating period on at least the first three commercial lots of Imagent . The release and stability data for these compounds must be used to reevaluate their acceptance criteria. These data and corresponding statistical analyses must be presented to the Agency, within the first year of commercial distribution, in a new correspondence or an annual report.

5. To perform surveillance study of adverse events in at least one thousand patients receiving marketed Imagent®. The goal is to capture post-marketing safety information on Imagent® as it is actually used in clinical practice. The protocol will be submitted within 2 months of product launch and implemented within 4 months of design agreement. A final report will be submitted within 6 months of completion.

Submit post market study commitment clinical and non-clinical protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of your commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have fulfilled the pediatric study requirement at this time.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Medical Imaging and Radiopharmaceutical Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please note, if you choose to use a proprietary name for this product, the name and its use in the label must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit any proprietary name to the Agency for our review prior to its implementation.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Tia Harper-Velazquez, Pharm.D., Regulatory Health Project Manager, at (301) 827-7510.

Sincerely,

{See appended electronic signature page}

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Florence Houn
5/31/02 11:22:51 AM

Division's Revised Proposed Package Insert

Imagent®

Kit for the Preparation of Perflexane Lipid Microspheres Injectable Suspension
For Intravenous Administration

DESCRIPTION

Imagent® Kit for the preparation of perflexane lipid microspheres for injectable suspension, is a sterile, non-pyrogenic white powder with a diluted perflexane headspace that, after reconstitution into a suspension of microspheres, is used for contrast enhancement during the indicated ultrasound imaging procedures.

The contents of the 200 mg *Imagent®* powder vial are sterile and non-pyrogenic. Each vial of *Imagent®* powder contains 9.2 mg 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC); 75 mg hydroxyethyl starch; 2.1 mg poloxamer 188; 75 mg sodium chloride; and 36 mg sodium phosphate buffer in a vial filled with a mixture of 17% v/v perflexane vapor in nitrogen.

After reconstitution with 10 mL of the provided Sterile Water for Injection, USP, the contents of the vial yield an opaque white suspension for injection. The reconstituted suspension must be withdrawn from the vial with the supplied vented 5 µm filter dispensing pin.

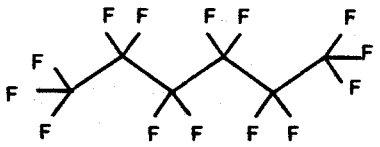
Each mL of reconstituted aqueous suspension contains a maximum of 13.7×10^8 microspheres, 92 µg perflexane, 0.92 mg DMPC; 7.5 mg hydroxyethyl starch; and 0.21 mg poloxamer 188. The reconstituted product is iso-osmolar and has a pH between 6.7 to 7.7.

Table 1. Microsphere Size Distribution

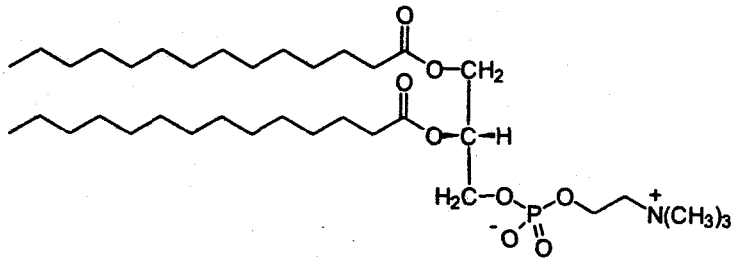
DIAMETER Mean Volume Weighted Median: 6 µm	Number per mL Mean (% of Total)
ALL SIZES (Total)	$5.9\text{-}13.7 \times 10^8$ (100%)
<3 µm	7×10^8 (78.8%)
3 - 10 µm	2×10^8 (21.0 %)
>10 µm	0.01×10^8 (0.2 %)
Upper limit 20 µm	

The active moiety, the microsphere, comprises two critical components: perflexane, the gaseous component, and DMPC, the lipid membrane component.

