

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**201373Orig1s000**

**PHARMACOLOGY REVIEW(S)**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: NDA201373  
(for a Prescription (Rx) to an Over The Counter (OTC) switch)

Supporting Documents: S001

Applicant's letter date: 03/25/2010

CDER stamp date: 03/26/2010

Product: ALLEGRA® oral suspension

Indication: For the temporary relief of symptoms due to hay fever or other upper respiratory allergies as well as for the reduction of hives in adults and children  $\geq 2$  years of age and the relief of itching due to hives (urticaria) in adults and children  $\geq 6$  years of age.

Applicant: Sanofi-aventis U.S. LLC

Review Division: Division of Nonprescription Clinical Evaluation

Reviewer: Cindy Li, Ph.D.

Secondary Reviewer: Paul Brown, Ph.D., ODE Associate Director for Pharmacology/Toxicology, OND

Division Director: Andrea Leonard-Segal, M.D.

Project Manager: Jess Diaz, R.N.

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of the present New Drug Application (NDA) submission (NDA201373) are owned by Sanofi-aventis U.S. LLC or are data for which Sanofi-aventis U.S. LLC has obtained a written right of reference. Any information or data necessary for approval of the present NDA submission that Sanofi-aventis U.S. LLC does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of the present NDA submission.

# 1 Executive Summary

## 1.1 Introduction

NDA201373 is a New Drug Application (NDA) for the **partial change** of ALLEGRA® oral suspension (fexofenadine hydrochloride) from prescription-to-nonprescription use. Fexofenadine was first approved in the United States (U.S.) in July 1996 for seasonal allergic rhinitis (SAR) or hay fever, and chronic idiopathic urticaria (CIU) or hives as a 60 mg capsule formulation (NDA 20625). The suspension formulation was first approved on October 16, 2006 for the treatment of SAR and CIU. The present application is a partial switch and the use of fexofenadine suspension for the treatment of CIU in pediatric patients 6 months to less than 6 years of age will be retained under the original NDA21963. The nonclinical information on the prescription product has been reviewed and found to be sufficient if used within the dosage limits and in the dosage forms established. No new nonclinical studies were submitted for this application.

## 1.2 Brief Discussion of Nonclinical Findings

None

## 1.3 Recommendations

### 1.3.1 Approvability

Based on the previous human use experience for this product as a prescription drug, the agency's review of the nonclinical information, as well as the lack of novel significant issues during the current review, the present NDA can be approved from the nonclinical perspective.

### 1.3.2 Additional Non Clinical Recommendations

None

### 1.3.3 Labeling

None. The OTC labeling for this product is suggested to have the statement: "If pregnant or breast-feeding, ask a health professional before use".

# 2 Drug Information

## 2.1 Drug

CAS Registry Numbers:  
Fexofenadine HCl, 138452-21-8

Generic Names:  
Fexofenadine HCl

## Code Names:

Fexofenadine HCl, MDL 16,455A

## Chemical Names:

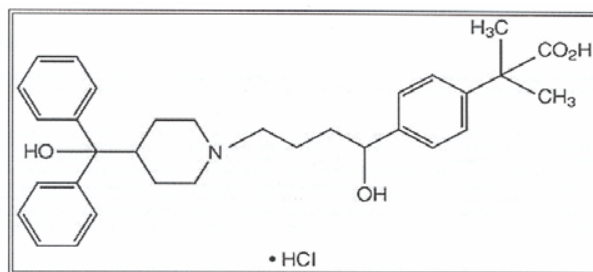
Fexofenadine HCl, ( $\pm$ )-4-[1-hydroxy-4-[4(hydroxydiphenylmethyl)-1-piperidiny]-butyl]- $\alpha$ ,  
 $\alpha$ -dimethyl benzeneacetic acid hydrochloride

## Molecular Formulae/Molecular Weights:

Fexofenadine HCl, C<sub>32</sub>H<sub>39</sub>NO<sub>4</sub> .HCl/538.18

## Structure or Biochemical Description

## Fexofenadine HCl



## Pharmacologic Class

Fexofenadine HCl: H1 receptor antagonist

**2.2 Relevant INDs, NDAs, and DMFs**IND43,573 (fexofenadine HCl), (b) (4) NDA20872  
(fexofenadine HCl tablets), NDA20625 (fexofenadine HCl capsules).**2.3 Drug Formulation**

ALLEGRA oral suspension is available as 30 mg/ 5 mL (6 mg/mL). ALLEGRA oral suspension, a white uniform suspension, contains 6 mg fexofenadine hydrochloride per mL and the following excipients: propylene glycol, edetate disodium, propylparaben, butylparaben, xanthan gum, poloxamer 407, titanium dioxide, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, artificial raspberry cream flavor, sucrose, xylitol and purified water. More detailed information regarding the formulation can be found in the original NDA review (NDA21963).

**2.4 Comments on Novel Excipients**

None.

**2.5 Comments on Impurities/Degradants of Concern**

None.

