CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-191

Chemistry Review(s)

NDA 21-191

Kit for the Preparation of
IMAVIST™ [IMAGENT®] (Perflexane Lipid Microspheres)
Injectable Suspension

200 mg pre-constituted powder and
a maximum of 13.7 x 10^8 microspheres /ml reconstituted

For Intravenous Administration, Single-Dose

Alliance Pharmaceutical Corporation

Milagros Salazar, Ph.D.
Division of Medical Imaging and Radiopharmaceutical DPs
HFD-160

Table of Contents

A. DRUG SUBSTANCE (PHF -gas component & DMPC-lipid/membrane component)

1. DESCRIPTION & CHARACTERIZATION: Adequate, Review#1, pp 4 & 11 and Microspheres characterization Last update Review #3, p 9
2. MANUFACTURER: Adequate, Review#1, pp 6 & 16.
3. SYNTHESIS: Adequate , Review#1, pp 6 & 16.
4. SPECIFICATIONS/TEST METHODS/REF.STD.: Adequate, Review #1 pp 7-9 (PFH) and 17-20 (*DMPC) Purity Profiles- pp 10 & 21

Last update *DMPC detector change to a [redacted] detector in the [redacted] assay

5. CONTAINER/CLOSURE SYSTEM: Adequate, Review#1, p 10 & 21.
6. STABILITY: Adequate, Review#1, pp 11- 21.

B. DRUG PRODUCT

1. COMPONENTS/COMPOSITION: Adequate, Review#1, pp 22-26

Last update Review #3, p 15

2. SPECIFICATIONS & METHODS FOR INGREDIENTS: Adequate, Review#1, pp 26-27.

CHEMISTRY NDA REVIEW DATA SHEET

1. NDA #: 21-191

2. REVIEW DATE: 3-MAY-2002

3. REVIEW #: 4

4. REVIEWER: Milagros Salazar, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	11-OCT-1999
Amendment BM	26-JAN-2000
Amendment BC	03-FEB-2000
Review #1	21-MAY-2000
Amendment BC	09-JUN-2000
Review #2	31-JUL-2000
Action Letter (Approvable)	14-AUG-2000
NC (Briefing document for CMC meeting)	18-OCT-2000
Meeting (on CMC non approval issues)	02-NOV-2000
General Correspondence (outline of responses)	07-MAR-2001

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment AZ	05-APR-2002
T-con	18-APR-2001
Meeting on outline of responses	12-Mar-2002
AZ	05-APR-2002
CMC Labeling (fax/email)	25-APR & 01-MAY-2002

7. NAME & ADDRESS OF APPLICANT: ALLIANCE PHARMARCEUTICAL CORP.
3040 Science Park Road
San Diego, CA 92121

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name	IMAVIST™ (IMAGENT®)
Non-Proprietary Name (USAN)	Perflexane-Lipid Microspheres
Code Name/#:	AF0150
Chem.Type/Submission Priority	**1 S**

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY/INDICAT.:

[redacted]

11. DOSAGE FORM: Powder for Injectable Suspension

12. STRENGTH/POTENCY: 200 mg powder
(Max. 13.7 x10^8 microspheres/mL constituted)

B. Other Documents:

DOCUMENT	APPLICATION No. / Supplier's Name	DESCRIPTION
NDA		
IND	Alliance Pharm. Corp.	AFO0150 Injection
510(k)		
510(k)		

18. STATUS OF CONSULTS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Overall: Acceptable 29-Oct-01	Requested 26-Nov-99	Virgilio Pacio, LA-DO
Biostatistics	NA		
LNC	Acceptable for Imavist (Perflexane Lipid Microspheres)	1-15-02 & 1-31-02 memos	Dan Boring, Ph.D. & / Milagros Salazar. Ph.D.
Methods Validation	In Progress	Requested	
OPDRA	Acceptable Pending as of	02-JUN-2000 03- MAY-2002	OPDRA for Imavist OPDRA for Imagent
Pharm/Tox	NA		
EA	Categorical Exclusion	21-MAY-2000	Milagros Salazar, Ph.D.
Microbiology	Approval	15-MAR-2000	Carol Vincent, M.S.
Biopharm	NA		
Other	NA		

Patent/Trademark: Patent nos. 5,605,673; 5.626,833; 5,639,443; 5,695,741; 5,720,938 ; 5,798,091; *6,258,339 ; 6,280,704; 6,280,705; and 6,287,539. Expiration Date: 30-JUL-2013 Type of patent: Drug Product- on formulation, composition & for method of use of AFO150/ Imagent® Patent owner: Alliance Pharmaceutical Corp.

Imagent® is a Trademark of Alliance Pharmaceutical Corporation.

Exclusivity: The Company requested 5 years under 21CFR 314.108 (b)(2) stating Imagent® active moiety is a new chemical entity.

19. ORDER OF REVIEW: NA

CHEMISTRY EXECUTIVE SUMMARY

I. Recommendations

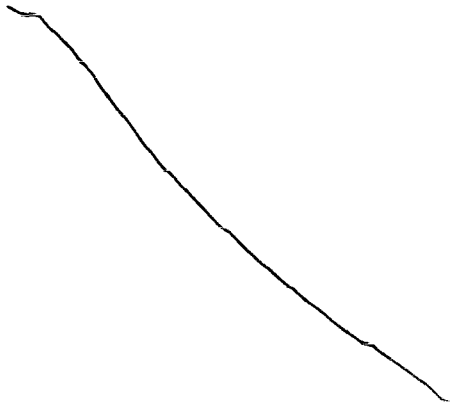
A. Recommendations and Conclusions on Approvability
The chemistry section is recommended for APPROVAL of *Imavist* ™ [*Imagent*®] powder product with the proposed expiry date of 24 and 30 minutes shelf life after reconstitution.

