# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPROVAL PACKAGE FOR:

# APPLICATION NUMBER

# 21-191

# Administrative Documents

ALLIANCE PHARMACEUTICAL CORP.
AF0150 New Drug Application

Patent No.: 6,280,704
Expiration Date: July 30, 2013
Type of Patent: Drug Product
Patent Owner: Alliance Pharmaceutical Corp.

The undersigned declares that U.S. Patent No. 6,280,704 covers the formulation, composition, and/or method of use of IMAVIST™. This product is the subject of this application for which approval is being sought.

Dated: 9/19/2007

By: _____
John E. Wurst
Patent Counsel and Assistant Secretary
Alliance Pharmaceutical Corp.

ALLIANCE PHARMACEUTICAL CORP.
AF0150 New Drug Application

Patent No.: 6,280,705
Expiration Date: July 30, 2013
Type of Patent: Drug Product
Patent Owner: Alliance Pharmaceutical Corp.

The undersigned declares that U.S. Patent No. 6,280,705 covers the formulation, composition, and/or method of use of IMAVIST™. This product is the subject of this application for which approval is being sought.

Dated: 9/19/2003

By: _____
John E. Wurst
Patent Counsel and Assistant Secretary
Alliance Pharmaceutical Corp.

ALLIANCE PHARMACEUTICAL CORP.
AF0150 New Drug Application

Patent No.: 6,287,539
Expiration Date: July 30, 2013
Type of Patent: Drug Product
Patent Owner: Alliance Pharmaceutical Corp.

The undersigned declares that U.S. Patent No. 6,287,539 covers the formulation, composition, and/or method of use of IMAVIST™. This product is the subject of this application for which approval is being sought.

Dated: 10/9/01

By: _____
John E. Wurst
Patent Counsel and Assistant Secretary
Alliance Pharmaceutical Corp.

ALLIANCE PHARMACEUTICAL CORP.
AF0150 New Drug Application

Patent No.: 5,605,673
Expiration Date: February 25, 2014
Type of Patent: Drug Product
Patent Owner: Alliance Pharmaceutical Corp.

The undersigned declares that patent no. 5,605,673 covers the formulation, composition, and/or method of use of IMAGENT®. This product is the subject of this application for which approval is being sought.

Dated: 6/2/99

By: _____
Christopher A. Dayton
Patent Counsel
Alliance Pharmaceutical Corp.

ALLIANCE PHARMACEUTICAL CORP.
AF0150 New Drug Application

Patent No.: 5,626,833
Expiration Date: May 6, 2014
Type of Patent: Method of Use
Patent Owner: Alliance Pharmaceutical Corp.

The undersigned declares that patent no. 5,626,833 covers the formulation, composition, and/or method of use of IMAGENT®. This product is the subject of this application for which approval is being sought.

Dated: 6/2/99

By: [signature]
Christopher A. Dayton
Patent Counsel
Alliance Pharmaceutical Corp.

ALLIANCE PHARMACEUTICAL CORP.
AF0150 New Drug Application

Patent No.: 5,639,443
Expiration Date: June 17, 2014
Type of Patent: Drug Product
Patent Owner: Alliance Pharmaceutical Corp.

The undersigned declares that patent no. 5,639,443 covers the formulation, composition, and/or method of use of IMAGENT®. This product is the subject of this application for which approval is being sought.

Dated: 6/2/99

By: _____
Christopher A. Dayton
Patent Counsel
Alliance Pharmaceutical Corp.

ALLIANCE PHARMACEUTICAL CORP.
AF0150 New Drug Application

Patent No.: 5,695,741
Expiration Date: December 9, 2014
Type of Patent: Drug Product and Method of Use
Patent Owner: Alliance Pharmaceutical Corp.

The undersigned declares that patent no. 5,695,741 covers the formulation, composition, and/or method of use of IMAGENT®. This product is the subject of this application for which approval is being sought.

Dated: 6/4/99

By: _____
Christopher A. Dayton
Patent Counsel
Alliance Pharmaceutical Corp.

ALLIANCE PHARMACEUTICAL CORP.
AF0150 New Drug Application

Patent No.: 5,720,938
Expiration Date: February 24, 2015
Type of Patent: Drug Product
Patent Owner: Alliance Pharmaceutical Corp.

The undersigned declares that patent no. 5,720,938 covers the formulation, composition, and/or method of use of IMAGENT®. This product is the subject of this application for which approval is being sought.

Dated: 6/2/99

By: [signature]
Christopher A. Dayton
Patent Counsel
Alliance Pharmaceutical Corp.

ALLIANCE PHARMACEUTICAL CORP.
AF0150 New Drug Application

Patent No.: 5,798,091
Expiration Date: August 25, 2015
Type of Patent: Drug Product and Method of Use
Patent Owner: Alliance Pharmaceutical Corp.

The undersigned declares that patent no. 5,798,091 covers the formulation, composition, and/or method of use of IMAGENT®. This product is the subject of this application for which approval is being sought.

Dated: 6/2/99

By: _____
Christopher A. Dayton
Patent Counsel
Alliance Pharmaceutical Corp.

EXCLUSIVITY SUMMARY FOR NDA #__21-191__ SUPPL #_____

Trade Name Imavist_____ Generic Name Perflexane-phospholipid microbubbles for injection

Applicant Name Alliance Pharmaceuticals HFD # 160____

Approval Date If Known _____

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?
YES /X/ NO /__/

b) Is it an effectiveness supplement?

YES /__/ NO /X/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /__/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /___/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # _____ YES /___/ ! NO /___/ Explain: _____
!
! _____

Investigation #2 !
!
IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!
_____ ! _____
!
_____ ! _____
!
!

Investigation #2 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!
_____ ! _____
!
_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /__/ NO /__/

If yes, explain: _____

_____

/S/

_____ _____

Signature Date

Title:_____

Note: Will be signed when approved.

/S/

_____ _____

Signature of Office/ Date

Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

# PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

| | | | |
|---|---|---|---|
| **NDA/BLA Number:** | 21191 | **Trade Name:** | IMAVIST(PERFLEXANE-PHOSPHOLIPID MICOBUBL |
| **Supplement Number:** | | **Generic Name:** | PERFLEXANE PHOSPHOLIPID MICROBUBBLES |
| **Supplement Type:** | | **Dosage Form:** | PDR |
| **Regulatory Action:** | AE | **Proposed Indication:** | / |

**ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?**

NO, No waiver and no pediatric data

**What are the INTENDED Pediatric Age Groups for this submission?**

____NeoNates (0-30 Days ) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

| | |
|---|---|
| **Label Adequacy** | Does Not Apply |
| **Formulation Status** | - |
| **Studies Needed** | - |
| **Study Status** | - |

**Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission?** NO

**COMMENTS:**

**This Page was completed based on information from ~~a~~ PROJECT MANAGER/CONSUMER SAFETY OFFICER, TIA HARPER-VELAZQUEZ**

/S/ 8/7/00

Signature Date

Alliance
PHARMACEUTICAL CORP.

## DEBARMENT CERTIFICATION STATEMENT

NDA 21-191
AF0150; Perflexane-phospholipid Microbubbles for Injection

Manufactured by:
ALLIANCE PHARMACEUTICAL CORP.

Section 306(k) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 335a(k)), as amended by the Generic Drug Enforcement Act of 1992 (GCEA), requires that:

> "...any application for approval of a drug product shall include a certification that the applicant did not and will not use in any capacity the services of any person debarred under subsections (a) or (b)[section 306(a) or (b)], in connection with such application"

***Alliance Pharmaceutical Corp. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.***

AB Vassos

Artemios B. Vassos, MD
Chief Scientific Officer
(858) 401-5200

10-11-99

Date

3040 Science Park Road, San Diego, CA 92121 (619) 558-4300 Fax: (619) 558-3625

Alliance
PHARMACEUTICAL CORP.

## FINANCIAL DISCLOSURE

NDA 21-191
AF0150; Perflexane-phospholipid Microbubbles for Injection

Manufactured by:
ALLIANCE PHARMACEUTICAL CORP.

The final rule on Financial Disclosure by Clinical Investigators (63 FR 72171, December 31, 1998) revised 21 CFR 54 to require that the sponsor of a marketing application submit certain information concerning financial interests of clinical investigators conducting covered clinical trials that were *ongoing as of February 2, 1999*, or to certify to the absence of such interests.

***Alliance Pharmaceutical Corp. hereby certifies that all studies conducted in support of this application and subject to this rule (i.e., Phase 3 studies IMUS-007-USA and IMUS-008-USA) were complete as of February 2, 1999. Thus, no financial information is required to be submitted for any clinical investigator, and FDA Form 3454 does not apply.***

***Additionally, Alliance certifies that:***

- ***There were no financial arrangements between the sponsor and any of the clinical investigators that would bias the clinical studies, and***
- ***There was no proprietary interest on the part of any clinical investigator.***

AB Vassos — 10-11-99

Artemios B. Vassos, MD
Chief Scientific Officer
(858) 401-5200

Date

3040 Science Park Road, San Diego, CA 92121 (619) 558-4300 Fax: (619) 558-3625

Alliance
PHARMACEUTICAL CORP.

**FIELD COPY CERTIFICATION**
**(21 CFR 314.50(k) (1))**

NDA 21-191
AF0150; Perflexane-phospholipid Microbubbles for Injection

Manufactured by:
ALLIANCE PHARMACEUTICAL CORP.

***Alliance Pharmaceutical Corp. hereby certifies that the Field Copy is a true copy of the technical section described in 21 CFR 314.50 (d)(1) (Chemistry, Manufacturing and Controls) contained in the archival and review copies of the application.***

AB Vassos

Artemios B. Vassos, MD
Chief Scientific Officer
(858) 401-5200

10-11-99

Date

3040 Science Park Road, San Diego, CA 92121 (619) 558-4300 Fax: (619) 558-3625

BRIEF DIVISION DIRECTOR MEMO TO THE FILE

| | |
|---|---|
| NDA: | 21,191 |
| DRUG: | Imagent or Imavist (Perflexane Lipid Microsphere) Powder for preparation of Injectable Suspension |
| ROUTE: | Intravenous |
| MODALITY: | Echocardiography contrast (1S) |
| INDICATION: | Endocardial border delineation and left ventricular opacification |
| SPONSOR: | Alliance Pharmaceutical Corporation |
| CATEGORY: | Resubmission (Response to approvable letter) |
| RECEIVED: | April 08, 2002 |
| FDUFA DATE: | September 07, 2002 |
| COMPLETED: | May 30, 2002 |

RELATED DRUGS:

Albunex NDA 21,207, approved as PMA, 1994, withdrawn 1999
Optison NDA 20,899, approved 1997
Definity NDA 21,064, approved 1999

RELATED REVIEWS:

| | |
|---|---|
| Chemistry: | Milagros Salazar Davi, PhD - 08/07/00; 12/19/01, 05/15/02 |
| Clinical: | B Parker, MD - 08/07/00, 12/19/01, 04/29/02 |
| | P. Love, MD - 08/07/00, 01/21/02 |
| Clinical Pharmacology: | D Lee, PhD - 08/11/00; 11/26/01, |
| | Y. M. Choi - 05/14/02 |
| Microbiology: | C Vincent, PhD - 03/15/00 |
| Pharmacology-toxicology: | J Chen, MD, PhD - 07/25/00; 10/22/01; 05/07/02 |
| | N Sadrieh, PhD - 08/07/00; 10/20/01 |
| Statistics: | S Castillo, PhD - 05/05/00; 11/26/01 |
| Project Manager: | Tia Harper Velazquez, PharmD |

BACKGROUND

Imagent[1] (perflexane Lipid Microsphere) Powder for preparation of Injectable Suspension is manufactured by Alliance Pharmaceutical Corporation. The original NDA was submitted October 14, 1999 and was found to be approvable on August 14, 2000. At that time there was improvement in the endocardial border delineation (EBD); however, the clinical relevance of the anatomic endpoint was in question. Other deficiencies included lack of data and manufacturing controls to characterize and ensure the upper limit of the microbubble size, pharmacology data to evaluate the potential for microembolization and clinical pharmacology data on metabolism and elimination.