Perflexane is chemically characterized as n-perfluorohexane with a molecular weight of 338 atomic mass units and an empirical formula of C_6F_{14}. Perflexane has the following structural formula:



DMPC is a semi-synthetic (not of animal origin) phospholipid and is chemically characterized as 1, 2,-dimyristoyl-sn-glycero-3-phosphocholine with a molecular weight of 678 atomic mass units and an empirical formula of $C_{36}H_{72}NO_8P$. DMPC has the following structural formula:



Imagent® Kit for the Preparation of Perflexane-Lipid Microspheres Injectable Suspension is supplied for single-use and each kit contains a 10-mL glass vial containing 200 mg of *Imagent®* powder, a 20-mL plastic vial of Sterile Water for Injection, a 10-mL disposable plastic sterile syringe, a sterile, vented 5 µm filter dispensing pin, and a package insert.

The powder vial must be reconstituted with 10 mL supplied Sterile Water for Injection and then withdrawn from the vial with the provided vented 5 µm filter dispensing pin as described under DOSAGE AND ADMINISTRATION – Drug Handling and Preparation.

CLINICAL PHARMACOLOGY

Pharmacodynamics

After reconstitution and intravenous injection, *Imagent®* increases the ultrasound reflectivity of blood in the left ventricle, thereby enhancing the ultrasound signal.

Using continuous echocardiographic imaging, after intravenous injections of 0.125 mg/kg, the onset of the echogenic effect occurs within approximately 40 seconds and the mean duration of useful contrast enhancement is approximately 2.6 minutes.

Imagent® microspheres are destroyed and contrast enhancement decreases as the mechanical index increases. The mechanical index setting when using *Imagent®* is below 1.0. (See Warnings and Precautions).

Pharmacokinetics

The single or multiple intravenous dose pharmacokinetics of the intact microsphere and of the other components, including DMPC, has not been studied in humans. However, pharmacokinetic information is available for perflexane gas from 12 healthy volunteers (7 men and 5 women.)

Protein Binding

Results of an *in vitro* study indicate that the solubility of perflexane, a critical component of *Imagent®*, is very low in albumin solutions, comparable to its solubility in water, suggesting a low affinity for protein binding. Protein binding studies have not been conducted with the intact microsphere or it's other critical component DMPC.

Metabolism

Perflexane is a stable compound that is not metabolized.

DMPC is a semi-synthetic phospholipid compound, and is expected to be handled by the normal metabolic routes for phospholipids.

Elimination

The elimination of perflexane was evaluated in healthy volunteers. Following administration of a single dose of *Imagent®* (4 mg reconstituted powder/kg [mg/kg] or 20 µg perflexane/kg) to 12 healthy volunteers, perflexane concentrations in both blood and expired air were shown to decline in a multi-exponential fashion with a mean terminal elimination half-life (± SD) in blood and expired air of approximately 5.3 hours (± 6.1 hours) and 9.0 hours (± 5.0 hours), respectively.

Total clearance and lung clearance of perflexane were 716 L/hr (± 735 L/hr) and 603 L/hr (± 94 L/hr), respectively. Approximately 75% of the administered dose of perflexane was recovered in expired air within 3 hours, and approximately 87% was recovered in expired air within 24 hours.

Special Populations

The pharmacokinetics of *Imagent®* have not been studied in subjects with hepatic or renal dysfunction.

Pulmonary

The pharmacokinetics of *Imagent®* have not been studied in subjects with respiratory dysfunction.

Age, Race

The effects of age and race on the pharmacokinetics of *Imagent®* have not been studied.

Gender

Females eliminate perflexane through the expired air more slowly than males (female terminal elimination half-life = 13 ± 4 hours, N = 5; male terminal elimination half-life = 6 ± 3 hours, N = 7). The clinical relevance of the gender differences observed is not known.

Pediatrics

The pharmacokinetics of *Imagent®* in pediatric subjects has not been studied (See WARNINGS).