B. Recommendations on Phase 4 (post-marketing) Commitments, Agreements and/or Risk Management steps , if approvable
In addition, Phase 4 (post-marketing) commitments have been made with the sponsor to re-evaluate statistically [redacted] storage conditions.

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance
Imavist™ is a kit for the preparation of perflexane lipid microspheres injectable suspension, is a sterile, non-pyrogenic white powder with a diluted perflexane headspace that, upon constitution into a suspension of microspheres is used for contrast enhancement during indicated ultrasound imaging diagnostic procedures. The kit is supplied for single-use and each kit contains a 10-mL glass vial containing 200mg of *Imavist*™ powder, a 20-mL plastic vial of Sterile Water for Injection (SWFI), a 10-mL disposable plastic sterile syringe and a sterile, vented 5 µm filter dispensing pin.

The hollow microspheres that exist in *Imavist*™ 200 mg powder contain 9.2 mg 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC); 75 mg hydroxyethyl starch (HES); 2.1 mg poloxamer 188; 75 mg sodium chloride; 36 mg sodium phosphate buffer in a 10 mL vial filled with a mixture of 17% v/v perflexane vapor in nitrogen.



Upon reconstitution and 5 µm filtration, each mL of Imavist contains a maximum of 13.7×10^8 microspheres ($5.9\text{-}13.7 \times 10^8$, [redacted] microspheres), 92 µg perflexane, 0.92 mg DMPC;

7.5 mg hydroxyethyl starch; 0.21 mg poloxamer 188. Constituted product is iso-osmotic and has a pH between 6.7 to 7.7. The primary container/closure system for Imavist powder comprises a 10-mL USP Type I clear glass vial, [redacted] and a [redacted]

The current submission responded satisfactorily to the following area of deficiencies found in Chemistry Review #3:

- The drug product stability data and studies were insufficient for both the pre- and post-constituted product.-Full term stability data and a revised stability protocol are presented.
- The validation of analytical methods, for the release and stability testing of drug product, were insufficient in support of FDA validation studies.-Data and information are provided.
- Labeling of the kit, vial, and package insert was not adequately supported by information and data within the application.–Revised labeling complying with FDA and USP are provided.

This submission also provided the status of the manufacturer/packager/labeler sites. [redacted] will be the primary site for these functions while [redacted] will no longer have any responsibility for packaging and release of the kits. The proposed a change in the name of the AFO150 product, to IMAGENT® (Alliance) instead of IMAVIST™ (Schering AG co-development partner) is due to modifications of licensing agreement between these companies. IMAGENT name is under a consult review by OPDRA and its approval is pending as of the day of this review.

B. Descriptions of How the Drug Product is Intended to be Used

Imavist™ is intended for single dose for intravenous administration and it is used as contrast enhancement for use in patients with suboptimal echocardiogram to opacify the left ventricle (LV), which enhances the delineation of the LV endocardial borders. The recommended dose is 0.00625 mL/kg (0.125 mg/kg) administered as a single intravenous bolus over a period of no less than 10 seconds and immediately followed by a saline flush. *Imavist*™ must be used within 30 minutes of constitution. Any unused portion should be discarded. Storage conditions for the kit components and constituted product are between 15°- 30°C (59°- 86°F).

C. Basis for Approvability or Not-approvability Recommendation

The recommendation for approval is based on the fact that the chemistry deficiencies have been resolved satisfactorily, and the CMC section complies with section 502 of the Act as follows:

- Presents an adequate characterization of the active moiety, the microspheres.
- The specifications: tests, acceptance criteria and analytical procedures, for the drug product, powder and reconstituted forms, are adequate to control the quality of the product at release and at expiry.
- The stability data and studies are adequate in support 24 months at CRT storage of *IMAVIST*™ powder product and 30 minutes post-constitution of *IMAVIST*™ Injectable Suspension.
- MV work and MV package appear suitable for regulatory purposes. The information and data are sufficient and adequate to request validation work by FDA Labs.
- EES overall recommendation status: Acceptable as per 29-Oct-2001 by LOS-DO and OC recommendation.
- Adequate microsphere nomenclature throughout the labeling to comply with FDA and USP recommendations has been provided.
- Microbiology section recommendation for approval.

III. Administrative

/S/

Milagros Salazar, Ph.D.
Review Chemist, HFD-820/160

/S/

Eldon Leutzinger, Ph.D.
Chemistry Team Leader, HFD-820/160

cc:
Org. NDA 21-191
HFD-160/Division File
HFD-160/Salazar/Leutzinger
HFD-160/ Harper-V
HFD-820/Duffy (NMEs only)

filename: **N21-191imavist-4.doc**

NDA 21-191

Immavist (Perflexane Lipid Microsphere) Injectable Suspension
200 mg Powder
(5.9 – 13.7 x 10^8 microsphere/mL constituted)

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Alliance Pharmaceutical Corp.