On August 20, 2001 a resubmission was received. Although a number of the deficiencies were resolved, several key issues continued. A second approvable letter was issued on February 6, 2002. At this time there were two critical deficiencies. The first was the continued lack of information on the clinical utility of the structural endpoint. The second was a deficiency in data on the safety of Imagent in pulmonary impaired patients.

[1] With the April 08, 2002 resubmission, a name change from Imavist to Imagent was proposed by the sponsor.

a. Clinical utility of the structural endpoint.

At the end of the second review, it was determined that the intuitive value of the microspheres was to delineate the border and to return the device to its inherent ability. However, for Imagent, the trend of this benefit was based on a limited 26 patient subset with a unique case report form that did not allow for the blinded readers to attempt to evaluate a suboptimally delineated border.

To resolve this the action letter requested a blinded re-read of the 26 patients with a MRI control

2. Safety in pulmonary disease

There was a collective deficiency in the data to characterize the potential for Imagent to effect the pulmonary vasculature or the elimination of the gas. In the previous submission, in lieu of human data, the sponsor submitted a proposal to do a phase 4 study in animals. Also, the sponsor noted that the animal study was ongoing. By default that meant the NDA did not have either animal or human data at the time of the action. Previously the oxygenation data from the existing patients had a limited NDA analysis. Therefore, in anticipation that the NDA would have animal data and not human PK data, the action letter requested the following:

a. For the subgroup of patients with COPD who had $Pa0_2$ monitored at the various specified time-points.

   - Provide clinical history on these patients in terms of disease type (e.g., asthma, bronchitis, emphysema, and bronchiolitis), including the status of disease (e.g., active vs. inactive), and concomitant medications, if any.

   - Reanalyze for changes (baseline vs. post-contrast) in magnitude of the $Pa0_2$ (%) in decrements of 2% for all patients at all measured time-points.

   - Indicate if the $Pa0_2$ changes were associated with symptoms and/or adverse events.

   - Provide information on the adverse event profile for this subgroup in comparison to the study population (minus the COPD subgroup).

b. Submit the results of a study in humans with the potential to have decreased expiration of oxygen or in an appropriate animal model must be submitted. Positive controls (e.g., carbon dioxide diffusion capacity) must be used. If animal data are to be submitted, the protocol must be submitted for our review before implementation.

In addition to the above concerns, the February 6, 2002 approvable letter requested CMC methods validation post approval protocol revisions, labeling revisions, and phase 4 commitments for pediatric studies, and animal studies.

On April 08, 2002 a complete response was received. All reviews are complete and the application is acceptable with labeling revisions and post approval commitments. The remainder of this memo expands upon the salient aspects of the resubmission.

I. EFFICACY:

As noted in my memo of January 21, 2002, when this class of products was originally approved, the anatomic/structural delineation of the endocardial border had implied clinical utility to enhance the clinically relevant functional segmental wall motion (SWM) and ejection fraction (EF) assessments. However, in 1999-2000, based on NDA data from Imavist and 2 other NDAs the expected improvement in SWM and EF was not documented. Additional data were requested to either achieve a SWM or EF indication or to establish a trend and achieve an EBD indication with restrictive labeling. The above

deficiencies and requests were identified in the original and resubmission action letters of August 14, 2000 and February 06, 2002.

Additionally, based on the last review cycle, it appeared that the primary benefit of ultrasound (US) contrast is in SWM assessments. In this context the contrast restores the ability of US to its original condition as if the wall was seen without contrast. The use of contrast does not increase the device capability. This interpretation must be made with caution; however, because the data to support the clinical benefit of the anatomic endpoint are marginal at best. Also, it appeared that future ultrasound cardiac contrast trial designs should focus on the clinical benefit endpoints (wall thickening, consistency in monitoring, ICU settings, or on perfusion imaging). Overall the supportive information was marginal but consistently logical (i.e., the border must be seen before it can be evaluated). Therefore, because the Imagent dataset to establish a trend was small, a blinded re-read of these data was requested.

The blinded re-read was requested because of a computerized dataset that did not allow the readers to attempt an SWM interpretation of the sub-optimal EBD. The re-read would analyze areas with ≥2 adjacent segments that were considered suboptimal at baseline. The analysis would be by reader and would report the percent improvement and the test statistics. In response to the request, instead of a blinded re-read, the sponsor proposed an alternative more restricted analysis on the existing dataset. Specifically, the analyzed areas would be those where 2 out of 3 blinded readers had ≥2 adjacent segments that were considered suboptimal at baseline and had improvement after Imavist. Because this was a more stringent analysis it was accepted for review.

The clinical and statistical reviewers continue to have reservations about the sample size of the critical subset and note that statistical significance is not possible. That is correct; however, the purpose of this analysis was to establish the trend to support the EBD indication. To that extent, Dr. Parker's review page 14 considers that 'efficacy' in this matter has been demonstrated. However, page 28 addresses the functional claim and notes that another study is needed. I agree that a new data are needed for a Segmental Wall Motion, Ejection Fraction, or other labeled functional indication. However, given the transitional nature of this NDA, it is acceptable for an anatomic indication with disclaimers on ejection fraction and the diagnosis of segmental wall motion defects.

Dr. Parker's review (page 9-13) adequately summarizes the results. The labeling will reflect the following:

> "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."

II. SAFETY:

A. Safety Update

1. Safety in pulmonary disorders:

As noted in the introduction, the NDA had incomplete information to characterize the safety of Imagent in pulmonary patients. The resubmission included a subset analysis of COPD patients with active and inactive disease. Dr. Parker's review page 20-25 describes the results. Overall, he concludes that the changes do not identify confirmed differences in patients with active or inactive COPD. In clinical trials, 97 patients had chronic obstructive lung disease. Of these, 26 had a ≥2% decrease in oxygen saturation and 6 patients with active COPD had a 4% decrease in oxygen saturation.

Additionally, the resubmission included the results of the effect of minute ventilation changes on the elimination of the gas (perfluorohexane) in anesthetized, mechanically ventilated dogs. This study provided limited information because the mechanical ventilation abnormalities only mimic one type of pulmonary deficiency. Also, Dr. Chen notes that the terminal gas elimination phase was not measured. Subsequently, the sponsor provided the following commitment.

> "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."

Collectively, the new subset analysis in COPD patients combined with the preliminary animal study and the phase 4 commitment are considered to be acceptable for approval. The labeling will state the unknown effects of Imagent on pulmonary patients. Also, pending the results of the animal study, additional data will be obtained as part of the phase 4 commitment.

2. QTC Prolongation:

At the end of the previous review cycles, QTc prolongation was noted on intermittent electrocardiographic monitoring. The approval letter requested additional information from ongoing studies. Updated ECG data were provided for patients in an ongoing Alliance sponsored study and two individual investigators INDs. All studies used doses higher than that proposed for market, used pharmacologic stress, and/or imaged a different area of the body (e.g., prostate). In the pharmacologic stress studies, the cardiovascular adverse events increased. Additionally the reports of QTc prolongation increased after pharmacologic stress (see Dr. Parker's review page 15 – 18). Of the prolongations, most were <30 msec.

In an individual investigator IND one patient undergoing a prostate biopsy after use of Imagent to guide the biopsy experienced bradycardia, syncope, and a seizure. Later that day the patient had a second seizure, a cardiac arrest, and received a pace maker. Subsequently, the pacemaker was removed and the patient was discharged. This onset of these events was coincident with both Imavist injection and prostate biopsy. The description of the event is consistent with a vasovagal reaction although the contribution of Imagent cannot be excluded because continuous ECG monitoring was not done. The labeling contains a warning about QTC prolongation.

3. Other Non-clinical safety studies:

Two non-clinical post approval commitments were requested in the February 6, 2002 approvable letter. The sponsor has agreed to the following:

> "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."

> "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."

These are acceptable pending the addition of time frames to the cavitation studies.

Overall the new safety data are consistent with findings in the previous submissions and the findings will addressed in labeling. Also, the proposed labeling includes adverse event table comparisons to placebo. Overall, only 81 subjects received placebo. The trials were not designed to document causality of the drug versus underlying disease. The comparative results should be deleted.

Additionally, because of the evolution of the class of microspheres, a postmarket surveillance study is needed to confirm the use of the product in larger numbers of patients. The following acceptable phase 4 commitment was submitted.

> " To perform a surveillance study of adverse events in at least one thousand patients receiving marketed Imavist®. 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."

III. PEDIATRICS:

On May 30, 2002, Alliance submitted a revised pediatric plan and commitment to conduct the requested studies. If the "Agency revises its 'pediatric rule', the sponsor reserved "the right to reconsider". This is acceptable.

IV. CMC:

All outstanding deficiencies have been addressed and based on the following post approval commitment, the CMC section is considered acceptable.

> " To test [redacted] throughout the expiration dating period on at least the first three commercial lots of Imavist™. 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. "

V. MICROBIOLOBY:

Sterility assurance was considered to be acceptable during the original review cycle.

VI. NOMENCLATURE:

The current resubmission included a name change from Imavist to Imagent. OPDRA noted that there is one similar sounding product, IM Gent. This is an intramuscular gentamycin. It is felt that the two products would not be used in the same area of the hospital and the dosing schedules are different. Overall, the change is acceptable to OPDRA.

Of note the sponsor had previously marketed another product known as Imagent-GI. That was an oral solution. The sponsor was advised that if they wish to re-market Imagent-GI, then the nomenclature of one or both may be reconsidered.

ASSESSMENT:

Based on the resubmission, subsequent amendments, phase 4 commitments, and agreed upon labeling revisions, the NDA database is acceptable for approval of the structural indication with a paragraph noting the trends and limitations in the segmental wall motion analysis.