DRUG-DRUG INTERACTIONS

Drug-drug interactions for *Imagent®* have not been studied.

CLINICAL TRIALS

Reconstituted *Imagent®* was evaluated in two multicenter randomized-blinded image interpretation clinical studies (Studies A and B) of subjects with suboptimal echocardiograms. In Study A, subjects were randomized in single-blind fashion to *Imagent®* or to saline.

These two studies evaluated a total of 409 adults (206 in Study A and 203 in Study B). In this group, 267 (65.3%) were male and 142 (34.7%) were female; 340 (83.1%) were White, 54 (13.2%) were Black, and 15 (3.7%) were classified as other racial or ethnic groups. The mean age was 58.9 years (range 22 to 84).

Eligible subjects had a suboptimal echocardiogram, defined as 2 to 9 non-visualized segments out of 12 segments in the apical 4- and 2-chamber views of the baseline continuous fundamental, two-dimensional echocardiogram. All *Imagent®* treated subjects received a single intravenous bolus injection of 0.125 mg/kg.

Two-dimensional echocardiography was performed before and following the administration of *Imagent®*. Three independent echocardiographers read the baseline non-contrast and the contrast echocardiograms in a blinded and randomized manner. The endpoints were the ability of *Imagent®* to improve endocardial border delineation, ejection fraction, and wall motion scores / measurements using continuous fundamental echocardiographic imaging.

Independent blinded readers (3 for each study) scored 16 left ventricular endocardial border segments on a four-point ordinal scale for delineation and on a six-point scale for wall motion, and measured ejection fraction. These 16 segments were in three views: the apical 4-chamber, apical 2-chamber, and apical long-axis views.

Endocardial Border Delineation

Table 2 presents data comparing a single bolus dose of 0.125 mg/kg reconstituted *Imagent®* to baseline. The mean change in endocardial border delineation score was statistically significant for all readers for all three views in both studies.

Table 2
MEAN (SD) ENDOCARDIAL BORDER DELINEATION SCORE BY APICAL 2- AND 4-CHAMBER VIEWS AND LONG AXIS VIEW BY STUDY, INTENT TO TREAT SUBJECTS

Study/View	Endocardial Border Delineation Score[a] – Blinded Read		
	Mean (SD)		
	Reader 1	Reader 2	Reader 3
Study A: (N = 206)			
Apical 2-chamber			
Baseline	7.5 (2.8)	9.7 (2.6)	7.2 (3.3)
Post-*Imagent®*	11.4 (3.9)*	11.5 (3.2)*	10.0 (3.1)*
Apical 4-chamber			
Baseline	8.4 (2.7)	10.3 (2.4)	7.7 (3.6)
Post-*Imagent®*	12.6 (3.4)*	12.3 (3.0)*	11.7 (3.3)*
Apical Long axis			
Baseline	5.5 (2.0)	6.3 (1.9)	4.8 (2.5)
Post-*Imagent®*	7.9 (2.8)*	7.4 (2.3)*	7.3 (2.5)*
Study B: (N = 203)			
Apical 2-chamber			
Baseline	6.1 (3.6)	5.2 (3.3)	8.1 (2.0)
Post-*Imagent®*	9.6 (4.2)*	8.2 (3.5)*	11.1 (1.9)*
Apical 4-chamber			
Baseline	5.6 (3.7)	5.8 (3.4)	7.5 (1.8)
Post-*Imagent®*	10.5 (4.5)*	9.5 (3.6)*	11.2 (2.0)*
Apical Long axis			
Baseline	3.7 (2.4)	3.3 (2.4)	5.6 (1.6)
Post-*Imagent®*	6.1 (3.0)*	5.5 (2.6)*	7.4 (1.4)*

Reconstituted *Imagent®* Bolus Dose = 0.125 mg/kg
[a] Total score for the view; maximum total score = 18 for the 2- and 4-chamber views and 12 for the long axis view. Missing values were imputed to assume there was no change between non-contrast and contrast images.
* Significant change from baseline (ANOVA model with effect for site, $p<0.05$)

