CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-704

Chemistry Review(s)

CHEMISTRY REVIEW #1

NDA 21704

Allegra-D 24 Hour (fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg) Extended Release Tablet

Aventis Pharma

Edwin Jao, Ph.D.
Division of Pulmonary and Allergy
Drug Products

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1. NDA 21704

2. REVIEW #: 1

3. REVIEW DATE: October 18, 2004

4. REVIEWER: Edwin Jao, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND66289	26-Nov-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date	Assigned Date
Original Submission N21-704n000	19-Dec-2003	7-Jan-2004
BC	03-Mar-2004	05-Mar-2004
BC	05-Mar-2004	05-Mar-2004
BC	27-Apr-2004	27-Apr-2004
BC	26-May-2004	26-May-2004
BC	01-Jul-2004	01-Jul-2004
BC	14-Jul-2004	14-Jul-2004
BC	26-Aug-2004	26-Aug-2004
BC	22-Sep-2004	22-Sep-2004
BZ	29-Sep-2004	29-Sep-2004
BZ	30-Sep-2004	30-Sep-2004
BZ	18-OCT-2004	18-OCT-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Aventis Pharmaceuticals Inc.

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Address: 200 Crossing Boulevard, P.O.Box 6890, Bridgewater, NJ08807
Representative: Kimberly S. Stranick, Ph.D. Director, Regulatory Liaison
Telephone: (908) 5304-6580

8. DRUG PRODUCT NAME/CODE/TYPE:

a. Proprietary Name: Allegra-D 24 Hour™
b. Non-Proprietary Name (USAN): fexofenadine hydrochloride and pseudoephedrine hydrochloride
c. Code Name/# (ONDC only):N/A
d. Chem. Type/Submission Priority (ONDC only):
   - Chem. Type: 3
   - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

10. PHARMACOL. CATEGORY: Histamine H_1-receptor antagonist

11. DOSAGE FORM: Oral tablets

12. STRENGTH/POTENCY: fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: _X_ Rx _____OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

_X_ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

a. (±)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α, α-dimethyl benzeneacetic acid hydrochloride

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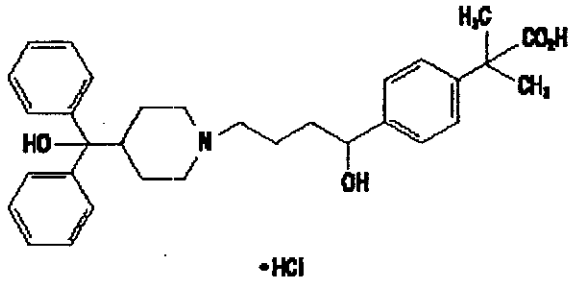
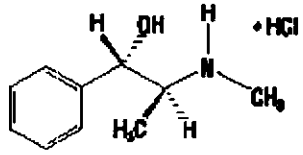


Molecular Formula: $C_{32}H_{39}NO_4 \cdot HCl$
Molecular Weight: 538.13

b. [S-(R*, R*)]-α-[1-(methylamino)ethyl]-benzenemethanol hydrochloride



Molecular Formula: $C_{10}H_{15}NO \cdot HCl$
Molecular Weight: 201.70

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS [2]	DATE REVIEW COMPLETED (Reviewer)	COMMENTS
	II		Pseudoephedrine HCl	3	Adequate	08-May-2003 (J.Salemme)	
	III			1	Adequate	13-Oct-2004 (E. Jao)	
	IV			1	Adequate	13-Oct-2004 (E. Jao)	
	III			3	Adequate	07-Apr-2004 (R. Lostritto)	To support N20872 (Allegra)
	III			3	Adequate	14-Feb -2000 (R. Ganunis)	
	III			3	Adequate	17-Sep-2001 (R.Frankewich)	
	III			3	Adequate	25-Apr-02 (J. Boal)	

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	III			4			Sufficient information provided in the NDA application
	III			3	Adequate	29-Apr-02 2003 (R. Frankewich, Ph.D.)	Additional information provided in the NDA application
	III		N	3	Adequate	26-Nov-95 (S. John))	Additional information provided in the NDA application
	III			3	Adequate	09-Sep-1998 (K. Srinivasachar)	Additional information provided in the NDA application
	III			3	Adequate	30-Jun-1999 (H. Khorshidi)	To support N20872 (Allegra)
	III			3	Adequate	30-Jun-1999 (H. Khorshidi)	To support N20872 (Allegra)
	III			4			Sufficient information provided in the NDA application
	IV			3	Adequate	20-May-1999 (D. Lin)	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
N20786	Aventis	Allegra-D	approved	24-Dec-1997	
N20872	Aventis	Allegra	approved	25-Feb-2000	