**ACTION**: Approval

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/s/
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Patricia Love
5/31/02 11:19:07 AM
MEDICAL OFFICER

To: Florence Houn
Director ODE III

From: John Leighton
Associate Director for Pharmacology/Toxicology, ODE III

Subject: NDA 21-191
Imagent (perflexane lipid microspheres)

Date: May 30, 2002

**Introduction**

Imagent (perflexane lipid microspheres) is used for contrast enhancement during certain ultrasound imaging procedures. A draft label is provided for review.

**Review of Draft Pharmacology/Toxicology Labeling Issues**

**Under "Carcinogenesis, Mutagenesis, and Impairment of Fertility":**

Study findings should be described based on actual doses administered (e.g., mg/kg/d rather than multiples of the human dose based on body surface). However, multiples of the human dose should be included for comparative purposes.

Describing reproductive toxicity findings as a % of fetuses with malformations is unusual and potentially misleading. Without additional information, combining fetal malformations in a single category for reporting is not useful.

In most cases, the product tested in studies conducted for this section is not the marketed formulation. The Division should ensure that the findings correctly refer to Imagent or perflexane lipid microspheres as the appropriate chemical descriptor.

**Under "Nursing mothers":**

If perflexane is excreted in rodent milk, this information should be included.

APPEARS THIS WAY
ON ORIGINAL

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/s/

John Leighton
5/31/02 10:00:20 AM
PHARMACOLOGIST

**NDA 21-191**

**IMAGENT**
**Kit for the Preparation of (Perflexane Lipid Microspheres) Injectable Suspension**

**CHEMISTRY DIVISION DIRECTOR REVIEW**

Applicant: Alliance Pharmaceutical Corp.
3040 Science Park Road
San Diego, CA 92121

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

Presentation: 10 mL clear vial, with a 20 mL plastic syringe [redacted]
510(k) [redacted] and a 20 mL vial containing WFI for reconstitution (Abbott Labs, NDA 18-801) along with a vented filter [redacted]
510(k) [redacted]

EER Status: Acceptable 29-OCT-2001

Consults: OPDRA –IMAGENT is acceptable 28-MAY-2002
Statistics – none
EA – no consult - waiver requested – granted
Micro – acceptable 3/15/2000

The drug product vials contain the lyophillized lipid components and excipients with perflexane/nitrogen headspace which are extemporaneously reconstituted into the perfexane entrapped microspheres suspension.

The perflexane **drug substance** (tetradecafluorohexane) is manufactured by [redacted] - see DMF [redacted] Because the lipid component is also considered as a drug substance by the Division, it was reviewed in this manner. The dimyristoylphosphatidyl choline (DMPC) manufacture is manufactured by [redacted] - see DMF [redacted] Note that the DMPC is of non-animal orign.

The manufacturing processes and controls were found acceptable. The specifications were found acceptable. And Alliance acceptance criteria were also found to be acceptable. A re-test period of [redacted] months is supported by submitted stability data for both.

**Conclusion**
Drug substances are acceptable.

The **drug product** is a perflexane/nitrogen entrapped microsphere with excipients and pH and tonicity adjusting components.

The manufacturing process consists [redacted] The manufacturing process is considered adequate. Adequate in-process controls are in place. The proposed regulatory specifications are acceptable – bubble sizing has been adequately addressed. Submitted stability data support the proposed 24 month expiry, and used within 30 min post reconstitution labeling. Labeling is acceptable – reconstitution instructions are similar to what was used in the clinical trials.

Deficiencies have been resolved in 4 review cycles.

All associated DMFs are acceptable.

**Overall Conclusion**
From a CMC perspective the application an approval action is recommended.

[redacted]
Eric P Duffy, PhD
Director, DNDC II/ONDC

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/s/

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Eric Duffy
5/28/02 04:49:14 PM
CHEMIST
Division Director's review.

DIVISION DIRECTOR MEMORANDUM TO THE FILE

| | |
|---|---|
| NDA: | 21,191 |
| DRUG: | Imavist (Perflexane Lipid Microsphere) Powder for preparation of Injectable Suspension |
| ROUTE: | Intravenous |
| MODALITY: | Echocardiography contrast (1S) |
| INDICATION: | Endocardial border delineation and left ventricular opacification |
| SPONSOR: | Alliance Pharmaceutical Corporation |
| CATEGORY: | Resubmission (Response to approvable letter) |
| SUBMITTED: | August 20, 2001 |
| FDUFA DATE: | February 20, 2002 |
| COMPLETED: | January 21, 2002 |

RELATED DRUGS:

Albunex NDA 21,207, approved as PMA, 1994, withdrawn 1999
Optison NDA 20,899, approved 1997
Definity NDA 21,064, approved 1999

RELATED REVIEWS:

Chemistry: Milagros Salazar Davi, PhD - 08/07/00; 12/19/01
Clinical: B Parker, MD:- 08/07/00, 12/19/01
P. Love, MD – 08/07/00
Clinical Pharmacology: D Lee, PhD - 08/11/00; 11/26/01
Microbiology: C Vincent, PhD - 03/15/00
Pharmacology-toxicology: J Chen, MD, PhD - 07/25/00; 10/22/01;
N Sadrieh, PhD - 08/07/00; 10/20/01
Statistics: S Castillo, PhD - 05/05/00; 11/26/01
Project Manager: Tia Harper Velazquez, PharmD

BACKGROUND

Imavist (perflexane Lipid Microsphere) Powder for preparation of Injectable Suspension is manufactured by Alliance Pharmaceutical Corporation. The original NDA was submitted October 14, 1999 and was found to be approvable on August 14, 2000. The application was considered approvable because there was sufficient data to suggest efficacy of endocardial border delineation (EBD), because the clinical relevance of this endpoint was currently in question, and because the application deficiencies were considered resolvable. Preliminary labeling was issued with a comment that the clinical section may be revised pending additional information. The deficiencies included the lack of sufficient data to validate the clinical utility of the primary endpoint (EBD), lack of data and manufacturing controls to characterize and ensure the upper limit of the microbubble size, pharmacology data to evaluate the potential for microembolization and clinical pharmacology data on metabolism and elimination.

Alliance has submitted information and data to address the majority of the deficiencies in the approvable letter. However, after review, the application remains approvable pending the submission of a safety update, a small subset reanalysis in the clinical section, CMC methods validation post approval protocol revisions, labeling revisions, and phase 4 commitments. Since the major outstanding matter is clinical efficacy, this will be discussed first (with preceding comment on the drug class efficacy issues). Following this the memo will briefly addresses the post approval safety commitments, CMC, pharmacology, and clinical pharmacology requests.

I. CLINICAL

A. Regulatory History-Drug Class

There is a complex regulatory history for the endpoints used to establish efficacy of microsphere contrast agents used in Echocardiography. The first product Albunex was approved by CDRH as a PMA with labeling for enhanced LVEBD and ventricular opacification in suboptimal in patients undergoing ventricular function and regional wall motion studies. The second product (Optison) was approved as an NDA with labeling for enhancement of the LVEBD and ventricular opacification only. At this point, the FDA position was that seeing the border would allow an accurate evaluation of border movement (i.e., segmental wall motion) and an accurate outline of the ventricle at end systole and end diastole. The latter would be used to calculate an ejection fraction (EF). Both the SWM and EF assessments were considered to be clinically relevant. Thus, the anatomic/structural delineation of the endocardial border had implied clinical utility.

In 1999-2000, 3 NDAs were submitted with data on EBD plus either ejection fraction or wall motion. All 3 drugs were found to provide substantial improvement in EBD; however, none of databases confirmed the expected improvement in SWM and EF assessment. Thus, the clinical usefulness of the anatomic endpoint (EBD) was in question. All 3 of these NDAs received approvable actions and were requested to either conduct new studies, reanalyze or re-read existing studies, or submit other data (e.g., literature) to establish the improvement in EF or SWM. This would result in an EF or SWM indication. Alternatively, if a sufficient trend should be established, the FDA would consider an EBD indication with restrictive labeling. Of the 3 NDAs, one (Definity) was resubmitted and approved with an EBD indication supported by a 12-47 patient subset from 2 studies that compared echocardiograph SWM results with MRI as a truth standard. The subset analysis was based on current practice position paper that required at least 2 adjacent suboptimal segments before using contrast[1]. The second NDA in question is the current Imavist resubmission. The third NDA has not been resubmitted.

[1] American Society of Echocardiography Position Paper, "Contrast Echocardiography: Current and Future Applications", J. American Society of Echocardiography, 13(4): 331-342, 2000.

B. Clinical Regulatory History - Imavist

After the Imavist approvable letter, during industry meetings, the division suggested that a re-read of the RVG for SWM may provide additional data on clinical utility. However, the sponsor indicated that the RVG sequences and site variations precluded this analysis. Also, the sponsor indicated that the NDA contained 26 patients who had an MRI truth standard. These patients were part of a protocol that planned for MRI in 203 patients. Because only 26 actually had MRI, these data were not sufficient to establish a wall motion indication. The sponsor agreed that they were not enough for a wall motion indication; however, they asserted that the 26 patients were sufficient to show a trend to support the EBD claim. The sponsor was advised that the original 26 patients would be reconsidered along with additional literature articles or other justifications.

In the resubmission, the relevance of the anatomic endpoint (EBD) is approached with submitted clinical practice guidelines, two articles using other drugs to show the importance of actual visualization of the endocardial border, an article that compares non-contrast echo with MRI, and a discussion of the previously submitted subset of the 26 patients with segmental wall motion evaluations compared to an MRI truth standard. Also, the sponsor indicates that a reanalysis of the existing RVG data would be useless because of technical difficulties in the RVG data. Overall, the sponsor's position is that the provided information and the 26 patient subset is a sufficient trend in the current context of trials that were designed in good faith and with agreed upon endpoints. Also, the sponsor changed the indication to an anatomic (EBD delineation) only and asserts that this is consistent with the FDA Guidance to Industry: Developing Medical Imaging Drugs and Biologics. Specifically, the proposed indication changed from use in

[redacted]

' to:

Because the change in indication does not eliminate the FDA concern about the clinical usefulness of the endpoint, Drs. Parker and Castillo extensively reviewed all data. The reviewers have concluded that the relevance of the EBD alone has not been confirmed. Thus, they recommend a continued approvable action and one additional study to confirm the correlation of SWM with an MRI truth standard. In considering this and recent agency actions, I agree in part: the application should remain approvable but with a reanalysis of the 26 patients for SWM improvement in any 2 adjacent suboptimal segments. This will provide data that are consistent with recent approvals and current practice guidelines. If these data are not sufficiently similar to the current results in these 26 patients, then a small bridging study is needed.