Indication: Ultrasound image enhancement/opacify the left ventricle in pts with suboptimal echocardiograms

Presentation: Lyophilized powder in a 10 mL vial

EER Status: Acceptable 29-OCT-2001

Consults: OPDRA – Imavist acceptable 13-JUN-2000
Microbiology – recommended for AP 15-APR-2000

Imavist is a kit consisting of a 10 mL vial containing the lyophylized liposome components with 17 % perfluorohexane gas/N_2 headspace, a 20 mL vial of sterile WFI, a sterile 10 mL syringe [redacted] and a 5 µm filter spike [redacted] The product is intended for extemporaneous constitution of the gas entrapped liposome microspheres by swirling. An opaque white colored suspension is obtained, which is to be used within 30 minutes of constitution. Labeling claims a defined microsphere size distribution.

The present CMC review is the 3rd cycle and covers a response to an AE action dated 16-AUG-2001. Significant issues addressed were:
Microsphere Characterization

- Microsphere characterization was provided.
- Demonstration that the reconstitution technique used in the clinical trials vs that recommended in the labeling did not significantly affect the microsphere physical characteristics.
- Perflexane was demonstrated to be contained within the microspheres.

Specification

- Requested changes to the specification were made, and are acceptable.

Stability

- The stability protocol has been revised, however requires additional revision
- Additional data were provided which support the 30 min constituted use period.

- Additional stability data were provided to support a proposed 24 month expiry, which upon analysis was found to support only [redacted] months.
- It is noted that the labeling recommends storage at 15 – 30° C (59 - 86° F). The currently recommended storage statement: "Store at 25° C (77° F); excursions permitted to 15 - 30° C (59 - 86° F). See USP Controlled Room Temperature."
- No stability data if found regarding the sterile Water for Injection.
- Note that the executive summary in accurately states that [redacted] should be statistically evaluated as a phase 4 commitment. The review states this to be a deficiency.

Methods Validation

- Additional methods validation information was provided, however additional information is requested.

Labeling

- Labeling has been found acceptable with the exception of the use of the term "Microspheres" to describe the product. This term should be used throughout.
- Labeling for the sterile Water for Injection has not been provided.

DMF which cover perflourohexane (DMF [redacted]) and 1,2-di(tetradecanoyl-sn-glycero-3-phosphocholine (DMF [redacted]) have been found acceptable.

FPL has been submitted and is acceptable.

Over-All Conclusion
From a CMC perspective an approvable action is recommended.

Additional Deficiencies
A deficiency comment regarding the storage temperature should be added to the AE letter. A deficiency comment should be included requesting stability data and a proposed expiry, and labeling for the sterile Water for Injection.

/S/ 1/25/02

Eric P Duffy, PhD
Director, DNDC II/ONDC

NDA 21-191

Kit for the Preparation of
***Imavist*™ (Perflexane Lipid Microsphere) Injectable Suspension**

200 mg Powder
(5. 9 – 13.7 x10^8 microspheres/mL constituted)

Alliance Pharmaceutical Corporation

Division of Medical Imaging and Radiopharmaceutical
Drug Products, HFD-160

Table of Contents

CHEMISTRY NDA/ANDA REVIEW DATA SHEET

1. NDA #: 21-191

2. REVIEW DATE: 20-NOV-2001

3. REVIEW #: 3

4. REVIEWER: Milagros Salazar, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	11-OCT-1999
Amendment BM	26-JAN-2000
Amendment BC	03-FEB-2000
Review #1	21-MAY-2000
Amendment BC	09-JUN-2000
Review #2	31-JUL-2000
Action Letter (Approvable)	14-AUG-2000
NC (Briefing document for CMC meeting)	18-OCT-2000
Meeting (on CMC non approval issues)	02-NOV-2000
General Correspondence (outline of responses)	07-MAR-2001
T-con	18-APR-2001

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment AZ	16-AUG-2001

7. NAME & ADDRESS OF APPLICANT: ALLIANCE PHARMARCEUTICAL CORP.
3040 Science Park Road
San Diego, CA 92121

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name	IMAVIST™
Non-Proprietary Name (USAN)	Perflexane-Lipid Microspheres
Code Name/#:	AF0150
Chem.Type/Submission Priority	**1 S**

9. LEGAL BASIS FOR SUBMISSION: **NA**

10. PHARMACOL. CATEGORY/INDICAT.: Echopharmaceutical and Contrast enhancement for use in patient with sub-optimal echocardiogram to opacify the left ventricle (LV)

11. DOSAGE FORM: Powder for Injectable Suspension

12. STRENGTH/POTENCY: 200 mg powder
($5.9 - 13.7 \times 10^8$ microspheres/mL constituted)

13. ROUTE OF ADMINISTRATION: Intravenous

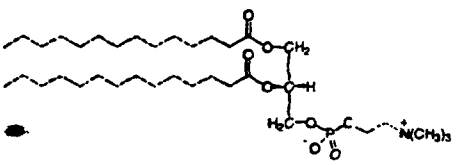
14. Rx/OTC: _X_ Rx ___ OTC

15. SPOTS (Special Products On-line Tracking): ___ Yes _X_ No

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: Chemical Structure of Microsphere components:

Gas Component:
Perflexane, (tetrafluorohexane, TFH)
C_6F_{14} / 338.04

Lipid Membrane Component:
dimyristoylphosphatidylcholine(DMPC)
$C_{36}H_{72}NO_8P$ / 677.96



Microspheres are unilamelar, negatively charged and micron-size DMPC coated vesicles filled with perflexane gas.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM	STATUS	REVIEW DATE	COMMENTS
	II			Acceptable	07-MAR-2000	Gas component for DS
	II			Acceptable	10-MAR-2000 & NDA review #3 Page 2	Lipid component for DS
	III			Adequate	NDA Review # 1 21-May-01	Container/Closure component
	III			Adequate	NDA Review # 1 21-May-01	Container/Closure Component
	NA			Adequate	NDA Review # 1 21-May-01	Container/Closure Component
	I			NA	NA	
	I			NA	NA	Packaging contract company
	I			NA	NA	Packaging contract company

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	18-801 / Abbott Laboratories	Sterile Water for Injection, USP 20 mL
IND	Alliance Pharm. Corp.	AFO0150 Injection
510(k)		
510(k)		

CHEMISTRY EXECUTIVE SUMMARY

I. Recommendations

A. Recommendations and Conclusions on Approvability
The chemistry section is "Approvable" pending change of the proposed expiry date from [redacted] to [redacted] months for *IMAVIST*™ powder product, revision of the post-approval stability protocol, and revisions of microsphere nomenclature throughout the labeling. See Deficiency Letter to Applicant.

B. Recommendations on Phase 4 (post-marketing) Commitments, Agreements and/or Risk Management steps , if approvable [redacted]
In addition, Phase 4 (post-marketing) commitments are necessary to re-evaluate statistically [redacted] storage conditions.

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance
Imavist™ is a kit for the preparation of perflexane lipid microspheres injectable suspension, is a sterile, non-pyrogenic white powder with a diluted perflexane headspace that, upon constitution into a suspension of microspheres is used for contrast enhancement during indicated ultrasound imaging diagnostic procedures. The kit is supplied for single-use and each kit contains a 10-mL glass vial containing 200mg of *Imavist*™ powder, a 20-mL plastic vial of Sterile Water for Injection (SWFI), a 10-mL disposable plastic sterile syringe and a sterile, vented 5 µm filter dispensing pin.

The hollow microspheres that exist in *Imavist*™ 200 mg powder contain 9.2 mg 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC); 75 mg hydroxyethyl starch (HES); 2.1 mg poloxamer 188; 75 mg sodium chloride; 36 mg sodium phosphate buffer in a 10 mL vial filled with a mixture of 17% v/v perflexane vapor in nitrogen.

Upon constitution and 5 µm filtration, each mL of Imavist contains 9×10^8 microspheres, 92 µg perflexane, 0.92 mg DMPC; 7.5 mg hydroxyethyl starch; 0.21 mg poloxamer 188. Constituted product is iso-osmotic and has a pH between 6.7 to 7.7. The primary container/closure system for Imavist powder comprises a 10-mL USP Type I clear glass vial, [redacted], and [redacted].

The current submission responded satisfactorily to the following area of deficiencies found in review #2:

- Complete characterization of the active moiety, the microspheres is adequate.
- The specifications and test methods for the drug product, powder and constituted product are adequate to control the quality of the product at release and at expiry.
- The stability data and studies are adequate in support of [redacted] months (instead of the [redacted] mo. Proposed) at CRT storage of *IMAVIST*™ powder product and 30 minutes post-constitution of *IMAVIST*™ Injectable Suspension. Revision of expiration and clarification of the stability protocol for the post-marketing is necessary before approval. See Recommendations Section above.
- MV work and MV package appear suitable for regulatory purposes. The information and data are sufficient and adequate to request validation work by FDA Labs.
- EES overall recommendation status: Acceptable by LOS-DO and OC recommendation.

B. Descriptions of How the Drug Product is Intended to be Used

Imavist™ is intended for single dose for intravenous administration and it is used as contrast enhancement for use in patients with suboptimal echocardiogram to opacify the left ventricle (LV), which enhances the delineation of the LV endocardial borders. The recommended dose is 0.00625 mL/kg (0.125 mg/kg) administered as a single intravenous bolus over a period of no less than 10 seconds and immediately followed by a saline flush. *Imavist*™ must be used within 30 minutes of constitution. Any unused portion should be discarded. Storage conditions for the kit components and constituted product are between 15°- 30°C (59°- 86°F).

C. Basis for Approvability or Not-approvability Recommendation

The recommendation for approvability is based on the fact that there are still deficient CMC issues to be resolved, they are as follows:

1. Change of the proposed expiry date from [redacted] to [redacted] months for *IMAVIST*™ powder product.
2. Revision of the post-approval stability protocol.
3. Revisions of microsphere nomenclature throughout the labeling.

Please refer to the list of deficiencies in page 39-Chemistry –Letter to Applicant.