C. Related Documents:

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DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE REQUESTED	STATUS/DATE	COMMENTS
EES CFN	Pseudoephedrine HCl	03-Feb-2004	Acceptable 03-Feb-2004	[redacted]
EES CFN	Fexofenadine HCl manufacturer & tester	03-Feb-2004	Acceptable 15-Mar-2004	Aventis, Germany
EES CFN	Alt. Fexofenadine HCl	03-Feb-2004	Acceptable 15-Mar-2004	[redacted]
EES CFN	Pseudoephedrine HCl	03-Feb-2004	Acceptable 24-Aug-2004	[redacted]
EES CFN	Pseudoephedrine HCl	03-Feb-2004	Acceptable 13-Feb-2004	[redacted]
EES CFN	DP manufacturer, packager, & tester	03-Feb-2004	Acceptable 13-Feb-2004	Aventis , Kansas city, MO
EES	**Overall Approval**	03-Feb-2004	**Acceptable** 24-Aug-2004	
Methods Validation				No request to the FDA lab will be submitted
OPDRA		N/A		No trademark provided for DP.
EA		N/A		
Microbiology		N/A		

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The Chemistry Review for NDA 21-621

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is considered to be **approval (AP)**.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No recommendations for phase 4 studies are proposed or agreed upon at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

1. There are two drug substances in this fixed combination drug product. They are: fexofenadine HCl, a histamine H_1-receptor antagonist, and pseudoephedrine HCl, an adrenergic (vasoconstrictor) agent.

2. Fexofenadine hydrochloride is a white to off-white crystalline powder. It is soluble in methanol and ethanol, slightly soluble in chloroform and water, and insoluble in hexane. Fexofenadine hydrochloride is a racemate and exists as zwitterions in aqueous media at physiological pH.

3. Pseudoephedrine hydrochloride occurs as fine, white to off-white crystals or powder. It is very soluble in water, freely soluble in alcohol, and sparingly soluble in chloroform. The applicant provides evidence that the particle size of pseudoephedrine hydrochloride does not have significant effects on its solubility (N000, p.49). The combinational use of these two drug substances has been approved in extended release tablet Allegra-D (N20786, 1997).

Drug Product

1. Allegra-D 24 Hour™tablet is an opaque white round, modified release tablet [redacted] The tablet has 308AV printed on one side in black ink.

2. Allegra-D 24 Hour™Extended-Release Tablets for oral administration contain 180 mg fexofenadine hydrochloride for immediate release and 240 mg pseudoephedrine

hydrochloride for extended release. The tablets also contain following excipients: microcrystalline cellulose, sodium chloride, cellulose acetate, polyethylene glycol, opadry white, povidone, talc, hypromellose, croscarmellose sodium, copovidone, titanium dioxide, magnesium stearate, colloidal silicon dioxide, brilliant blue aluminum lake, acetone, isopropyl alcohol, methyl alcohol, methylene chloride, water, and black ink.

3. There is no change in formulations between clinical trial batches and proposed commercial drug product (3.2.P, p.51).

4. Allegra-D 24 Hour™Extended-Release Tablets are indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. Allegra-D 24 Hour™is intended to target those patients who require both the antihistaminic properties of fexofenadine hydrochloride and the nasal decongestant properties of pseudoephedrine hydrochloride.

5. Allegra-D 24 Hour tablets have been formulated to provide an immediate release 180 mg dose of fexofenadine HCl and a sustained release 240 mg dose of pseudoephedrine HCl. This is achieved through [ ] an immediate release outer layer containing fexofenadine HCl [ ]. The tablet [ ] contains pseudoephedrine HCl, which is designed to release over a 24-hour period [ ]

] the tablet and dissolves both NaCl and pseudoephedrine HCl. It is noticed that the currently marketed Allegra-D (12 hours) uses a [ ] system to control the slow release of pseudoephedrine HCl.

6. The manufacturing process attributes (critical parameters) that have major impact on drug product quality and batch reproducibility are: the manufacturing of [ ] pseudoephedrine HCl, [ ] and fexofenadine HCl [ ]

7. Allegra-D 24Hour Tablets will be packaged for commercial distribution in 30-ct, 100-ct and — high density polyethylene (HDPE) opaque, white bottles. Even though the original application indicates the intention of including [ ] blister package as one of the commercial presentations (3.2.P., p.766), [ ] package will be distributed only as physician samples (BC dated XXX).