Segmental Wall Motion:

In a retrospectively analyzed, subset of subjects (n=23 to 25, depending on reader) having at least 2 adjacent segments non-evaluable in at least 2 of the 3 views on non-contrast imaging, reconstituted *Imagent®* converted a baseline non-evaluable image to an evaluable image in 43 to 79% of the subjects, depending on the reader. In the converted images, the ability to interpret wall motion (i.e., normal versus abnormal) improved in 10-46% of the subjects, depending on the reader, however, improvement in the specific diagnostic assessments (e.g., hypokinetic, akinetic etc.) was not established. Also, in 20% of the subjects for one reader, reconstituted *Imagent* was found to obscure the wall motion rendering the image non-evaluable.

Ejection Fraction: When ejection fractions derived from echocardiography were compared to radionuclide ventriculography, no improvement over non-contrast studies was observed.

Optimal reconstituted *Imagent®* doses and device settings for harmonic imaging have not been established.

INDICATIONS AND USAGE

Reconstituted *Imagent®* (Perflexane Lipid Microspheres) Injectable Suspension is indicated for use in subjects with suboptimal echocardiograms to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

CONTRAINDICATIONS

None known.

WARNINGS

Cardiac Shunts: The safety of *Imagent®* in subjects with right to left, bi-directional, or transient right to left cardiac shunts has not been studied. In these subjects, microspheres can bypass filtering by the lung and directly enter the arterial circulation. In a microcirculatory study of the musculature in both normal and hyperlipidemic rats after intra-arterial administration of *Imagent®* at a dose of 40 mg/kg (52-fold human dose based on body surface area), microsphere trapping was seen in small arterioles and capillaries ≤7 um. The extent of microsphere trapping tended to be greater in hiperlipdemic rats than in normal rats. Extreme caution should be exercised when considering the administration of *Imagent®* to subjects that may have cardiac shunts.

Pulmonary Vascular Compromise: The safety of *Imagent®* in subjects with compromised pulmonary vascular beds or with small cross-sectional pulmonary vascular surface area has not been studied. The relationship of the size and concentration of microspheres with the possibility of pulmonary microembolism has not been established. In an animal model with artificially induced acute pulmonary hypertension, *Imagent®* did not alter pulmonary artery pressures; however, this acute model does not test the effects on pulmonary occlusion of a histopathologically compromised vasculature. Therefore, *Imagent®* should be administered with caution to subjects with severe emphysema, pulmonary vasculitis, or a history of pulmonary embolism.

Mechanical Index: *Imagent®* microsphere destruction increases (and contrast enhancement diminishes) as mechanical index increases. The mechanical index setting when using *Imagent®* should be below 1.0. For microsphere products, reports in the medical literature note the development of ventricular arrhythmias and endothelial damage in association with systolic triggering or microsphere destruction at a high mechanical index.

PRECAUTIONS

General

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

Diagnostic procedures involving the use of ultrasound microspheres should be conducted under supervision of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed. Appropriate facilities should be immediately available to treat any complication of the procedure, and to treat severe reactions.

Physical stress (such as treadmill test) and pharmacological stress with *Imagent®* have not been studied in humans.

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 with microsphere products. The safety of reconstituted *Imagent®* at mechanical indices greater than 1.0 has not been established. The safety of reconstituted *Imagent®* with the use of end-systolic triggering has not been established.

ECG parameters for the 0.125 mg/kg dose were monitored in 445 subjects baseline; 5 minutes, 1 hour, and 24 hours after *Imagent®* injection. QTc prolongations of >30 msec were noted in 75 (17%) subjects. Malignant cardiac arrhythmias were not reported in these subjects, and the results were similar to those in 81 subjects who received placebo.

Information for subjects

Subjects receiving *Imagent®* should be instructed to:

1. Inform your physician or health care provider if you may be pregnant, are trying to become pregnant, or are nursing.
2. Inform your physician or health care provider if you have a congenital heart defect (See WARNINGS).