III. Administrative

/S/

Milagros Salazar, Ph.D.
Review Chemist, HFD-820/160

/S/

Eldon Leutzinger, Ph.D.
Chemistry Team Leader, HFD-820/160

cc:
Org. NDA 21-191
HFD-160/Division File
HFD-160/Salazar/Leutzinger
HFD-160/ Harper-V
HFD-820/Duffy (NMEs only)

filename: **N21-191imavist-3.doc**

Redacted 25

pages of trade

secret and/or

confidential

commercial

information

9 pages redacted from this section of the approval package consisted of draft labeling

Redacted 4

pages of trade

secret and/or

confidential

commercial

information

19 pages redacted from this section of the approval package consisted of draft labeling

ATTACHMENT 6

(EES report)

CONFIDENCIAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21191/000
Stamp: 14-OCT-1999 Regulatory Due: 20-OCT-2001
Applicant: ALLIANCE PHARM
3040 SCIENCE PARK RD
SAN DIEGO, CA 92121

Priority: 1S Org Code: 160
Action Goal: District Goal: 15-JUN-2000
Brand Name: IMAVIST(PERFLEXANE-PHOSPHOLIPID MICOBUBL
Established Name:
Generic Name: PERFLEXANE PHOSPHOLIPID MICROBUBBLES
Dosage Form: PDR (POWDER)
Strength: 200 MG

FDA Contacts: T. HARPER VELAZQUEZ (HFD-160) 301-827-7510 , Project Manager
M. SALAZAR DRIVER (HFD-160) 301-827-7510 , Review Chemist
E. LEUTZINGER (HFD-160) 301-827-7510 , Team Leader

Overall Recommendation:

ACCEPTABLE on 29-OCT-2001 by J. D AMBROGIO (HFD-324) 301-827-0062
WITHHOLD on 08-AUG-2000 by EGASM

Establishment: 2027835
ALLIANCE PHARMACEUTICAL COR
6175 LUSK BLVD
SAN DIEGO, CA 92121

DMF No:
AADA No:

Profile: SVT OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 25-OCT-2001
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities:

Establishment:

DMF No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-NOV-1999
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities:

Establishment:

DMF No:
AADA No:

Profile: POW OAI Status: NONE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Responsibilities:

Last Milestone: **OC RECOMMENDATION**
Milestone Date: **21-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **26-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

Establishment:

DMF No:

Profile: **POW** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **26-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **08-AUG-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**

Responsibilities:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Last Milestone: **OC RECOMMENDATION**
Milestone Date: **26-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: [redacted]

DMF No:
AADA No:

Profile: **POW** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **14-JAN-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: [redacted]

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS
(HFD-160)
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-191 **DATE REVIEWED:** 31-JUL-00

REVIEW #: 2 **REVIEWER:** Milagros Salazar, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMEND N-000 BC	9-JUN-00	13-JUN-00	14-JUN-00

NAME & ADDRESS OF APPLICANT: ALLIANCE PHARMARCEUTICAL CORP.
3040 Science Park Road
San Diego, CA 92121

DRUG PRODUCT NAME

Proprietary:	IMAVIST™
Established:	Perflexane-Lipid Microsphere (tentative)
Code Name/#:	AF0150
Chem.Type/Ther.Class:	1 S

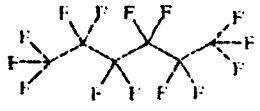
PHARMACOL. CATEGORY/INDICATION: Echopharmaceutical and Contrast enhancement for use in patient with sub-optimal echocardiogram to opacify the left ventricle (LV)

DOSAGE FORM:	Powder for Injectable Suspension
STRENGTHS:	200 mg
ROUTE OF ADMINISTRATION:	Intravenous injection
Rx/OTC:	_X_ Rx __ OTC
SPECIAL PRODUCTS:	__ Yes _X_ No

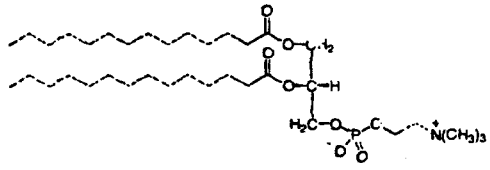
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: **Chemical Structure of microbubble is undetermined**

Structure of Microbubble components:

Vapor Component: perflexane (tetrafluorohexane)
C_6F_{14} / 338.04



Lipid Membrane Component: dimyristoylphosphatidylcholine (DMPC)
$C_{36}H_{72}NO_8P$ / 677.96



REMARKS: The CMC Section has been amended to provide with additional stability data for up to ⁓ months both at CRT and accelerated storage conditions. Statistical analyses were also provided. The analytical method for the analysis of DMPC assay and stability has been changed and the validation work presented in this amendment. No final specification for this component is provided due to limited stability data to date.

The CMC section has still major deficiency issues as follows:

- Complete characterization of the active moiety, the microsphere.
- The specifications and test methods for the drug product, powder and constituted are insufficient and not ready.
- The stability data and studies are insufficient.- The update stability data provides data for [redacted] months. However, the stability testing performed on the pre- and post- constituted kit are not adequate according to review note listed in Chemistry Review #1.
- MV are insufficient and not ready.
- EES withhold recommendation from LOS-DO and OC.

CONCLUSIONS & RECOMMENDATIONS: After the review of this amendment and the stability data provided in it, this application is still deficient in the CMC for the drug product under section 505 (b)(1) of the Act. Not approval is recommended.