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

The recommended dose of ALLEGRA-D 24 HOUR Extended-Release Tablets is one tablet once daily administered before a meal for adults and children 12 years of age and older. The recommended storage conditions for ALLEGRA-D 24 HOUR Extended-Release Tablets are 20-25°C (68-77°F). The proposed expiry dating is 24 months.

C. Basis for Approvability or Not-Approval Recommendation

The application is currently recommended as **approval (Ap)** based on the information provided in the original NDA.

However, the applicant informed the Agency in an amendment dated September 22, 2004, that a key manufacturing equipment [ ] has **recently** been replaced at [ ] where the extended release pseudoephedrine HCl — will be manufactured for commercial marketing. As the result of such change, the dissolution profile [ ] can no longer be duplicated to the one established by the biobatch and three NDA batches. During a telecon between the Agency (Drs. Lostritto and Jao) and Aventis (Kevin Hibbert, Ian Davidson, and Denise Flanagan) the applicant indicated that the old equipment can not be reinstalled. Aventis commits to conduct all the necessary investigations to establish the equivalency of the new equipment and the corresponding new process parameters and report the result to the Agency when they are available.

Since this manufacturing process change has affected the controlled release character of the drug product, it is classified as a majaor change and requires a prior approval from the Agency before the drug product can be marketed (Guidance for Industry, Changes to an Approved NDA or ANDA, April 2004).

Therefore, Aventis is not allowed to market Allegra D-24 with this approved NDA. The applicant is recommended to conduct all the necessary investigations to establish the equivalency of the drug product manufactured by the new equipment/process parameters, and report the result to the Agency in a Prior Approval Supplement.

In the amendment dated September 30, 2004, the applicant indicated that they are in the process of re-evaluating [ ] manufacturing step, which involves [ ] (BZ dated 9/30/04., pp.5-6). The applicant proposed tentative timelines as follows:

1. Batch release data from comparison study (four batches at commercial scale): February 28, 2005.

2. Three-month stability data from comparison batches: June 30, 2005.

The followings are the basis for Approval (AP) of the original NDA:

1. The drug substances Fexofenadine HCl and pseudoephedrine HCl have been approved for use in oral dosage forms. The combinational use of these two drug substances has been approved in extended release tablet Allegra-D manufactured by the same applicant (N20786, 1997).

2. The manufacturing and testing sites for the drug substance Fexofenadine HCl used in the currently marketed Allegra-D is found "acceptable" by EES for the new drug product Allegra-D 24 hours. The DMF to which the CMC of drug substance pseudoephedrine HCl is referenced is found adequate for this application. The DMF holder manufacturing site is found "acceptable" by EES for this application.

3. All excipients in the drug product are either compendial or referenced to DMFs, which are found adequate for this application. The levels of use of compendial excipients are all within the ranges of use for approved products.

4. The critical manufacturing process attributes that have major impact on drug product quality and batch to batch reproducibility are adequately controlled.

5. The release and stability data from three NDA registration batches ([commercial scale) appear to support the intended drug product dissolution profiles.

6. The [ ] long term stability data and statistical analysis from three NDA registration batches indicate that the drug product is chemically and physically stable in the proposed commercial container/closure systems up to 24 month, which is the proposed expiry dating. However, the stability data only support an 18-month expiry dating for [ ] blister packaging configuration, due to less protection of this packaging to the drug product from moisture permeation. Additionally, because the stability testing was conducted on — blister configuration instead of — blister (which is made of same materials), the 18-month expiry dating is approved under the condition that the applicant will agree to a post approval stability testing on [ ] [ ] blister physician sample.

7. All drug product scale up process developments (from pilot to commercial scales) were performed at the intended commercial sites.