Laboratory Tests

In a clinical study in healthy volunteers (N=64), a temporary increase in the serum complement marker C3a was observed following administration of *Imagent®* in some subjects. Clinical sequelae were not noted following these increases. Subjects should be observed for the possibility of hypersensitivity-like reactions.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

The carcinogenic potential of *Imagent®* has not been studied in animals.

Imagent® was negative in the following genetic toxicity studies: 1) an *in vitro* bacterial reverse mutation assay, 2) an *in vitro* chromosomal aberration assay with human lymphocytes, 3) an *in vitro* forward mutation assay with mouse lymphoma cells, and 4) an *in vivo* micronucleus assay in mice.

Potential impairment of fertility in either males or females for *Imagent®* has not been studied in humans. After daily intravenous administration of *Imagent®* for a minimum of 28 successive days at a dose of 200 mg/kg/day (259 times the human dose based on body surface area) the no observable effect level (NOAEL) for male fertility in rats was 100 mg/kg/day (130 times the human dose based on body surface area). There were no effects on fertility or other reproductive performance parameters in female rats.

Pregnancy Category C

An increase in the incidence of fetal malformations, including fetal external and skeletal anomalies (such as microphthalmia, spina bifida, fused and forked ribs), was seen in rabbits given *Imagent®* intravenously in single daily doses of 100 and 200 mg/kg (260 and 520 times the human dose based on body surface area) during the period of organogenesis (gestation days 7–20). The NOAEL for the embryofetal toxicity in rabbits was 50 mg/kg/day (130 times the human dose based on body surface.) Similar effects were not seen in a study conducted in rats treated with the same doses of *Imagent®*.

Imagent® has also been associated with an increase in total postnatal deaths (by 2-fold) and decreases in both neonate live birth (by 7%) and gestation survival index (by 5%) in rats when given intravenously at a daily dose of 200 mg/kg (259 times the human dose based on body surface area) during the prenatal and postnatal development period (from gestation day 6 through lactation day 20). The NOAEL for the neonatal toxicity in rats was 100 mg/kg/day (130 times the human dose based on body surface area) .

Adequate and well-controlled studies have not been conducted in pregnant women. *Imagent®* should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers

It is not known whether *Imagent®* is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when *Imagent®* is administered to a nursing mother.

Pediatric Use

The safety and effectiveness of *Imagent®* in pediatric subjects has not been established.

Geriatric Use

Imagent® was administered to 173 subjects ≥65 years of age in the pivotal clinical studies. Differences in the safety and efficacy with *Imagent®* in the geriatric population were not found when compared to other adult populations, but greater sensitivity to adverse events for some geriatric subjects cannot be excluded.

ADVERSE REACTIONS

A total of 777 subjects were evaluated in clinical trials of *Imagent®*. Of these, 676 subjects received *Imagent®* and 101 subjects received saline. In the *Imagent®* treated participants, there were 432 men and 244 women with a mean age of 57 years (range 19–87). The racial and ethnic representation was 79% Caucasian, 15% Black, and 6% other races.

Deaths and serious adverse events: Among the 676 *Imagent®* subjects, 4 subjects (0.6%) reported a total of 8 serious adverse events. One of these events (myocardial infarct) resulted in death, which occurred 3 days after *Imagent®* administration. Serious adverse events reported for the 3 other subjects included chest pain, atrial fibrillation, heart failure, dyspnea, hypotension, cardiogenic shock, and heart arrest. All 8 serious adverse events appeared related to the course of the illness (i.e., recent myocardial infarction) and the relationship to *Imagent®* administration is not clear.

Overall, of the 561 subjects who received *Imagent®*, 77 (14%) reported at least one adverse event, compared to 11 (11%) of the 101 subjects who received saline.