/S/

Milagros Salazar, Ph.D.
Review Chemist, HFD-820/160

cc:
Org. NDA 21-191
HFD-160/Division File
HFD-160/Salazar
HFD-160/ Harper-V
HFD-160/Leutzinger
HFD-820/Gibbs (NMEs only)
R/D Init by: ELeutzinger

/S/ 8/7/2001

filename: **N21-191imavist-2.doc**

4 pages redacted from this section of the approval package consisted of draft labeling

ATTACHMENT 2

(updated EES report)

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21191/000**
Priority: **1S** Org Code: **160**
Stamp: **14-OCT-1999** Regulatory Due: **14-AUG-2000**
Action Goal: District Goal: **15-JUN-2000**
Applicant: **ALLIANCE PHARM**
3040 SCIENCE PARK RD
SAN DIEGO, CA 92121
Brand Name: **IMAVIST(PERFLEXANE-PHOSPHOLIPID MICOBUBL**
Established Name:
Generic Name: **PERFLEXANE PHOSPHOLIPID MICROBUBBLES**
Dosage Form: **PDR (POWDER)**
Strength: **200 MG**

FDA Contacts:
T. HARPER VELAZQUEZ (HFD-160) 301-827-7510 , Project Manager
Y. LU (HFD-550) 301-827-2526 , Review Chemist
E. LEUTZINGER (HFD-160) 301-827-7510 , Team Leader

Overall Recommendation:

Establishment: **2027835**
ALLIANCE PHARMACEUTICAL COR
6175 LUSK BLVD
SAN DIEGO, CA 92121
DMF No:
AADA No:

Profile: **SVT** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **17-MAY-2000**
Decision: **WITHHOLD**
Reason: **EIR REVIEW-CONCUR W/DISTRICT**
Responsibilities:

Establishment:
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **26-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities:

Establishment:
DMF No:
AADA No:

Profile: **POW** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **21-MAR-2000**
Responsibilities:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: [redacted]

DMF No: —
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **26-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:
AADA No:

Profile: **POW** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **26-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

Establishment: [redacted]

DMF No: —
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **INSPECTION PERFORMED**
Milestone Date: **28-JUN-2000**

Responsibilities: [redacted]

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**

Responsibilities: —

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Last Milestone: **OC RECOMMENDATION**
Milestone Date: **26-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment:

DMF No:
AADA No:

Profile: **POW** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **14-JAN-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:

APPEARS THIS WAY
ON ORIGINAL

SUMMARY OF CHEMISTRY REVIEW# 1

NDA 21-191

IMAVIST™ 200 mg Powder

Kit for the Preparation of Perflexane Lipid Microsphere Injectable Suspension

Alliance Pharmaceutical Corporation

A. DRUG SUBSTANCE (PHF -gas component & DMPC-lipid/membrane component)

1. DESCRIPTION & CHARACTERIZATION: Adequate, Review#1, pp 4 & 11 .
2. MANUFACTURER: Adequate, Review#1, pp 6 & 16.
3. SYNTHESIS: Adequate , Review#1, pp 6 & 16.
4. SPECIFICATIONS / TEST METHODS/REF.STD.: Adequate, Review #1 pp 7-9 (PFH) and 17-20 (DMPC) Purity Profiles- pp 10 & 21
5. CONTAINER/CLOSURE SYSTEM: Adequate, Review#1, p 10 & 21.
6. STABILITY: Adequate, Review#1, pp 11- 21.

B. DRUG PRODUCT

1. COMPONENTS/COMPOSITION: Adequate, Review#1, pp 22-26.
2. SPECIFICATIONS & METHODS FOR INGREDIENTS: Adequate, Review#1, pp 26-27.
3. MANUFACTURER: Adequate, Review#1, p 28.
4. MANUFACTURING AND PACKAGING: Adequate, Review#1, pp 29-34.
5. SPECIFICATIONS AND TEST METHODS: **Deficient**, Review# 1, pp 34-37.
6. CONTAINER/CLOSURE SYSTEM: Adequate, Review#1, p 38.
7. STABILITY: **Deficient**, Review#1, pp 38-43.

C. INVESTIGATIONAL FORMULATIONS: Satisfactory, Review#1, pp 44-48.

D. ENVIRONMENTAL ASSESSMENT: Satisfactory, Review#1, pp 48-49.

E. METHODS VALIDATION: Deficient, Review#1, pp 49-54.

F. LABELING: Deficient, Review#1, pp 55-58.

G. ESTABLISHMENT INSPECTION: DO Withhold recommendation-Deficient, Review#1, p 58.

H. DEFICIENCY LETTER TO APPLICANT: YES, Review# 1, pp 59-64.

ATTACHMENT 1 Table 54. Method description, rationale, and specification justification
ATTACHMENT 2 Sampling requirements for Release and Stability Testing
ATTACHMENT 3 Copy of Package Insert
ATTACHMENT 4 EES report
ATTACHMENT 5 Copy of Representative commercial-scale lot, stability data

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS
(HFD-160)
Review of Chemistry, Manufacturing, and Controls

NDA #: **21-191** **DATE REVIEWED:** 21-MAY-00

REVIEW #: 1 **REVIEWER:** Milagros Salazar, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	11-OCT-99	15-OCT-99	11-FEB-009
AMENDMENT BM	26-JAN-00	28-JAN-00	11-FEB-00
AMENDMENT BC	3-FEB-00	7-FEB-00	11-FEB-00

NAME & ADDRESS OF APPLICANT: ALLIANCE PHARMARCEUTICAL CORP.
3040 Science Park Road
San Diego, CA 92121