8. Initial review of the application revealed certain CMC deficiencies and/or needed clarifications, which were sent to the applicant on June 15, 2004. The major issues are as follows:

   a. Additional controls and clarifications are needed for manufacturing, container/closure system, holding time, and acceptance criteria of pseudoephedrine HCl containing [ ] manufactured at [ ] The ~ are drug product [ ] to be shipped to Aventis, MO for further processing.

   b. Since [ ] instead of — is used for the final drug product assay testing, adding ~ testing of the drug substance fexofenadine [ ] as an additional process control is recommended.

   c. The acceptance criteria for drug product [ ] should be revised to reflect the data and manufacturing capacities.

   d. The moisture contents in certain trade packages and bulk containers display upward trends (although still within specifications) during stability testing, and more so for [ ] blister (physician sample) and bulk containers (to be repackaged into commercial presentations later at other Aventis sites or by other contract packagers). The applicant is asked to provide evidence that the drug product stored in the proposed bulk containers to the proposed maximum storage

time can still be stored in the proposed trade packages to the balance of the proposed expiry dating.

e. HDPE canister or pouch containing activated carbon are to be included in the HDPE bottle commercial presentations to remove odor alleged from [ ] [ ] which is introduced from manufacturing process and can not be eliminated. Since the concentration of [ ] in the drug product is controlled at below ICHQ3C level, this is not a safety issue; but the odor might lead to potential consumer complains. The applicant is asked to provide stability data to prove the adsorptive efficacy [ ] during the entire shelf life of the drug product.

f. The DMF referenced for the above mentioned carbon pouch is found inadequate because of total lack of CMC information. The NDA applicant is asked to contact the DMF holder for clarifications.

9. A full response to those deficiencies from the applicant was received on September 2, 2004.

10. A second IR letter was sent to the applicant on September 13, 2004, regarding certain specification, analytical method validation, and labeling issues.

11. A full response to the second IR letter was received on October 5, 2004.

12. The third IR letter was sent to the applicant on October 15, 2004, seeking confirmation of post approval agreements.

13. A full response to the third IR letter was received on October 18, 2004. All CMC issues have been resolved satisfactorily. The following post approval agreements have been reached (duplicated from the amendment dated 10/18/2004):

Commitment 1

Aventis commits to revise the drug product specifications according to the proposed agreements contained in our amendments dated August 26, 2004 and September 29, 2004. Specifically, a) Aventis will use [ ] for drug product identification; b) Aventis commits to an acceptance criterion for Total Degradation Products during shelf-life of NMT — and c) Aventis commits to an acceptance criterion for [ ] of NMT — μg/tablet, and for [ ] of NMT — μg/tablet. These acceptance criteria will be implemented on an interim basis and subject to reexamination based on data from approximately — batches of post approval commercial production.

Commitment 2

Aventis commits to revise the system suitability testing [ ] criteria for the following analytical methods according to the proposed agreements contained in our amendment dated September 29 2004:

a) NMT — for the system suitability testing . and Degradation Products for fexofenadine HCl and pseudoephedrine HCl.
b) NMT — for the system suitability injections in [ ] testing method for [ ]
c) NMT — for the system suitability injections in the HPLC testing method for Dissolution.

Commitment 3

Aventis understands and concurs with the Agency on the following expiry dating and holding time issues:

a) Agree (as per our amendment dated August 26, 2005) that the expiry-dating clock starts prior [ ] our Kansas City site.
b) A 24-month expiry dating is acceptable for the drug product packaged in 30ct, 100ct [ ] HDPE bottle.
c) A [ ] holding time is acceptable for bulk drug product packaged in [ ] and a [ ] holding time is acceptable for bulk drug product packaged in [ ]. As per our amendment dated August 26, 2004, Aventis agrees to perform an additional hold study to confirm that the finished tablets stored in these bulk containers for the time periods indicated above, and then packaged in bottles (30ct [ ] and blisters, remain within specification throughout the proposed shelf life of 24 month for bottles and 18 months for blisters.
d) A [ ] holding time is acceptable for [ ] pseudoephedrine — , a [ ] holding time is acceptable for [ ] pseudoephedrine - and - - total holding time for [ ] combined is acceptable.

Commitment 4

Aventis agrees to [ ] testing of the HDPE bottles at the — and — months stability time points for the NDA stability batches to further demonstrate the effectiveness of the [ ] throughout the remaining proposed shelf life of the product, as stated in our amendment dated August 26, 2004.

Commitment 5

Aventis accepts an [ ] expiry dating for the drug product packaged as [ ] blister physician samples and commits to conduct both long term and accelerated stability testing on this — blister sample for the first three (3) commercial batches. Aventis will include this presentation in our regular annual stability testing protocol.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

C. CC Block

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✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Edwin Jao
10/18/04 02:41:56 PM
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Richard Lostritto
10/18/04 03:03:19 PM
CHEMIST