Table 3
Overall Incidence of Adverse Events Reported in≥0.5% of Subjects that Received *Imagent®*

Body System **Preferred Term**	***Imagent®*** **(n=561)** **n (%)**
Any	77 (13.7%)
Body as a Whole	27 (4.8%)
Headache	14 (2.5%)
Asthenia	4 (0.7%)
Chest pain	3 (0.5%)
Abdominal Pain	3 (0.5%)
Cardiovascular System	27 (4.8%)
Hypertension	7 (1.2%)
Hypotension	5 (0.9%)
Atrial Fibrillation	3 (0.5%)
Vasodilatation	3 (0.5%)
Digestive	16 (2.9%)
Nausea	7 (1.2%)
Diarrhea	5 (0.9%)
Metabolic and Nutritional Disorders	8 (1.4%)
Creatine Phosphokinase Increased	3 (0.5%)
Nervous	6 (1.1%)
Dizziness	3 (0.5%)
Special Senses	5 (0.9%)
Taste perversion	4 (0.7%)

Adverse events following the administration of *Imagent®* that occurred in <0.5% of subjects include the following:

Body as a Whole	Chills, fever, injection site hypersensitivity, injection site reaction, and malaise
Cardiovascular System	Angina pectoris, atrial flutter, bradycardia, congestive heart failure, electrocardiogram abnormal, extrasystoles, heart arrest, heart failure, myocardial infarct, palpitation, shock, sinus bradycardia, supraventricular tachycardia, syncope, T inverted, and tachycardia
Digestive System	Anorexia, dyspepsia, flatulence, tongue disorder, and vomiting
Musculoskeletal System	Myalgia
Nervous System	Confusion, dry mouth, hallucinations, insomnia, paresthesia, and vasodilatation
Respiratory System	Asthma, dyspnea, epistaxis, hypoxia, lung edema, pneumonia, and rhinitis
Skin and Appendages	Sweating
Special Senses	Conjunctivitis and eye pain

OVERDOSAGE

The clinical consequences of overdosing with *Imagent®* are not known. Treatment of an overdose should be directed toward the support of all vital functions and prompt institution of symptomatic therapy. (See Warnings and Precautions.)

DOSAGE AND ADMINISTRATION

***Imagent®* must be reconstituted and withdrawn from the vial via the supplied vented 5 µm filter dispensing pin.**

The recommended dose is 0.00625 mL/kg (0.125 mg/kg) administered as a single intravenous bolus over a period of not less than 10 seconds and immediately followed by a saline flush. *Imagent®* must be used within 30 minutes of reconstitution. Table 4 provides the dose volume (mL) for body kilogram (and pound) weights. **Discard any unused portion.**

The safety and clinical benefit of repeated doses of *Imagent®* have not been established.

The mechanical index setting when using *Imagent®* should be below 1.0. Higher settings will cause microsphere rupture (See Warnings and Precautions).

Table 4. Dose Volumes of Reconstituted *Imagent®* Based on Body Weight

Body Weight (kg)	Body Weight (lb)	Dose (mL)	Body Weight (kg)	Body Weight (lb)	Dose (mL)	Body Weight (kg)	Body Weight (lb)	Dose (mL)
40	88	0.25	84	185	0.53	128	282	0.80
44	97	0.28	88	194	0.55	132	291	0.83
48	106	0.30	92	203	0.58	136	300	0.85
52	115	0.33	96	212	0.60	140	309	0.88
56	123	0.35	100	220	0.63	144	317	0.90
60	132	0.38	104	229	0.65	148	326	0.93
64	141	0.40	108	238	0.68	152	335	0.95
68	150	0.43	112	247	0.70	156	344	0.98
72	159	0.45	116	256	0.73	160	353	1.00
76	168	0.48	120	265	0.75	164	362	1.03
80	176	0.50	124	273	0.78	168	370	1.05

Drug Handling and Preparation:

FOR SINGLE USE ONLY. When properly reconstituted, *Imagent®* should have an opaque white appearance. Do not use if particulates or if any change in color are observed. *Imagent®* does not contain preservatives. If the solution becomes clear during preparation or dosing, discard it because its safety and efficacy have not been established Use *Imagent®* within 30 minutes of reconstitution.