Salient features of the provided information and perspectives on the reviewer's recommendation are noted below:

C. NDA Data

The original NDA contained a study of segmental wall motion in 203 patients. By protocol all were to have MRI as a truth standard. Apparently because of local clinical site decisions, only one site with 26 patients actually completed the MRI portion of the protocol. These patients form the basis of the analysis. Also, there were 12 patients at another site. ***Additional data on these 12 patients is requested.*** Of the 26 patients, by patient, 10 (38%) agree with MRI before contrast and 13 (50%) after contrast. The improvement is driven by the improvement in normal assessments. Specifically, across all 3 readers, the number of patients scored as abnormal before or after contrast is essentially the same (10 or 13, 8 or 7, 9 or 13). For normal patients, the number increases from zero to either 4, 1 or 4 (for each of 3 readers).

In these 26 patients, the strength of the analysis is in the segment evaluation. Of these 26 patients, approximately 416 segments could be evaluated. Segments were scored for EBD as 0=not visualized, 1=mild/fair, 2 = moderate/good, 3=excellent visualization. If the EBD was 0 or 1, the SWM was not scored. Of the 416 possible segments, the sponsor reported that EBD was optimal in 25% before contrast and 66% after contrast. Also, after the segments were seen, on average for the 3 blinded readers, approximately 50% of SWM scores agreed with MRI before contrast and approximately 70% agreed after contrast.

This evaluation was based on a computer constraint that excludes the possibility of reader guessing. The reviewers were concerned about this because it eliminated the use of reader skill when the segment was scored as 1 (fair); i.e., the computer constraint did not allow the reader to guess the SWM when the EBD was scored as suboptimal. Therefore, how this related to the proposed indication for use in suboptimal images was unclear. Also, the statistician was concerned that the constraint meant that a smaller number of segments were actually evaluated.

In considering this further, the following table was developed from Dr. Parker's review page 8 and his original review. The table presents all of the factors in the analysis before and after Imavist. Specifically, the first set of columns reflects before the information before Imavist. The first column shows the number of segments that were constrained or not read because of a suboptimal EBD score of 0 or 1. The second column is the number of EBD segments seen optimally (scored as 2 or 3). The third column is the number with correct SWM scores. This column has two sub-columns for normal and abnormal (hypokinetic) SWM assessments. The forth column shows the number of incorrect SWM assessments. The next set of columns repeats these parameters for after Imavist. The last two columns show the percent correct if seen. For the table all correct or incorrect numbers are in comparison to the MRI.

This table (for reader 1) shows that once a segment is considered optimal, approximately 51% before and 68% were correctly scored in reference to the MRI truth standard. [The results for reader 2 and 3 are similar and are shown on page 16-17]. The results have not been replicated in another set of patients. Hence, the potential improvement in correct responses has not been confirmed. Therefore, the results are at least as good as the device would be if the segments could be seen. This is consistent with the anticipated benefit of the drug to return the device to its capability when the segments are visualized.

**Table 1: Segmental Wall Motion Results Before and After IMAVIST Compared to MRI * Reader 1**

| Segment | BEFORE | | | | | AFTER | | | | | % RIGHT IF SEEN | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Constraint | Any Seen | RIGHT NL | RIGHT Hypo | Any wrong | Constraint | Any Seen | RIGHT NL | RIGHT Hypo | Any wrong | Before | After |
| 1 | 20 | 6 | 3 | 0 | 3 | 7 | 19 | 10 | 2 | 7 | 50% | 63% |
| 2 | 14 | 12 | 5 | 1 | 6 | 4 | 22 | 11 | 2 | 9 | 50% | 59% |
| 3 | 21 | 5 | 1 | 0 | 4 | 10 | 16 | 7 | 0 | 9 | 20% | 44% |
| 4 | 24 | 2 | 0 | 0 | 2 | 11 | 15 | 9 | 1 | 5 | 0% | 67% |
| 5 | 23 | 3 | 2 | 0 | 1 | 7 | 19 | 15 | 1 | 3 | 67% | 84% |
| 6 | 26 | 0 | 0 | 0 | 0 | 11 | 15 | 11 | 0 | 4 | 0% | 73% |
| 7 | 12 | 14 | 4 | 0 | 10 | 7 | 19 | 11 | 0 | 8 | 29% | 58% |
| 8 | 6 | 20 | 10 | 3 | 7 | 5 | 21 | 11 | 2 | 8 | 65% | 62% |
| 9 | 19 | 7 | 3 | 2 | 2 | 14 | 12 | 6 | 0 | 7 | 71% | 50.0% |
| 10 | 24 | 2 | 1 | 0 | 1 | 17 | 9 | 6 | 0 | 4 | 50% | 67% |
| 11 | 20 | 6 | 3 | 2 | 2 | 12 | 14 | 11 | 1 | 5 | 83% | 86% |
| 12 | 24 | 2 | 1 | 0 | 1 | 12 | 14 | 11 | 1 | 4 | 50% | 86% |
| 13 | 21 | 5 | 1 | 0 | 4 | 14 | 12 | 10 | 1 | 1 | 20% | 92% |
| 14 | 20 | 6 | 1 | 0 | 5 | 11 | 15 | 10 | 1 | 4 | 17% | 73% |
| 15 | 17 | 9 | 7 | 0 | 2 | 11 | 15 | 9 | 2 | 4 | 78% | 73% |
| 16 | 23 | 3 | 2 | 0 | 1 | 13 | 13 | 9 | 0 | 4 | 67% | 70% |
| | 314 | 102 | 44 | 8 | 51 | 166 | 250 | 157 | 14 | 86 | 51% | 68% |

*Prepared by Dr. Parker after completion of his review

As noted earlier, the review staff was concerned that the data did not provide a 1:1 link between the segments that images were suboptimal at baseline, the was not information on at least 2 contiguous suboptimal segments, and the readers could not interpret the wall motion of suboptimal segments. To address this, Dr. Parker and I reviewed the line listings and determined that all patients had more than 2 to 9 suboptimal segments at baseline and >2 contiguous suboptimal segments. The conversion of these is largely reflected in the number of segments that were seen and available for evaluation. (Derived from volume 47, listing 4, page 242, and volume 50, listing 7, page 243) ***The sponsor should confirm these findings in a formal statistical analysis.***

Also, the review staff was concerned about the patient level improvement seen only in the normal patients. Improvement in more normal patients (or segments) has been seen in other datasets and may reflect the fact that (except in massive heart failure) the vast majority of the segments are functioning normally. Also, it may be easier to see obvious abnormalities, but more difficult to distinguish between normal and mildly abnormal segments. In considering this it seems that the importance of a patient based or segment analysis depends upon the purpose of the US. If the identification of any abnormality is sufficient for diagnosis or treatment planning, then the patient based analysis is most relevant. If the segment must be seen in order to evaluate extension of disease, then the segment analysis is important. Likewise, if the identification of normal segments decreases further intervention, these segments are as important as the identification of disease.

D. Publicly Available Sources:

1. Literature for EBD and EF:

One abstract was submitted that compared pre and post contrast harmonic Echocardiograhic LV volume assessments with a new contrast CT technique (electron beam). Using end diastolic, end systolic, stoke volumes, and EF calculations, the abstract reports similar EBCT and contrast echo results. Also, the article asserts that non-contrast EF results are usually an underestimate and that validation of this assumption was difficult because of poor truth standards.

*Comment: This is an abstract from a professional meeting. Although the contrast agent used in the abstract is not identified, Alliance stated that published data on Imavist are not available. Additional data are needed to confirm the findings. Also, the imaging technique references harmonic imaging. Imavist was not studied with this technology. Also, the approval status of the EBCT technology is not clear. Therefore, this abstract does not provide sufficient information to establish the relevance of the EBD endpoint for Imavist.*

In addition, the sponsor notes that the original NDA dataset showed that both before and after Imavist the correlation with RVG was approximately 0.5. The sponsor interprets this to reflect the overall ability of ultrasound to agree with RVG.

2. Literature for EBD and SWM

According to the sponsor, the literature does not contain any articles that used Imavist. However, the submission contained two articles to demonstrate that seeing the EB is a needed step in evaluating SWM. One article used a contrast drug and one did not. In addition, literature review by the review team identified one other article that used an approved contrast agent. Overall, the sponsor asserts that these articles are consistent

with their approach to using Imavist. Imavist outlines the wall by left ventricular filling (not perfusion of the wall). Also, the NDA data analyses discussed in item I.C above are based on definitive visualization of the wall as reported in the Hundley article (2.a below) and show improved blinded reader agreement as reported in the Reilly article (2.b).

a. The first article by Hundley et.al.[2] used an unapproved microbubble in a study of 2D, fundamental imaging in 40 patients, the EBD and SWM results were compared to MRI. In a blinded read, 60 [EBD] segments not seen before contrast, 56 were seen after contrast. Of the overall 420 the number of segments were seen and agreed with MRI increased from 274 (65%) before contrast to 329 (78%) agreed after contrast ($p<0.0001$-McNemars).

*This article suggests that segments need to be seen in order to be evaluated. The actual patient level assessments are not presented. The contrast drug studied is not approved. Therefore, this article provides limited support of the sponsor's position.*

b. A second article by Reilly[3] found on PubMed search during the review reported the results of fundamental and harmonic echo in 70 randomly selected patients. Optison (approved on the basis of EBD) was used in this study. All patients were in the ICU. In a blinded read, the endpoints were confidence in wall motion (by segment) {scored as A= not interpretable, B=interpretable but not sure, C=convincing EBD and SWM evaluation); and the EF percent.

In this study, EBD was found to be uninterpretable before contrast in 5.4 (34%) of segments per patient. After contrast, the number and percent of uninterpretable segments decreased to 1.1 (7%) segment per patient. With improvement EBD, the percent blinded reader agreement of standard B mode imaging confidence scores increased from 61% before contrast to 91% after contrast. The article noted that results were consistent with the "known limitations in contrast reading of posterior wall in parasternal long axis and lateral wall on apical view [from shadowing]". Also, noted was the absence of a truth standard to confirm the SWM assessments.

*This article is suggestive of the benefit of seeing the wall and then being able to make an interpretation. However, the improvement in confidence is subjective and is a weak endpoint that is not routinely accepted to establish efficacy.*

c. A third article by Yang et al[4] was submitted to demonstrate that visualization of Echo segments is needed for evaluation. The study actually was a comparison of MRI with non-contrast Echo. Approximately 90 patients were enrolled with equal groups

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[2] W. G. Hundley, ET. al, "Effect of contrast enhancement on transthoracic echocardiographic assessment of left ventricular regional wall motion", American Journal of Cardiology,, 84 (11): 1365-1368, 1999.
[3] J.P. Reilly et al, "Contrast echocardiography clarifies uninterpretable wall motion in intensive care unit patients". J. American College of Cardiology, 35(2): 485-490, 2000.
[4] PC Yang, et al. "New Real-Time Interactive Cardiac Magnetic Resonance Imaging System Compliments Echocardiography", J Ame Cardiology, 32:2049-2056, 1998.

of fully visualized echocardiograms, suboptimal cardiograms, and severe lung disease that obscured the echocardiograms. The results of each group were compared with MRI SWM. In the suboptimal group, the segments were seen in 38% of the echoes and 97% of the MRIs. In the lung patients, the segments were seen in 58% of the echoes and 99% of the MRIs. In the fully visualized group, all segments were seen and the SWM results were reported as statistically comparable to MRI. The actual percents were not provided in the narrative.

