CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-963

CHEMISTRY REVIEW(S)

ALLEGRA (FEXOFENADINE HYDROCHLORIDE) SUSPENSION
NDA 21-963

Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls

Applicant: Sanofi Aventis
200 Crossing Boulevard, PO Box 6890
Bridgewater, NJ 08807

Indication: To relieve symptoms of seasonal allergic rhinitis and for treatment of chronic idiopathic urticaria in children.

Presentation: Immediate-release oral suspension containing 6 mg/mL of fexofenadine hydrochloride and the following excipients: polypropylene glycol, edentate disodium, propylparaben, butylparaben, xanthan gum, poloxamer 407, titanium dioxide, [redacted] artificial raspberry cream flavor, sucrose, xylitol, and water. The drug product is packaged in [redacted] mL amber polyethylene terephathalate (PET) bottles [redacted]

EER Status: Acceptable 23-JAN-2006

Consults: EA – consulted to OPS, environmental assessment provided and EIC greater than 1 ppb, FONSI dated 10-APR-2006 (see CR#1)

Original Submission: 15-DEC-2005

Post-Approval Agreements:
[redacted]

Drug Substance:

Fexofenadine hydrochloride is a histamine H_1-receptor antagonist. According to the labeling, this compound is a white crystalline powder that is soluble in methanol and poorly soluble in water. The Biopharmaceutics Classification System places this compound in the low solubility/low permeability category. All drug substance information is cross-referenced to the approved NDA 20-625 for Allegra Capsules. No new information on drug substance is provided in this NDA. Other Allegra formulations also use the same drug substance.

Conclusion: Drug substance is acceptable.

Drug Product:

The drug product is a buffered, white, aqueous suspension with raspberry cream flavor that was developed for pediatric patients. The drug product is manufactured at Aventis' facility in Kansas City, MO. Critical steps include [redacted] Drug product specifications

[redacted]

Adequate stability data were provided to support the proposed expiration dating of 24 months at 25°C for drug product packaged in the commercial bottle and 18 months for the physician's sample bottle.

Conclusion: Drug product is satisfactory.

Additional Items:

All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

A method validation package, describing the test methods and validation procedures, including information supporting the reference standard, is provided. As the analytical methods used in the testing procedures (release and stability) are well known or have been established in previous Allegra submissions, revalidation by Agency laboratories will not be requested.

Overall Conclusion:

From a CMC perspective, the application is recommended for approval.

Blair A. Fraser, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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/s/

Blair Fraser
4/18/2006 07:48:15 AM
CHEMIST

NDA 21-963

Allegra Suspension 6 mg/mL

Aventis

Martin Haber
Division of Pre-Marketing Assessment I

Consult Review for
Division of Pulmonary and Allergy Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-963

2. REVIEW #1

3. REVIEW DATE: April 17, 2006

4. REVIEWER: Martin Haber, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NA	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original electronic NDA	12/15/05

7. NAME & ADDRESS OF APPLICANT:

Name:	Sanofi Aventis
Address:	200 Crossing Boulevard, PO Box 6890, Bridgewater, NJ 08807
Representative:	Lori Birkenberger, Ph.D.
Telephone:	(908) 231-3126

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Allegra
b) Non-Proprietary Name (USAN): Fexofenadine HCl
c) Code Name/# (ONDC only):

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3 (new formulation)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: Anti-histamine

11. DOSAGE FORM: Aqueous Oral Suspension

12. STRENGTH/POTENCY: 6 mg/mL

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

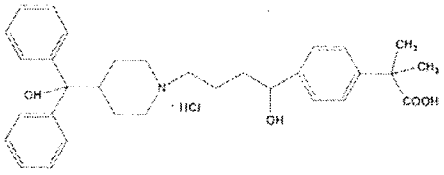
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name: Benzeneacetic acid, 4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]-α,α-dimethyl-, hydrochloride, (±)