WARNING: *Imagent®* must be reconstituted with the supplies provided in the kit. Replacing any component could compromise product reconstitution and performance.

The kit must be at room temperature before use.

Patient Preparation

1. Prepare patient with intravenous catheter of 20 gauge or larger.
2. Determine the appropriate volume to administer a dose of 0.125 mg/kg (or 0.00625 mL/kg) based on the weight of the patient (see Table 4, Dosage and Administration section).

Reconstitution Procedure for Imagent®

1. Connect the 10 mL syringe and dispensing pin into one assembly. Fully depress syringe plunger to expel air (Fig. 1).
2. Grasp the dispensing pin and push down through the center of the Sterile Water for Injection (SWFI) stopper.
3. Invert the SWFI and dispensing pin assembly and slowly withdraw 10 mL into the syringe (Fig. 2).
4. Remove the dispensing pin assembly from the SWFI.
5. Push and twist the dispensing pin assembly into the *Imagent®* vial until fully inserted. **DO NOT INJECT AIR INTO THE *IMAGENT®* VIAL**
6. Holding the vial and syringe at a 45-degree angle with the side vent facing up and the syringe facing down, slowly (over 10 seconds) inject 7 mL SWFI. Briefly swirl to wet the powder (Fig. 3).
7. Add the remaining SWFI (about 3 mL) and shake until dissolved and the solution is an opaque white liquid that may have a foamy appearance (Fig. 4).
8. **Do not allow reconstituted *Imagent®* to sit for longer than 30 minutes before administration. *Imagent®* must be discarded after 30 minutes of reconstitution.**


Fig. 1

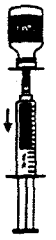


Fig. 2

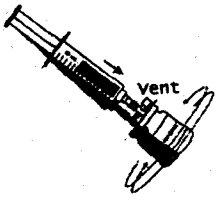


Fig. 3

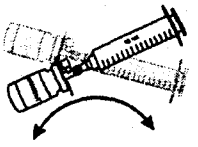


Fig. 4

Administration Procedure for Imagent®

1. Immediately (within one minute) before injection, repeat agitation of vial (Fig. 4) to resuspend its contents, invert and allow foam to rise to the surface of the liquid, avoiding the foam that was allowed to rise.
2. Withdraw 1 mL of reconstituted *Imagent®* to remove any residual water from the dispensing pin assembly. Detach the 10-mL syringe and contents from the dispensing pin and discard (Fig. 5). The product is now ready for administration.
3. Based on the calculated volume need, connect an appropriately calibrated 1-3 mL syringe (not supplied) to the dispensing pin. Slowly withdraw the dose. (Fig. 6). **Do not push/pull the plunger rapidly. If excessive pressure/vacuum is applied and the microspheres are damaged, the product may become clear and should not be used. Immediately after withdrawing the dose, inject it over 30 seconds into the intravenous line.**
4. Immediately after injection slowly (over a 30 second period) flush the catheter with 1-2 mL of saline to clear the catheter.

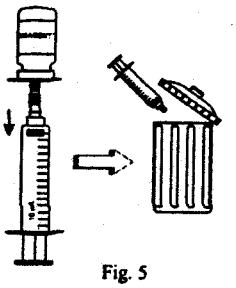


Fig. 5

Fig. 6

HOW SUPPLIED

Imagent® Kit for the preparation of Perflexane-Lipid Microspheres for Injectable Suspension is supplied for single-use. Each kit contains the following parts:

- One 10-mL glass vial containing 200 mg of *Imagent®* Powder for Injectable Suspension.
- One 20-mL plastic vial of Sterile Water for Injection, USP.
- One 10-mL disposable plastic sterile syringe.
- One vented 5 µm filter dispensing pin.
- One package insert.