*These data provided intuitive support to the sponsor's position that the ability to visualize is a prerequisite to making the SWM assessment. The article does not provide information on contrast enhancement.*

3. Practice guidelines

Dr. Parker's summary of current practice (see his review page 11-17 identifies a number of other uses for Echo (perfusion, myocardial viability, wall thickening, etc.). Also, Dr. Parker notes that regional wall thickening (not wall motion) is now thought to be a more appropriate measure of myocardial function.

One problem with several of the provided guidelines is that they were written between 1995 and 1998. Hence, only one or two contrast agents were on the market and the guidelines contain disclaimers or cautious comments about the benefits of contrast. Thus, largely the quittance reflects experience with the US device alone. In this regard, the guidelines state that the major limitation is technical (e.g., inability to see the structures because of problems with the acoustic window). The contrast agents are designed to overcome this problem and allow visualization of the window.

In considering theses aspects, it appears that technology and off label uses are moving faster than the drug development. Also, the uses are reflections of the device innovations. The study design model used for Albunex and Optison has been modified by the addition of EF and SWM measures. This model was used by the pending NDAs and only partially consistent with current use. Also, the clinical settings of use are not one-time measures in stable patients but settings such as long term monitoring after a truth standard MRI or acute ICU use when an MRI is otherwise contraindicated.

It is noteworthy that all of the guidelines do emphasize the need to see the border and that seeing is a necessary element before an interpretation can occur. However, after it is seen, echo itself is still secondary to MRI or other imaging techniques. Based on what has been submitted to the FDA, although a systematic comparison has not been made, it appears that the contrast drug delineation of EBD for EF/SWM at best restores the US to the device level of accuracy. Stated another way, it only allows the border to be seen, after that any other technical US deficiencies still exist. Overall the evaluation of EF is problematic for a number of modalities and their cross comparison is challenging. This suggests that whatever method is used should be used consistently in the same patient.

Changing imaging modalities could introduce error. For SWM, MRI is considered to be the gold standard; however, consistent monitoring with echocardiography in the same patient or the use of echocardiography when an MRI is not obtainable/contraindicated is an established practice. Also, the guidelines state that SWM the identification of normal segments is reported to have a strong negative predictive value. In a position paper published by the American Society of Echocardiography[5], it notes that contrast should be given when at least 2 adjacent segments are suboptimal. As noted in item I.C above, this analysis should be performed in the 26 patients discussed in section A.

*Comment: The practice guidelines and sponsor's position returns us to the anatomic structural indication in the guidance document and essentially asserts that there is enough information (direct and indirect) to show clinical relevance of the delineation and to allow approval on this basis. As the field has evolved and additional experience with US contrast agents is provided, it appears that the primary benefit of US is in SWM assessments. In this context the contrast restores the ability of US to its original condition as if the wall was seen without contrast. The use of contrast does not increase the device capability. This interpretation must be made with caution, however, because the data to support the clinical benefit of the anatomic endpoint are marginal at best. Also, the preceding information supports the division's position that future US contrast trial designs should focus on the clinical benefit endpoints (wall thickening, consistency in monitoring, ICU settings, or on perfusion imaging).*

Efficacy Assessment: Collectively, the application contains the following:

1) Data from a 26 patient subset analysis of patients with suboptimal segments at baseline that show a limited improvement on a patient analysis, but a marked increase in the percent of segments that could be seen after contrast. Once the segments are seen, the actual agreement with MRI is similar before or after contrast. This analysis is not replicated in this NDA. However, there are soft endpoints (i.e., improved reader agreement) that are replicated.
2) Literature and practice guidelines that indicate the need to see the segment in order to evaluate the SWM. One literature from an approved drug that shows improved soft endpoints (reader agreement) and one literature article with an unapproved drug that showed improved agreement with MRI. One guideline indicates that at least 2 adjacent segments should be suboptimal before contrast is given.

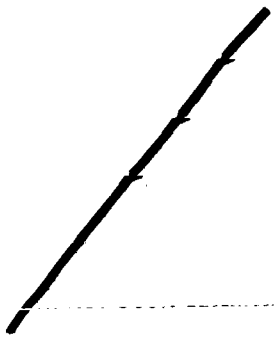
In considering this information, overall the supportive information is marginal but consistently logical (i.e., the border must be seen before it can be evaluated). The question is whether this limited information (along with previous FDA action) is sufficient to establish the clinical utility on the basis of the historic or indirect method allowed in the Medical Imaging Guidance document. In the face of an evolving drug class, these data are limited and not sufficient to support a drug class decision. Thus far

[5] See footnote number 1.

of the 3 NDAs approved, only 2 ultrasound contrast drugs are marketed. The 1st agent that was approved has been withdrawn from the market presumably because of limited duration of imaging. The provided guidelines basically address the limitations of the device and conceptually indicate why a drug that increased the identification of structures would be helpful. However, the guidelines specifically state that they do not address contrast agents. While I agree that intuitively it is necessary to see the border, this set of information is not sufficient to make a class decision that the surrogacy of the EBD structural indication is sufficiently established. To do so would mean that all other products could be approved without any other evaluation of clinical utility.

An alternative position is that the EBD indication could be approved if all NDAs contained additional evidence of clinical usefulness (e.g., wall motion, and wall thickening) or studied these in a appropriate setting. From that perspective, the sponsor's assertion of clinical utility is an NDA specific evaluation that must consider the collective set of data (e.g., the 26 patients plus the literature). From that perspective the data are limited, but apparently consistent with the most recently approved labeling. Before approval, however, the sponsor should confirm the results in a blinded re-read that allows a SWM assessment of all EBD segments. The analysis should include a linked evaluation of regions with at least 2 adjacent suboptimal segment analysis. If the findings are not consistent with the current results, then a new study with this type of analysis should be performed in comparison to MRI.

Although labeling for this section will not be provided at this time, tentative language may read as follows:



E. Safety and Clinical Inspections:

Clinical inspection problems were not identified. The overall safety in the clinical database was considered acceptable with labeling during the original review cycle. Also, during the original review a safety update is considered to be consistent with the original data. However, the sponsor did not submit another safety update in the resubmission. . A safety update

is required before approval 21 CFR 314.50(d)(5)(vi)(b). This requirement was identified in the approvable letter.

Additionally, for the class of microspheres there is concern that the use of varying high mechanical indices and the underlying disease may be associated with drug-device interactions that result in electrophysiologic adverse events; e.g., prolonged QTc, ventricular arrhythmias). During the original NDA, QTc prolongation was noted in 77 (17%) of the patients. This information was derived from monitoring at 5 and 60 minutes, and 24 hours. None of these patients had continuous ECG monitoring. Based upon information provided by Dr. Parker, the mean change in QTc interval is noted below. This mean change only provides a population change; it does not assess the possible risk to an individual patient.. Dr. Parker's original review (page 96-100) contains a discussion and itemized listing of the QTc abnormalities seen in patients who received Imavist or Saline. His table #59, reproduced on page 18 of this review, lists 36/445 (3.8%) patients who had > 30 msec change from baseline. Of these patients, 16 had > 30 msec QTc prolongation at 5 minutes; 13 had > 30 msec QTc prolongation at 60 minutes; and 8 patients had QTc prolongation at both 5 and 60 minutes. Additionally, he notes two patients who had abnormal QTc intervals of > 450 milliseconds before Imavist had more prolongation (>500 msec) after Imavist. Notably, none of these patients were reported to have an associated arrhythmia.

| QTc Interval (milliseconds) Change from Baseline* | | | | |
|---|---|---|---|---|
| Time point monitored | Imavist (N=445) | | Saline (N=81) | |
| | Mean | Mean Change | Mean | Mean change |
| Baseline | 407.8 | N/A | 406.9 | N/A |
| 5 minutes | 407.4 | -0.6 | 405.8 | -1.1 |
| 60 minutes | 408.8 | 0.9 | 402.9 | -4.0 |
| 24 hours | 408.7 | 0.9 | 409.4 | 2.6 |
| *Slight adaptation from NDA volume 044-237, table VIII.6.7 | | | | |

In Dr. Parker's review table 60, he identified 9 patients who had a QTc prolongation and an ECG change. Based on the review, these patients had < 30 msec of QTc prolongation. Also, with the possible exception of patient (#IMUS-007 03-063) who had mild unspecified tachycardia 22 hours after Imavist, these patients did not have a severe arrhythmia associated with the QTc interval change. At the time the original review, the drug-device and underlying disease could not be evaluated further. Also, an animal cardiovascular safety pharmacology study did not reveal evidence of QTc interval prolongation. Thus, the sponsor was asked to submit updated information from ongoing studies. This was not provided. These data are needed to determine if other pre or post market risk management steps are needed. ***A safety update of cardiovascular events should be provided in the resubmission.***

F. Pediatrics:

The letter should note the applicability of the pediatric rule and advise of any pertinent information related to the recent pediatric legislation.

CLINICAL PHARMACOLOGY

The approvable letter identified the following deficiencies, the essence of which is stated below:

> *"1. The application lacks PFH gas plasma protein binding and distribution information. In order to resolve this deficiency, submit data (such as in vitro data) on PFH binding to proteins.*
>
> *2. The application lacks data to describe the metabolism of the intact PFH filled microspheres. Intact microsphere pharmacokinetic data should be provided, if feasible, to complete the proposed dosage assessment."* [This section acknowledged the technical difficulties and requested additional assay development.]
>
> *3. The application lacks sufficient data to characterize the lipid components of the microspheres. Specifically, supportive information regarding DMPC metabolism should be submitted.*
>
> *4. The application lacks sufficient information to complete the PFH gas assay assessment. Based upon the application, it appears that PFH gas assay blood samples were analyzed at three different starting days, 6/29, 7/6, and 7/12."* [Specific assay information was requested]

Overall, the reviewing clinical pharmacologist found the responses to these to be acceptable within the limits of technical ability. Also, items #2-3, include matters that are addressed in the pharmacology section

> *5. "Please submit pharmacokinetic information from pulmonary impaired subjects/patients with impaired pulmonary function."*

These data in humans were not submitted. Instead the sponsor proposed a phase 4 animal study in anesthetized, ventilated dogs with different tidal volumes. Although animal data might justify the deferral of human data until phase 4, at this point the application does not contain any data in pulmonary disease. Therefore, ***before approval either human or adequate animal data must be submitted. If animal data are submitted, the protocol should be submitted for review and comment before implementation. Also, a commitment is needed to perform a human PK study if indicated by the animal results.***

PHARMACOLOGY-TOXICOLOGY

In the approval letter, the following four deficiencies were noted. Two of these deficiencies were to be addressed before approval and two could be addressed before or after approval. The two to be addressed before approval were