DRUG PRODUCT NAME

Proprietary:	IMAVIST™
Established:	Perflexane-Lipid Microsphere (tentative)
Code Name/#:	AF0150
Chem.Type/Ther.Class:	1 S

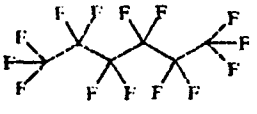
PHARMACOL. CATEGORY/INDICATION: Echopharmaceutical and Contrast enhancement for use in patient with sub-optimal echocardiogram to opacify the left ventricle (LV)

DOSAGE FORM: Powder for Injectable Suspension
STRENGTHS: 200 mg
ROUTE OF ADMINISTRATION: Intravenous injection
Rx/OTC: _X_ Rx __ OTC
SPECIAL PRODUCTS: __ Yes _X_ No

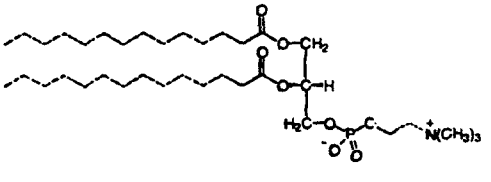
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: Chemical Structure of microbubble is undetermined

Structure of Microbubble components:

Vapor Component: perflexane (tetrafluorohexane)
C_6F_{14} / 338.04



Lipid Membrane Component: dimyristoylphosphatidylcholine (DMPC)
$C_{36}H_{72}NO_8P$ / 677.96



SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
IND [redacted]	AF0150	Alliance Pharm. Corp.	Active	NA	NA
DMF [redacted] Type II	[redacted]	[redacted]	Acceptable	7-Mar-00	16-Sep-99
DMF [redacted] Type II	[redacted]	[redacted]	Acceptable	10-Mar-00	11-Feb-00
DMF [redacted] Type III	[redacted]	[redacted]	NA	NA	NA
DMF [redacted] Type III	[redacted]	[redacted]	NA	NA	NA
DMF [redacted] Type I	[redacted]	[redacted]	NA	NA	NA
DMF [redacted] Type 1	[redacted]	[redacted]	NA	NA	NA
DMF [redacted] Type 1	[redacted]	[redacted]	NA	NA	NA
510(k) [redacted]	[redacted]	[redacted]	NA	NA	NA
NDA 18-801	Sterile Water for Injection, USP 20 mL	Abbott Laboratories	NA	NA	NA
510(k) [redacted]	[redacted]	[redacted]	NA	NA	NA

NA in the above table means - Not Applicable
RELATED DOCUMENTS: **See above**
CONSULTS: **None**

PATENTS/TRADEMARK: **Patent no. 5,605,673 Exp. Date: Feb25,2014 Type: Drug product (formulation, composition & for method of use of Imagent) Patent owner : Alliance Pharmaceutical Corporation. Imavist is a Trademark of Schering , AG**

REMARKS: The Chemistry, Manufacturing, and Controls (CMC) Section, NDA Section 4, consisted of 8 volumes and 2 amendments. The Microbiology section for this [redacted] sterilized product was recommended for approval. After establishment inspection, 3/20-30/00, Alliance Pharmaceutical-Lusk facility, manufacturer of commercial product, has been recommended for withhold of approval by the LOS-DO and OC. The inspection of [redacted] facility, [redacted] has been requested by OC but not scheduled by IB. All other facilities are acceptable.

The CMC section has major deficiency issues as follows:

- The specifications and test methods for the drug product, powder and constituted are insufficient and not ready.
- The stability data and studies are insufficient.
- MV are insufficient and not ready.
- EES withhold recommendation from LOS-DO and OC.

CONCLUSIONS & RECOMMENDATIONS: The application is deficient in CMC for the drug product under section 505 (b)(1) of the Act. Not approval is recommended.

/S/ 21-May-00

Milagros Salazar, Ph.D.
Review Chemist, HFD-820/160

cc:
Org. NDA 21-191
HFD-160/Division File
HFD-160/Salazar
HFD-160/ Harper-V
HFD-160/Leutzinger
HFD-820/Gibbs (NMEs only)
R/D Init by: ELeutzinger

/S/ 5/30/2000

filename: **N21-191imavist.doc**

51 pages redacted from this section of the approval package consisted of draft labeling

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confidential

commercial

information

The information for the following DMF's is included in the chemistry NDA review for cycle 1:

—	—	.
—	—	
No #	—	**(decided not to have a DMF but information was submitted to the NDA.)**

Harper

DMF REVIEW COVER FORM

DMF # [redacted] Type II

TITLE: DMPC

1. CHEM REVIEW No. 1 2. REVIEW DATE: 10-Mar-00

3. ITEM REVIEWED

A. IDENTIFICATION name(s)

IUPAC:	1,2-di (tetradecanoyl)-sn-glycero-3-phosphocholine
Trade name:	NA
Manufacturer's code:	NA
Chemical name:	1,2-dimyristoyl-sn-glycero-3-phosphocholine
CAS number:	18194-24-6
Abbreviations:	DMPC, MMPC

B. LOCATION IN DMF

Type of Submission	Date of Submission	Location of Information
Type II resubmission	7-Feb-00	Vol.3.1 (Y-report and consolidation)

4. PREVIOUS DOCUMENTS

Type of Document	Date of Document	Location	Description
Type IV DMF			
Amend & Annual Report	18-Jan-99	Vol. 2.1	Agent appointment and Y-report
NC	2-Mar-99	Vol. 2.1	Change from Type IV to Type II

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

NAME:

ADDRESS: [redacted]

Tel. [redacted]

REPRESENTATIVE or U.S. AGENT : [redacted]

CONTACT PERSON'S NAME: [redacted]

ADDRESS: [redacted]

TELEPHONE NUMBER: [redacted] FAX Number: [redacted]

6. DMF REFERENCED FOR:

NDA #: **21-191**

PRIMARY DMF: Yes, it is one of two DMFs of the 2 critical components for the DP

APPLICANT NAME: Alliance Pharmaceutical Corp.