The powder in the vial must be reconstituted with 10 mL supplied SWFI and withdrawn from the vial via the supplied vented 5 µm filter dispensing pin as described under DOSAGE AND ADMINISTRATION – Reconstitution Procedure for *Imagent®*.

U.S. Patent Nos: (5,605,673); (5,626,833); (5,639,443); (5,695,741); (5,720,938); (5,798,091); (6,258,339); (6,280,704); (6,280,705); and (6,287,539)

NDC xxxxx-xxxx-xx.

STORAGE

Store the kit components and reconstituted *Imagent®* at 25°C (77°F); excursions permitted to 15 – 30°C (59° – 86°F). [see USP Controlled Room Temperature]

Use reconstituted *Imagent®* Injectable Suspension within 30 minutes.

***Month*, 2002**

Manufactured by Alliance Pharmaceutical Corp., San Diego, CA U.S.A 92121

For Customer Service call 1-800-IMAGENT (1-800-462-4368)

LABEL FOR IMMEDIATE CONTAINER , 10ML GLASS VIAL-

(OPTION 2 OF EMAIL DATED 1-MAY-02)

Lot # 000000
Exp: MMMYY

***Imagent*®**
Perflexane Lipid Microspheres
Powder For Injectable Suspension
200 mg
For intravenous use only

Single-dose vial. Contains no preservatives. Rx Only

Use within 30 minutes of reconstitution. Discard unused portion.

See package insert for Product Description, Dosage, Reconstitution, and Administration instructions.

Do not use if seal is broken.

Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F)

Reconstitute with 10 mL SWFI prior to use and remove from vial using provided vented 5 μm filter dispensing pin.

Upon reconstitution, each mL contains:
- **Maximum of 13.7×10^8 microspheres**
- **92 μg perflexane**
- **0.92 mg DMPC**
- **7.5 mg hydroxyethyl starch**
- **0.21 mg poloxamer 188.**
- **Product is iso-osmotic, pH 6.7 to 7.7**

Alliance Pharmaceutical Corp.
San Diego, CA 92121 U.S.A.
NDC # xxxxx-xxxx-xx

Artwork Rev. xx/xx

TOP PANEL - Carton **Actual Size: 9 1/8 x 7 3/4**

Imagent® Kit for the Preparation of Perflexane Lipid Microspheres
Injectable Suspension
Rx Only

For intravenous use only.

Each kit contains one 10-mL glass vial containing 200 mg of *Imagent* Powder for Injectable Suspension, one 20-mL plastic vial of Sterile Water for Injection, USP, one 10-mL disposable plastic sterile syringe, one vented Mini-Spike 5 µm filter dispensing pin, one package insert.

Carton contains 4 kits.

Catalog Number XXXXXXX

For Customer Service Call 1 - XXX – XXX- XXXX

Alliance Pharmaceutical Corp.

FRONT SIDE PANEL - Carton **Actual Size: 9 1/8 x 5 3/4**

Imagent® Kit for the Preparation of Perflexane Lipid Microspheres
Injectable Suspension
Carton contains 4 kits.

Alliance Pharmaceutical Corp.

See package insert for Product Description, Dosage, Reconstitution, and Administration.

REAR SIDE PANEL - Carton **Actual Size: 9 1/8 x 5 ¾**

LOT # 000000

EXP. DATE: XX/XXXX

LEFT SIDE PANEL - Carton **Actual Size: 7 3/4 x 5 3/4**

Imagent® Kit for the Preparation of
Perflexane Lipid Microspheres
Injectable Suspension

Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F)

[see USP Controlled Room Temperature]

Patents, see Insert

Alliance Pharmaceutical Corp., San Diego, CA 92121

RIGHT SIDE PANEL - Carton **Actual Size: 7 3/4 x 5 3/4**

Imagent® Kit for the Preparation of
Perflexane Lipid Microspheres
Injectable Suspension
Rx Only

For intravenous use only.

Alliance Pharmaceutical Corp., San Diego, CA 92121

Made in USA

NDC #xxxxx-xxxxxx

Artwork revision number will be placed inside box flap