> *"1. Perform a microcirculation study to assess the potential for coalescence, clumping, and aggregation as well as to visualize microspheres as they transverse vessels. We note your commitment to complete such a microcirculation study. As requested in our March 30, 2000, teleconference, this study should include a direct arterial injection of IMAVIST. Also, based upon data in the NDA, in addition to evaluating the microcirculation of normal animals, the use of animals with compromised vasculature (e.g., atherosclerosis) is recommended.*
>
> *2. Provide available data on blood gas analysis in non-anesthetized animals receiving IMAVIST."*

For item #1, the sponsor submitted an acceptable intraarterial injection study. It showed that any slugging resolved quickly. The effect was the greatest in hyperlipidemic animals. For item #2, new data were not submitted. The reviewer therefore deferred to the clinical database. In patients, there COPD and CHF patients in the NDA and there are 190 patients who were monitored with pulse oxymetry. However, although the data are available, as noted in Dr. Parker's original review, the relationship of these two groups is not clear. ***Clarification should be provided in the resubmission.***

The issues identified for completion either before or after approval were:

> *"1. Studies in chronic or subacute pulmonary embolism animal models are needed to further assess the potential pulmonary impact of IMAVIST in chronically compromised patients and*
>
> *2. Macrophage vacuolation and cecal lesions were found in some animal species. However, underlying mechanisms are not identified. The pathogenesis and clinical consequences of these abnormalities should be addressed."*

The sponsor committed to studying a pulmonary embolizism model; however, they did not agree to further study of the cecal lesions. Drs. Tuschar and Sadrieh noted that the submitted pharmacologic hypertensive model provides sufficient safety assurance for marketing with an existing phase 4 commitment for further study. However, because of the sponsor did not complete the requested PK study in humans, the overall dataset in any type of pulmonary compromise is decreased. Therefore, before approval, the ***sponsor should an adequate PK elimination study in dogs with a variety of pulmonary***

***abnormalities that could compromise gas elimination. These abnormalities could include, but are not limited to those in a chronically compromised PE model. The absence of the cecal study is replace by a requested phase 4 commitment to study gas exchange and the fate of the shell.***

In addition, Dr. Chen identified a recent literature reference that reported endothelial hemorrhage after the approved Optison microspheres were exposed to high mechanical index values. Whether this is a microsphere class phenomenon is not known. Also, not known is whether this type of endothelial damage has long term consequences; e.g., predisposition to atherosclerosis. In the original NDA, Imavist microspheres were shown to rupture at mechanical index values >1.0. ***Therefore, when Imavist is otherwise approvable, labeling should restrict exposure to values less than this. Also, the sponsor should commit to further determine if the ruptured microspheres cause endothelial damage. If so, then a commitment is needed to study the long-term consequences of the endothelial hemorrhage.***

CHEMISTRY

In the resubmission, the majority of the CMC deficiencies have been addressed. Imavist is provided in the vial as a powder of hollow microspheres with porous openings to allow gas incorporation. The structure is documented on electron microscopy and other studies. The vial also contains a phosphocholine, perflexane vapor in nitrogen, and various stabilizers. After reconstitution with normal saline and "gentle swirling of the vial", the microspheres engulf the gases (air and perflexane) and are coated with the lipid monolayer. Subsequently the original microspheres dissolve and the shell becomes a reorganized lipid monolayer. These particles are demonstrated by EM, x-ray and polarized light microscopy. The release specifications have been improved and appear to ensure the absence of microspheres above 20 um. The manufacturing site inspection and environmental assessments are acceptable.

Dr. Salazar-Davi's review notes that the submitted data only support an — month vial expiration date and a 30-minute reconstituted shelf life. ***The review concludes that several changes are needed in the labeling to reflect these findings. Also, the post approval stability protocol must be strengthened.*** These changes must be made before approval. I agree with these recommendations.

MICROBIOLOBY: Sterility assurance was considered to be acceptable during the original review cycle.

**RESUBMISSION ASSESSMENT**:

During the original review, the primary endpoints of endocardial border delineation and left ventricular opacification were established. With one caveat, the resubmission

contains data to support the clinical relevance of these anatomic endpoints. Restrictive labeling can be developed in a manner that is consistent with recently approved products. Additionally, Alliance has acceptably addressed most of the other deficiencies cited in the approvable letter. However, the outstanding issues include:

1. Absence of a safety update with a subset of cardiovascular and QTc prolongation evaluations. Also, additional data are needed on any patient that had QTc prolongation at both 5 and 60 minutes after Imavist or saline injection.

2. Absence of sufficient safety data to ensure safe use in the intended clinical setting.

   Therefore, a post market safety study is apt to be needed. A final decision on this is deferred until the review of the responses to this action letter are received and evaluated.

3. Absence of sufficient data to ensure acceptability of the 26 patient subset analyzed to document clinical utility.

   A blinded re-read of SWM regardless of EBD score. The reanalysis should link all regions with at least 2 adjacent segments that were suboptimal at baseline. If this analysis is not acceptable, then a bridging study is needed.

   Additionally, the sponsor should provide detailed information on the 12 patients with MRI data or suboptimal EBD both before and after Imavist. This should include a by patient analysis of whether the Echo was performed at baseline, with Imavist and whether MRI was done. If a patient had all three, then they should be analyzed.

4. Absence of an adequate CMC stability and methods validation protocol.

   These should be revised and found to be acceptable before approval

5. Absence of a gas elimination data in compromised population of use

   Before approval, data are needed either in patients or in an acceptable animal model. If animal studies are submitted, then the protocol should be submitted for review and comment before implementation. A commitment is needed to complete a human study after the animal data are provided.

6. Labeling revisions in all sections as needed for consistency. Final labeling for clinical will not be issued until the reanalysis is found to be acceptable.

ACTION: Approvable

Tables 2 and 3 were prepared by Dr. B. Parker from volume 47, listing 4, page 242, and volume 50, listing 7, page 243.

**Table 2: Segmental Wall Motion Results Before and After IMAVIST Compared to MRI Reader 2**

| SEGMENT | BEFORE | | | | | AFTER | | | | | IF SEEN, % Right | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Constraint | Any Seen | RIGHT NL | RIGHT Hypo | Any Wrong | Constraint | Any Seen | Right NL | Right Hypo | Any Wrong | Before | After |
| 1 | 21 | 5 | 3 | 0 | 2 | 11 | 15 | 9 | 0 | 6 | 60% | 60% |
| 2 | 13 | 13 | 7 | 2 | 4 | 5 | 21 | 13 | 1 | 7 | 69% | 67% |
| 3 | 14 | 12 | 6 | 1 | 5 | 9 | 17 | 9 | 0 | 8 | 58% | 53% |
| 4 | 22 | 4 | 4 | 0 | 0 | 15 | 11 | 11 | 0 | 0 | 100% | 100% |
| 5 | 23 | 3 | 2 | 0 | 1 | 8 | 18 | 15 | 1 | 2 | 67% | 89% |
| 6 | 24 | 2 | 1 | 0 | 1 | 10 | 16 | 14 | 1 | 1 | 0% | 94% |
| 7 | 25 | 1 | 0 | 0 | 1 | 11 | 15 | 10 | 0 | 5 | 0% | 67% |
| 8 | 11 | 15 | 7 | 1 | 7 | 10 | 16 | 9 | 0 | 7 | 53% | 56% |
| 9 | 16 | 10 | 4 | 0 | 6 | 16 | 10 | 4 | 0 | 6 | 40% | 40% |
| 10 | 23 | 3 | 3 | 0 | 0 | 19 | 7 | 5 | 0 | 2 | 100% | 71% |
| 11 | 22 | 4 | 3 | 1 | 0 | 17 | 9 | 8 | 0 | 1 | 100% | 89% |
| 12 | 24 | 2 | 2 | 0 | 0 | 15 | 11 | 11 | 0 | 0 | 100% | 100% |
| 13 | 25 | 1 | 1 | 0 | 0 | 14 | 12 | 9 | 0 | 3 | 100% | 75% |
| 14 | 25 | 1 | 0 | 0 | 1 | 14 | 12 | 9 | 0 | 3 | 0% | 75% |
| 15 | 17 | 9 | 5 | 1 | 3 | 12 | 14 | 11 | 1 | 2 | 67% | 86% |
| 16 | 18 | 8 | 5 | 0 | 3 | 11 | 15 | 11 | 0 | 4 | 63% | 73% |
| | 323 | 93 | 53 | 6 | 34 | 197 | 219 | 158 | 4 | 57 | 63% | 74% |

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| Table 3: Segmental Wall Motion Results Before and After IMAVIST Compared to MRI Reader 3 | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BEFORE | | | | | AFTER | | | | | IF SEEN, % Right | |
| SEGMENT | Constraint | Any Seen | Right NL | Right Hypo | Any wrong | Constraint | Any Seen | Right NL | Right Hypo | Any wrong | Before | After |
| 1 | 22 | 4 | 1 | 1 | 2 | 5 | 21 | 9 | 1 | 11 | 50% | 48% |
| 2 | 13 | 13 | 6 | 2 | 5 | 1 | 25 | 10 | 2 | 13 | 62% | 48% |
| 3 | 19 | 7 | 2 | 1 | 4 | 3 | 23 | 11 | 1 | 11 | 43% | 52% |
| 4 | 24 | 2 | 1 | 1 | 0 | 2 | 24 | 18 | 0 | 6 | 100% | 75% |
| 5 | 24 | 2 | 1 | 0 | 1 | 4 | 22 | 20 | 0 | 2 | 50% | 91% |
| 6 | 22 | 4 | 3 | 0 | 1 | 5 | 21 | 20 | 0 | 1 | 0% | 95% |
| 7 | 10 | 16 | 8 | 0 | 8 | 2 | 24 | 15 | 0 | 9 | 50% | 63% |
| 8 | 5 | 21 | 10 | 2 | 9 | 0 | 26 | 14 | 2 | 10 | 57% | 62% |
| 9 | 18 | 8 | 4 | 1 | 3 | 7 | 19 | 12 | 2 | 5 | 63% | 74% |
| 10 | 24 | 2 | 2 | 0 | 0 | 6 | 20 | 15 | 0 | 5 | 100% | 75% |
| 11 | 21 | 5 | 4 | 1 | 0 | 6 | 20 | 17 | 0 | 3 | 100% | 85% |
| 12 | 23 | 3 | 3 | 0 | 0 | 7 | 19 | 18 | 0 | 1 | 100% | 95% |
| 13 | 19 | 7 | 2 | 1 | 4 | 3 | 23 | 17 | 1 | 5 | 43% | 78% |
| 14 | 19 | 7 | 2 | 1 | 4 | 2 | 24 | 18 | 1 | 5 | 43% | 79% |
| 15 | 14 | 12 | 6 | 1 | 5 | 4 | 22 | 14 | 2 | 6 | 58% | 73% |
| 16 | 14 | 12 | 5 | 1 | 6 | 3 | 23 | 15 | 1 | 7 | 50% | 70% |
| | 291 | 125 | 60 | 13 | 52 | 60 | 356 | 243 | 13 | 100 | 58% | 72% |