LOA DATE: 11-Feb-00

DRUG PRODUCT NAME: IMAVIST™ (perfluoro-phospholipid microbubbles) Inj.

DOSAGE FORM: Injectable (powder for constitution) CODE: SVT

STRENGTH: 200 mg microbubble powder

ROUTE OF ADMINISTRATION: intravenous CODE: INJECTION

7. SUPPORTING DOCUMENTS: NONE

8. CURRENT STATUS OF DMF:
DATE OF LAST UPDATE OF DMF: 7-Feb-00
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAS BEEN PROVIDED: 11-Feb-00

9. CONSULTS: NONE

10. COMMENTS:

11. CONCLUSION: **DMF ACCEPTABLE - The information and data provided on the chemical identity, manufacture, control, label, and stability of product DMPC is satisfactory to support its use as a component of IMAVIST Inj.**

[redacted] 10-Mar-00
Milagros Salazar, Ph.D.,
Review Chemist, HFD-160/820

[redacted] 4/17/2000
Eldon Leutzinger, Ph.D.
Chemistry Team Leader, HFD-160/820

cc:
Original DMF # [redacted] (2 copies)
HFD-160 Division File
HFD-160/Salazar
HFD- 160/Leutzinger
HFD-160/Harper-V
R.D. init by:MSD
File Name c:\...\dmf\DMF.[redacted]-dmpc.doc

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information

Harper v.

DMF REVIEW COVER FORM

DMF # [redacted] Type II

TITLE: Perfluorohexanes, % (APF-60M)

1. CHEM REVIEW No. 1 **2. REVIEW DATE:** 7-Mar-00

3. ITEM REVIEWED

A. IDENTIFICATION name(s)

USAN:	perflexane
IUPAC:	n-perfluorohexane
Trade name:	[redacted]
Manufacturer's code:	
Chemical name:	tetradecafluorohexane
CAS number:	355-42-0
Abbreviations:	PFH, n-PFH

B. LOCATION IN DMF

Type of Submission	Date of Submission	Location of Information
Original	22-Sep-98	Vol 1.1
Amendment & Annual Update	16-Sep-99	Vol. 1.1

4. PREVIOUS DOCUMENTS

Type of Document	Date of Document	Location	Description
NONE			

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

NAME: [redacted]

ADDRESS: [redacted]

CONTACT PERSON'S NAME: [redacted]

ADDRESS: same as above

TELEPHONE NUMBER: [redacted]

FAX Number: [redacted]

6. DMF REFERENCED FOR:

NDA #: **21-191**

PRIMARY DMF: Yes, it is one of two DMFs of the 2 critical components for the DP

APPLICANT NAME: Alliance Pharmaceutical Corp.

LOA DATE: 16-Sep-99

DRUG PRODUCT NAME: IMAVIST™ (perfluoro-phospholipid microbubbles) Inj.

DOSAGE FORM: Injectable (powder for constitution) CODE: SVT

STRENGTH: 200 mg microbubble powder

ROUTE OF ADMINISTRATION: intravenous CODE: INJECTION

7. SUPPORTING DOCUMENTS: NONE

8. CURRENT STATUS OF DMF:
DATE OF LAST UPDATE OF DMF: 16-Sep-99
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED: 16-Sep-99

9. CONSULTS: NONE

10. COMMENTS: The original submission provided all necessary information for a comprehensive review. The amendment and annual update presented stability data and revised specifications and label for the product for consistency with manufacturing data. I.e., Perfluorohexanes, [redacted] % and testing and certification for [redacted] This last test replaced the distillation range specification and certification from the information given in the original submission dated 9/22/98. Manufacturing data for Perfluorohexanes, [redacted] % ([redacted] is provided also in the amendment of 09/16/99.

11. CONCLUSION: **DMF ACCEPTABLE - The information and data provided on the chemical identity, manufacture, control, label, and stability of product APF-60M is satisfactory to support its use as a component of IMAVIST Inj.**

[redacted] 7-MAR-00
Milagros Salazar, Ph.D.,
Review Chemist, HFD-160/820

[redacted] 4/10/2000
Eldon Leutzinger, Ph.D.
Chemistry Team Leader, HFD-160/820

cc:
Original DMF # [redacted] (2 copies)
HFD-160 Division File
HFD-160/Salazar
HFD- 160/Leutzinger
HFD-160/Harper-V
R.D. init by:MSD
File Name c:\...\dmf\DMF [redacted] '-PFH.doc

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SEE CHEMIST'S REVIEW (CYCLE 1)

TAB C-1, PAGES 48-49

NOT APPLICABLE

addressed in Chemist's review