## 2.6 Proposed Clinical Population and Dosing Regimen

For Seasonal Allergic Rhinitis

Children 2 to 11 Years: The recommended dose of ALLEGRA oral suspension is 30 mg twice daily. (b) (4)

For Chronic Idiopathic Urticaria

Children 6 to 11 years: The recommended dose of ALLEGRA oral suspension is 30 mg (5 mL) twice daily. (b) (4)

## 2.7 Regulatory Background

This submission supports the nonprescription use of fexofenadine oral suspension, 6 mg/mL (henceforth referred to as fexofenadine suspension) for allergic rhinitis and CIU. Reference is made to NDA20625 and NDA20872, which presented the efficacy and safety data for 30 mg, 60 mg, and 180 mg tablets of fexofenadine, and NDA 21963 which supported the efficacy and safety of the fexofenadine suspension. On 27 February 2000, the 60 mg tablets twice daily (BID) were approved for the treatment of symptoms of SAR and CIU in adults and adolescents 12 years of age and older (ie,  $\geq 12$  years of age), the 30 mg tablets BID were approved for the same indications in pediatric patients 6 to 11 years of age, inclusive (ie,  $\geq 6$  years to  $\leq 11$  years of age), and the 180 mg tablet was approved as a treatment of symptoms of SAR in adults and adolescents 12 years of age and older. The fexofenadine suspension was approved on 16 October 2006 for the treatment of SAR and CIU in pediatric patients 2 to less than 12 years of age, inclusive (ie,  $\geq 2$  to  $< 12$  years of age), at a dose of 30 mg BID and for the treatment of CIU in pediatric patients 6 months to less than 2 years of age, inclusive (ie,  $\geq 6$  months to  $< 2$  years of age), at a dose of 15 mg BID. The further Pediatric Exclusivity Labeling Supplements to NDA (sNDA) 20-625 S8-012, NDA 20-872 S8-011, and NDA 20-786 S8-014, approved on 27 January 2003, summarized relevant pharmacokinetic and safety and efficacy information for fexofenadine in pediatric subjects 6 months to less than 6 years of age, inclusive, and complemented information that had been submitted to the agency earlier in July 2000 for fexofenadine in pediatric subjects 2 to less than 6 years of age, inclusive. In addition, 1 study (Study PJPR0057, current prescription-to-nonprescription switch NDA 201613) has been conducted to support the treatment of symptoms of perennial allergic rhinitis (PAR) at the same dose as for the treatment of SAR. This present submission applies for the partial switch from prescription-to-nonprescription use of the fexofenadine suspension in adult and pediatric patients 2 years of age and older for the treatment of SAR and in adult and pediatric patients 6 years of age and older for the treatment of CIU. The use of fexofenadine suspension for the treatment of CIU in pediatric patients 6 months to less than 6 years of age, inclusive, will be retained under the original NDA 21963.

## 3 Studies Submitted

### 3.1 Studies Reviewed

None.

No new nonclinical studies were conducted or submitted for the current NDA. Nonclinical information submitted and reviewed for the approval of fexofenadine hydrochloride (HCl) product can be found in the following table:

**Table 1 - Location of nonclinical pharmacology, toxicology, and metabolism information previously submitted in related fexofenadine HCl new drug applications**

	NDA 20-625	NDA 20-786	NDA 20-872	NDA 21-704
	Fexofenadine HCl 60 mg capsule	Fexofenadine HCl 60 mg and pseudoephedrine HCl 120 mg tablet	Fexofenadine HCl 30, 60, and 180 mg tablet	Fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg tablet
<b>Submission Date</b>	July 31, 1995	December 20, 1996	July 17, 1998	December 19, 2003
<b>Approval Date</b>	July 25, 1996	December 24, 1997	February 27, 2000	October 19, 2004
<b>Overall Summary</b>	S5-V1.15-P1	S5-V1.14-P3	S5-V1.14-P6	S5.A P1
<b>Pharmacology</b>	S5-V1.15-P9	S5-V1.14-P4	S5-V1.14-P10	S5.B P2
<b>Toxicology</b>	S5-V1.17-P1	S5-V1.14-P4	S5-V1.14-P24	S5.C P3
<b>Metabolism</b>	S5-V1.19-P1	S5-V1.14.P4	S5-V1.14-P43	S5.D P6

### 3.2 Studies Not Reviewed

None.

### 3.3 Previous Reviews Referenced

See reviews by C. Oberlander, (b) (4) 3/1/83 and L. Sancilio, NDA 20265, 7/31/95; NDA20786, 3/12/97; NDA 20872, 7/17/98; NDA21704, 12/19/03.

## 4 Integrated Summary and Safety Evaluation

Fexofenadine HCl is a histamine H1-receptor antagonist and was first approved in the US in July 1996 for seasonal allergic rhinitis (SAR) or hay fever, and chronic idiopathic urticaria (CIU) or hives as a 60 mg capsule formulation under NDA20625. In subsequent submissions, a tablet formulation of 3 different dose strengths (30 mg, 60 mg, and 180 mg) was approved in 2000 and 2005 for SAR and CIU or hives (NDA20872). This present submission applies for the partial switch from prescription-to-nonprescription use of the fexofenadine suspension in adult and pediatric patients 2 years of age and older for the treatment of SAR and in adult and pediatric patients 6 years of age and older for the treatment of CIU. The use of fexofenadine suspension for the treatment of CIU in pediatric patients 6 months to less than 6 years of age, inclusive, will be retained under the original NDA 21963. The present NDA submission is for an Rx to OTC switch of the same product.