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## TABLE 59: EKG Data (IMUS-007 and IMUS-008)
## Baseline and Post-Contrast

| QTc (msec): Abnormal = (1) Increase > 30 msec from baseline , Or (2) Any QTc > 500 msec | | | Baseline | 5 minutes | | 1 hour | | 24 hours | |
|---|---|---|---|---|---|---|---|---|---|
| **IMUS-007 AF0150-tx (N = 213)** | 1. | 02-003 | 406 | ***449*** | ***43 msec*** | ***448*** | ***42 msec*** | ***439*** | ***33 msec*** |
| | 2. | 02-007 | 410 | 431 | 21 msec | 417 | 7 msec | ***441*** | ***31 msec*** |
| | 3. | 02-014 | 418 | 435 | 17 msec | 430 | 12 msec | ***457*** | ***39 msec*** |
| | 4. | 03-007 | 377 | 350 | -27 msec | 369 | -8 msec | ***424*** | ***47 msec*** |
| | 5. | 03-016 | 371 | 359 | -12 msec | 358 | -13 msec | ***427*** | ***56 msec*** |
| | 6. | 03-021 | 373 | ***406*** | ***33 msec*** | 370 | -3 msec | 401 | 28 msec |
| | 7. | 03-024 | 384 | 321 | -63 msec | 390 | 6 msec | ***422*** | ***38 msec*** |
| | 8. | 03-026 | 363 | 357 | -6 msec | ***399*** | ***36 msec*** | 378 | 15 msec |
| | 9. | 03-028 | 375 | ***412*** | ***37 msec*** | ***414*** | ***39 msec*** | ***420*** | ***45 msec*** |
| | 10. | 03-044 | 410 | 424 | 14 msec | 423 | 13 msec | ***454*** | ***44 msec*** |
| | 11. | 03-053 | 389 | 410 | 21 msec | ***422*** | ***33 msec*** | 400 | 11 msec |
| | 12. | 03-056 | 402 | 426 | 24 msec | ***434*** | ***32 msec*** | ***434*** | ***32 msec*** |
| | 13. | 03-063 | 370 | 376 | 6 msec | ***402*** | ***32 msec*** | ***408*** | ***38 msec*** |
| | 14. | 03-064 | 420 | ***453*** | ***33 msec*** | ***465*** | ***45 msec*** | 398 | -22 msec |
| | 15. | 04-002 | 325 | 351 | 26 msec | 352 | 27 msec | ***372*** | ***47 msec*** |
| | 16. | 04-009 | 350 | 380 | 30 msec | ***390*** | ***40 msec*** | ***386*** | ***36 msec*** |
| | 17. | 04-015 | 342 | 353 | 11 msec | ***373*** | ***31 msec*** | 369 | 27 msec |
| | 18. | 04-019 | 353 | ***394*** | ***41 msec*** | ***387*** | ***34 msec*** | 361 | 8 msec |
| | 19. | 04-021 | 390 | ***425*** | ***35 msec*** | 357 | -33 msec | ***428*** | ***38 msec*** |
| | 20. | 05-005 | 409 | ***445*** | ***36 msec*** | ***445*** | ***36 msec*** | 394 | -15 msec |
| | 21. | 05-010 | 381 | 381 | 0 msec | 392 | 11 msec | ***438*** | ***57 msec*** |
| | 22. | 06-005 | 394 | ***430*** | ***36 msec*** | ***458*** | ***64 msec*** | 410 | 16 msec |
| | 23. | 08-010 | 430 | 443 | 13 msec | 459 | 29 msec | ***462*** | ***32 msec*** |
| | 24. | 08-012 | 351 | ***384*** | ***33 msec*** | 369 | 18 msec | ***399*** | ***48 msec*** |
| | 25. | 09-001 | 409 | 421 | 12 msec | 428 | 19 msec | ***447*** | ***38 msec*** |
| | 26. | 09-005 | 344 | ***375*** | ***31 msec*** | 362 | 18 msec | 369 | 25 msec |
| | 27. | 10-012 | 370 | ***411*** | ***41 msec*** | 388 | 18 msec | 395 | 25 msec |
| | 28. | 10-030 | 409 | 416 | 7 msec | ***442*** | ***33 msec*** | 410 | 1 msec |
| | 29. | 10-031 | 369 | ***405*** | ***36 msec*** | ***414*** | ***45 msec*** | 368 | -1 msec |
| | 30. | 10-034 | 408 | ***445*** | ***37 msec*** | 437 | 29 msec | 417 | 9 msec |
| | 31. | 10-036 | 360 | ***399*** | ***39 msec*** | ***414*** | ***54 msec*** | 380 | 20 msec |
| | 32. | 12-002 | 422 | 414 | -8 msec | ***461*** | ***39 msec*** | 442 | 20 msec |
| | 33. | 12-010 | 390 | 408 | 18 msec | 411 | 21 msec | ***427*** | ***37 msec*** |
| | 34. | 13-015 | 413 | ***448*** | ***35 msec*** | 411 | -2 msec | 423 | 10 msec |
| | 35. | 16-017 | 409 | 419 | 10 msec | 408 | -1 msec | ***444*** | ***35 msec*** |
| | 36. | 16-022 | 368 | ***399*** | ***31 msec*** | 387 | 19 msec | 390 | 22 msec |
| **IMUS-007 Saline-tx (N = 81)** | 1. | 03-004 | 387 | 401 | 14 msec | 385 | -2 msec | ***421*** | ***34 msec*** |
| | 2. | 04-001 | 373 | 373 | 0 msec | 373 | 0 msec | ***416*** | ***43 msec*** |
| | 3. | 05-009 | 389 | ***423*** | ***34 msec*** | 398 | 9 msec | 380 | -9 msec |
| | 4. | 06-010 | 406 | ***443*** | ***37 msec*** | 420 | 14 msec | ***444*** | ***38 msec*** |
| | 5. | 06-013 | 419 | 427 | 8 msec | ***450*** | ***31 msec*** | 430 | 11 msec |
| | 6. | 07-004 | 354 | 348 | -6 msec | ***407*** | ***53 msec*** | ***442*** | ***88 msec*** |
| | 7. | 07-010 | 402 | ***435*** | ***33 msec*** | 371 | -31 msec | 403 | 1 msec |
| | 8. | 09-004 | 370 | 397 | 27 msec | ***411*** | ***41 msec*** | ***417*** | ***47 msec*** |
| | 9. | 09-008 | 317 | 284 | -33 msec | 338 | 21 msec | ***357*** | ***40 msec*** |

**Source: Volume 75 pp 001 – 349, and Volume 76 pp 001 – 212 & *263 - 281*)**
Bolded italicized numbers are the significant abnormal values.

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

/s/
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Patricia Love
2/4/02 03:45:49 PM
MEDICAL OFFICER

DIVISION DIRECTOR'S MEMO TO THE FILE

| | |
|---|---|
| NDA: | 21,191 |
| DRUG: | Imavist (perflexane lipid microsphere) Powder for Injectable Suspension. |
| ROUTE: | Intravenous |
| MODALITY: | Echocardiography |
| INDICATION: | Left ventricular endocardial border delineation & ejection fraction |
| CATEGORY: | 1S |
| SPONSOR: | Alliance Pharmaceutical Corporation |
| PDUFA DATE: | August 14, 2000 |
| COMPLETED: | August 07, 2000 |

RELATED DRUGS:

Optison (Albumin human 1% with perfluoropane microbubbles); NDA #20899; approved
Albunex (Albumin human 5% sonicated); PMA P900059; approved

REVIEW TEAM:

Chemistry: M Salazar, PhD 08/07/00
Clinical: B Parker, MD, 08/07/00
Clinical Pharmacology: D Lee, PhD, 07/26/00
Microbiology: C Vincent, PhD, 03/15/00
Pharmacology: J Chin, PhD 07/28/00, N Sadrieh 08/07/00
Statistics: S Castillo, PhD 05/05/00
Project Manager: Tia Haper-Velazquez, PhD

BACKGROUND:

IMAVIST (perflexane lipid microsphere) powder for injectable suspension (with a code name of AFO150) is an echopharmaceutical (microbubble or microsphere contrast agent) that has been developed by Alliance Pharmaceutical Corporation. Imavist is the 5th member of new class of imaging contrast agents known as either echopharmaceuticals, microspheres, microaerosomes, or microbubbles. These gas filled flexible particles provide acoustic enhancements when exposed to ultrasound waves. Thus far, two such drugs have been approved for the evaluation of the left ventricular border delineation and left ventricular opacification. In the evolution of the class of microspheres/microbubbles, several safety and efficacy issues are emerging. These include 1) the destruction of microbubbles in response to the device instrument settings that may result in different efficacy and the production of ventricular arrhythmia, 2) the embolic occlusion of high risk vascular beds from various sizes, concentrations or characteristics of microspheres, and 3) the clinical relevance of the anatomic endpoints that formed the basis of the original drug approvals.

The Imavist database is comprehensively developed and addresses many of the safety and efficacy issues identified during drug development. Thus, the review team has collectively recommended approvable. However, deficiencies have been identified in the chemistry and manufacturing controls for the safety of the upper particle size and major deficiencies were identified during inspection of the manufacturing facilities. Further, the efficacy database does

not support the clinical utility of the anatomic endpoints. Additionally, there are clarifications and documentation needed to complete the clinical pharmacology and pharmacology assessments. Some of the latter may be addressed either before or after approval.

Collectively, the individual reviews are comprehensive, and cogently written. I agree with the collective recommendation as approvable. A few salient points are identified in this memo.

CHEMISTTY:

Imavist consists of two key ingredients, a lipid membrane and fluorocarbon gas. The lipid membrane consists of dimyristoylphosphatidylcholine (DMPC) with a molecular formula of $C_{36}H_{72}NO_8P$. The gas is tetradecadluorohexane or perflexane (PFH) with a molecular formula of $C_6F_{14}$.

| Table 1: Contents of Imavist Dry Powder * | |
|---|---|
| Ingredient | Concentration |
| DMPC | mg |
| PFH | mg |
| Hyroxyethyl starch | mg |
| Poloxamer 188 | mg |
| Sodium chloride | mg |
| Dibasic sodium phosphate | mg |
| Monobasic sodium phosphate in perflexane | mg |
| Nitrogen headspace | |
| *Derived from Dr. Salazar's review | |

Imavist is supplied as a dry powder of evacuated microspheres. These must be reconstituted with 10 ml of sterile water for injection and vigorous agitation. After reconstitution, Imavist contains $9.8 \times 10^8$ microspheres, — PFH/ml and — mg DMPC/ml. The recommended dose for injection is 0.0065 ml/kg. — The mean diameter of the microspheres is $9.8 \times 10^8$ µm. The number and percent of the microsphere particle sizes is shown in the following table.

| Table 2: Concentration of Microspheres per Milliliter (a) | |
|---|---|
| Mean number | $9.8 \times 10^8$ ($5.9 - 13.7 \times 10^8$) |
| <3 µm | Not provided |
| 3-10 um | — |
| > 10 um (b) | — |
| | — |
| (a) Derived from Dr. Salazar's review and package insert<br>(b) Based on — % of total mean and range | |

The recommended dose is 0.00625 mg/kg followed by as saline infusion. The Dosing and Administration section of the package insert provides the volume of Imavist for a range of body

weights up to 168 kg. Based upon the maximum number of particle size per mL, the following table lists the total number of particles over 10 μm.