Mol Formula: $C_{32}H_{39}NO_3 \cdot HCl$

Mol Weight: 538.1

CAS Reg No: HCl Salt:[138452-21-8]
Base :[83799-24-0]



(USAN 2000, p 302)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	IV	[redacted]		1	Adequate	2/13/06	Reviewed by M. Haber
	III			3	Adequate	4/2/99	Reviewed by T. Broadbent
	III			3	Adequate	6/15/00	Reviewed by A. Shaw
	III			3	Adequate	8/12/04	Reviewed by S. Pope
	III			3	Adequate	8/12/03	Reviewed by R. Frankewich
	III			3	Adequate	6/9/03	Reviewed by D. Klein

[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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	1/23/06	S. Ferguson, OC

Chemistry Review Data Sheet

Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	NA		
OPDRA	NA		
EA	FONSI	4/10/06	Bai Nguyen, OPS
Microbiology	NA		

The Chemistry Review for NDA 21-963

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend approval.

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

NA

II. Summary of Chemistry Assessments

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

Allegra [redacted] Oral Suspension is indicated for treatment of seasonal allergic rhinitis. The proposed drug product is a buffered, white, aqueous suspension with a raspberry cream flavor that was developed for pediatric patients. Allegra (fexofenadine HCl) 6 mg/mL [redacted] Suspension is an immediate release oral suspension intended for twice-a-day oral dosing. Each 5-mL (one teaspoon) dose contains 30 mg of the active. The following excipients are present: polypropylene glycol, edentate disodium, propylparaben, butylparaben, xanthan gum, poloxamer 407, titanium dioxide, [redacted] artificial raspberry cream flavor, sucrose, xylitol and water. The drug product is manufactured at Aventis' facility in Kansas City, MO. Critical aspects of the manufacturing process include:

[redacted] Drug product specifications include: [redacted]

suspension is packaged in [redacted] (physician's sample) and [redacted] amber polyethylene terephathalate (PET) plastic bottles [redacted] The drug product packaged in the commercial bottle and the physician's sample bottle is stable at 25°C for 24 months and 18 months, respectively.

Fexofenadine hydrochloride is a non-sedating, long-acting anti-histamine with selective peripheral histamine H1-receptor agonist activity. All chemistry information on the drug substance, fexofenadine hydrochloride, is provided by cross-reference to the approved NDA 20-625 for Allegra Capsules (approved 7/25/96) from the same sponsor, Aventis, and all subsequent supplements and

annual reports made thereto. No new information on the drug substance is provided in this NDA 21-963. Although there are two approved manufacturers, only drug substance manufactured from Aventis' Frankfurt, Germany facility will be used for the [redacted] Oral Suspension product. There is no USP monograph. Other NDAs, NDA 20-872 (approved 2/25/00) for Allegra Tablets and Allegra-D formulations (NDA's 21-704 and 20-786) from the same sponsor, Aventis, also use the same drug substance.

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

Allegra [redacted] Oral Suspension is indicated for relief of symptoms associated with seasonal allergic rhinitis in children 2 to 11 years of age and for treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in children 6 months to 11 years of age. The recommended dose is 30 mg (5 mL), twice daily, [redacted] The bottle should be shaken well before use. The drug product packaged in the commercial bottle and the physician's sample bottle is stable at 20-25°C for 24 months and 18 months, respectively.

C. Basis for Approvability or Not-Approval Recommendation

The chemistry information provided for the drug product is adequate. Chemical manufacturing, controls, and quality testing for the drug product are adequate. No major chemistry deficiencies were found. No new information on drug substance is provided in this NDA. The cGMP status of all manufacturing facilities is satisfactory as per EER on 1/23/06. There are no pending CMC deficiencies.

III. Administrative

A. Reviewer's Signature

See DFS

B. Endorsement Block

See DFS

C. CC Block

See DFS

29 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 2

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

/s/

Martin Haber
4/17/2006 06:03:57 PM
CHEMIST

Blair Fraser
4/18/2006 05:27:49 AM
CHEMIST