**Table 3: Total number of particles injected based on body weight (a)**

| Weight | | 72 kg | 88 kg | 150kg | 168kg |
|---|---|---|---|---|---|
| Volume injected (mL) | | 0.45 | 0.55 | 0.88 | 1.05 |
| Number of particles | Minimum | [redacted] | | | |
| | Mean | 2,822,400 | 3,449,600 | 5,519,360 | 6,585,600 |
| | Maximum | [redacted] | | | |

(a) Calculated from dosing chart and particle size ranges

As with other microsphere echopharmaceuticals, the number of microspheres > 10 um has a potential to cause pulmonary microemboli. Although the actual maximum particle size produced has not been identified, the sponsor provided a safety perspective on the general particle size range. In reference to the macroaggregated albumin (MAA) particle sizes and the size of pulmonary capillaries, the sponsor asserts that MAA occludes approximately 0.5% of the capillaries and that this is an acceptable amount of occlusion. The sponsor states that the lung contains 280 x $10^9$ capillaries. Based on the dose to an 88kg patient (0.55 ml), direct calculation of the number of bubbles divided by the number of capillaries would result in the occlusion of approximately 0.0017% of the capillaries. Since this is less than the percent occluded by MAA, along with the pharmacology data, the sponsor concludes that the particle size range is acceptable.

In considering this, I disagree with the calculation of the percent occluded by MAA and with the general perspective. MAA is generally given in doses of 200,000 to 700,000 particles. This divided by the number of capillaries produces a maximum percentage of 0.00025%; not the 0.5% identified by the sponsor. More importantly, a direct calculation of this type is probably not the appropriate model to assess the risk. There are many other factors that contribute to the potential for occlusion. These include the total number of particles of all sizes, the dilution, the volume and the rate of injection. Also, the rate of blood flow, regional perfusion differences, the status of the vessels, and other physiologic and pathophysiologic parameters will affect the overall impact of the injected particles. Therefore, the percentage of the number of microspheres to the number of capillaries can not be used to determine the safety of the particle sizes. Additional chemistry data (as well as information discussed in other sections of this memo) will be needed to characterize the safety profile.

In addition to this concern, the chemistry review identified deficiencies in the specifications & test methods, stability, and methods validation sections of the application. Additionally, major facility deficiencies were identified during the inspection of the key facility for the finished dosage form site for drug substance/drug product, stability testing and primary packaging. At the time of this memo, a repeat inspection and inspection of the [redacted] facility in [redacted] are pending. Because of the key facility deficiencies, Compliance recommended a "withhold approval".

Based upon these deficiencies, the chemistry reviewer recommended non-approval. Upon further consideration of these issues, these deficiencies should be resolvable. If the testing methodologies are not sufficiently established to confirm the relationship of the pilot and commerical lots to the investigational lots, then additional bridging studies may be needed. Therefore, these deficiencies must be addressed before approval.

MICROBIOLOGY: The microbiology section is considered acceptable for sterility assurance. Imavist does not contain a preservative and must be appropriately labeled and handled.

PHARMACOLOGY-TOXICOLOGY:

A comprehensive set of preclinical data was submitted in support of the Imavist NDA. Notably, this data set contains the first detailed information from an acute pulmonary hypertension model and histology data after a direct ascending aorta injection. These data were thoroughly reviewed by Dr. Jin Chen. Based upon these data, he recommends approvable with additional clarifications, labeling and phase 4 commitments. Dr. Chen's review and Dr. Sadrieh's team leader memo can be read for details. In general I agree with the recommendation with a few minor caveats. These will be identified briefly below.

1. Potential for vascular occlusion

   In order to address the toxicity related to the size of the microspheres several studies were completed in the following animal settings: acutely induced pulmonary hypertension, and intra ascending aorta injection. In the acute pulmonary hypertensive model, hypertension was induced in rats with thromboxane A. In this model Imavist the NOEL was 26 x MHD based on body surface area. For the intra ascending aorta injection, 3 dose groups of rats were injected with either Imavist or saline. Animals were observed and sacrificed at 8 days or after unscheduled death. In these models, although clinical signs of toxicity were absent, there was evidence of ischemic brain and kidney lesions. These abnormalities were seen in all treatment groups. However, in one study there was a trend toward more renal lesions in the Imavist treated group. In the other study, there were more renal and brain lesions in the Imavist treated group. Depending upon the study, the NOEL was 5 – 20 x MHD based on body surface area.

   In standard toxicity studies, evidence of lung lesions or cecal lesions was evidence a high dose multiples > 100 x MHD based on body surface area. Collectively, these findings suggest that in normal animal models, suggests a reasonably high therapeutic-toxicity index. However, in models that mimic disease states, the risk of toxicity from vascular occlusion increases. These findings should be included in labeling.

2. Cardiovascular toxicity: Cardiovascular safety studies did not reveal evidence of QTc prolongation or severe arrhythmias. However, studies of Imavist with pharmacologic stress agents demonstrated that the tachycardia was seen after stress may be increased with Imavist.

Based upon these are other data discussed in Dr. Chen's review, I agree with the approvable recommendation pending information to address the following items.

a) A microcirculation study to assess the potential for coalescence, clumping, and aggregation as well as to visualize the microspheres as they traverse the vessels. This should be completed with an intra-arterial injection. Also, the use of animal disease models could be included; e.g., atherosclerosis, hyperlipidemia, or drug induced vasoconstriction.

b) The completion of a chronically compromised pulmonary vasculature study with histopathology for micropulmonary emboli.

CLINICAL PHARMACOLOGY-BIOPHARMACEUTICS:

As identified in Dr. Lee's review, which may be read for details, the Imavist database provided comprehensive information on the pharmacokinetics of the perflexhane gas, the persistence of microsphere, its thermodynamics, and diffusion equilibrium. Based on these data, the results are similar to other drug products in the class. The PFH gas is eliminated through expired air in approximately 3 hours (75%) and 24hours (88%). The duration of imaging is approximately 2.5 minutes.

Although these data are acceptable for labeling, Dr. Lee recommends approvable pending data to complete the characterization of the PK-PD profile. Specifically, data are needed on protein binding of the perflexhane, the pharmacokinetics of the intact microsphere and the DMPC shell, and assay documentation. I agree with this recommendation.

CLINICAL-STATISTICAL:

During early drug development, the sponsor pursued a perfusion indication for use in acute myocardial infarction. During drug development, it was determined that this indication would be delayed and the initial NDA would focus on an anatomic and functional indication. As such, the NDA was submitted to support the following labeling:

The Imavist NDA includes data from 10 clinical studies of which 2 were identified as key (IMUS-007 and IMUS-008). Also submitted was the safety data from 3 ongoing studies.

Overall, the Imavist NDA clinical evaluations were evaluated in a total of 776 participants of whom 676 received Imavist and 101 a saline placebo. The total included 466 men and 278 women with an age distribution of was 503 (66%) < 65 years, 239 (31%) were between 65-80 years, and 25 (3%) were > 80 years of age. Racial and ethnic representation was Caucasian (79%), Black (14%), Asian (2%) and other (5%).

These data have been reviewed by the medical and statistical reviewers who collectively recommended efficacy as approvable for the LVEB delineation. However, the ejection fraction is recommended for non- approval pending a reanalysis of the data. The wall motion indication is considered not-approvable because of an insufficient sample size. The salient features of the data are briefly listed below. However, as background to these data (and as noted in the medical review summary) the anatomic endpoints of LVEB and LV opacification are considered to be

surrogate markers for the improvement in ejection fraction and segmental wall motion analyses. Although the wording of the proposed indication is lengthy, it includes this concept as well. The Optison NDA approval is based upon this premise. Therefore, if the functional uses are not confirmed, then the clinical relevance of the anatomic endpoints is unclear. This issue will be revisited in the NDA assessment section at the end of this memo.

A. Efficacy

Two similar key clinical studies were conducted, study # IMUS-007 and IMUS-008 (with 206 and 203 patients respectively). Both were multi-center studies of patients with suboptimal segmental echocardiograms. IMUS-007 was saline controlled for safety. These patients were randomized and imaged; however, the saline produced images were not evaluated for efficacy. All patients treated with Imavist 0.00625 ml/kg for imaging. Otherwise the studies were identical.

All patients had suboptimal echocardiograms defined as 2-9 out of 12 segments not visualized. This status was identified on a "qualifying" or screening echo. A "confirming echo" was done the day of dosing and is used as the baseline for the clinical evaluation. Within 48 hours, all patients had a radionuclide ventriculography (RVG) study as the standard of truth for the ejection fraction. In a subset of patients and additional MRI was obtained as a standard of truth for wall motion only.

Two dimensional echocardiographic images were collected with continuous and gated modes. The tapes were masked and provided in 3 views (4 chamber, 2 chamber, and long axis). For the blinded read, the entire tape was used for the LVEB delineation determination. However, for EF, the core lab identified the best segment for calculation. If the blinded reader, did not agree, the tape was returned for a re-draw. Only one such reassessment appeared to occur. Three blinded, independent readers scored 16 segments on a four-point ordinal scale of 0 = no delineation; 1 = mild or fair delineation; 2 = moderate or good delineation; 3 = excellent delineation. The EF was compared to the standard of truth using six ranges (> 65%, 55-65%, 45-54%, 35-44%, 25-34%, and <25%). The primary statistical analyses were 2 sided with p=0.05.

Drs. Castillo and Parker identified several protocol or procedural concerns.

1. The core lab's identification of the EF region is a protocol amendment that could introduce bias.
2. The method of image acquisition changed during the study. Reportedly, the machine settings were too high and lead to microbubble destruction. Specific directions for machine settings were provided to the clinical sites. The intent to treat population is those patients imaged after the machine setting directions were provided.
3. The use of a different post-hoc ANOVA to analyze the LVEB score
4. Several post hoc subset analyses were performed

Results:

Table 4 presents the synthesis of the statistical reviewer's analysis; i.e., the proportion of images for which Imavist provided additional image segment enhancement. A more comprehensive table of these results is included in labeling. A segment is considered sub-optimal when the EBD score was rated as 0 or 1, and considered optimal if its EBD score was rated as 2 or 3. Column 1 lists the chamber and the segment, columns 2-4 list the by reader results from study IMUS-007, columns 5-7 list the results for study IMUS-008. Based upon these data, Imavist provided more