No new nonclinical studies were conducted or submitted in this sNDA. Based on the current labeling information for the prescription Allegra products, several reproductive and developmental findings were noted and included reduced implants, post implantation loss, and decreases in pup weight gain and survival. The overall clinical relevance of these findings is not clear since the findings were observed in rats or rabbits but not in mice, and may be considered as a species-specific observation. These findings were seen at a ~3 fold margin when compared to the maximum human exposure. None of the above stated findings are considered to have a significant impact for the Rx to OTC switch. The OTC labeling for this product is suggested to have a statement such as "If pregnant or breast-feeding, ask a health professional before use".

This will limit the use of this product during pregnancy and will be consistent with the prescription labeling "There are no adequate and well-controlled studies in pregnant women. The product should be used only if the potential benefit justifies the potential risk to the fetus".



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/s/  
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XINGUANG LI  
11/23/2010

PAUL C BROWN  
11/23/2010

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

**NDA/BLA Number:** 201373 **Applicant:** sanofi-aventis U.S. LLC **Stamp Date:** 03/26/2010

**Drug Name:** ALLEGRA® **NDA/BLA Type:** 505(b)(1)  
oral suspension

**Background:**

Fexofenadine hydrochloride is an antihistamine with selective peripheral H1-receptor antagonist activity. The indication of the proposed product is for the temporary relief of symptoms due to hay fever or other upper respiratory allergies (runny nose, sneezing, itchy, watery eye, itching of nose or throat), as well as for the reduction of hives and the relief of itching due to hives (urticaria). For the oral suspension formulation provided in this NDA, the use for allergic rhinitis is for adults and children  $\geq 2$  years of age and itching due to hives in adults and children  $\geq 6$  years of age.

This submission is a 505(b)(2) New Drug Application (NDA) for the **partial change** of ALLEGRA® oral suspension (fexofenadine hydrochloride) from prescription-to-nonprescription use. Fexofenadine was first approved in the United States (U.S.) in July 1996 for seasonal allergic rhinitis (SAR) or hay fever, and chronic idiopathic urticaria (CIU) or hives as a 60 mg capsule formulation (NDA 20-625), a dosage formulation that is not currently marketed in the US. In subsequent submissions, a tablet formulation of 3 different dose strengths (30 mg, 60 mg, and 180 mg) was approved in 2000 and 2005 for SAR and chronic idiopathic urticaria (CIU) or hives (NDA 20-872). The suspension formulation was approved on October 16, 2006 for the treatment of SAR and CIU in pediatric patients 2 to less than 12 years of age, inclusive (ie  $\geq 2$  to  $<12$  years of age) at a dose of 30 mg twice daily [BID] and for the treatment of CIU in pediatric patients 6 months to less than 2 years of age, inclusive (ie,  $\geq 6$  months to  $<2$  years of age), at a dose of 15 mg BID.

Reference for the nonclinical information of this NDA is made to NDA 20625, NDA 20-872, and 21-963 which presented the efficacy and safety data for fexofenadine 30 and 60 mg twice daily (BID), and 180 mg once daily (QD) and oral suspension. The applicant did not conduct any new nonclinical studies for the current prescription-to-nonprescription partial switch applications. Fexofenadine suspension for pediatric patients younger than 6 years of age with CIU will not be switched from prescription-to-nonprescription status. The Sponsor will maintain NDA 21-963 for the prescription use of fexofenadine suspension for CIU in pediatric patients 6 months to less than 6 years of age.

The location of the nonclinical information submitted and reviewed during the approval of the fexofenadine hydrochloride (HCl) mono-product new drug applications can be found through the cross-references noted below.

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

Nonclinical information is also summarized in the current United States package insert (USPI) for the Allegra® mono-products (1).

**Table 1 - Location of nonclinical pharmacology, toxicology, and metabolism information previously submitted in related fexofenadine HCl new drug applications**

	NDA 20-625	NDA 20-872
	Fexofenadine HCl 60 mg capsule	Fexofenadine HCl 30, 60, and 180 mg tablet
<b>Submission date</b>	July 31, 1995	July 17, 1998
<b>Approval date</b>	July 25, 1996	February 27, 2000
<b>Overall summary</b>	S5-V1.15-P5	S5-V1.14-P6
<b>Pharmacology</b>	S5-V1.15-P9	S5-V1.14-P10
<b>Toxicology</b>	S5-V1.17-P1	S5-V1.14-P24
<b>Metabolism</b>	S5-V1.19-P1	S5-V1.14-P43
	NDA 20-625 annual update, 2002	
	NDA 20-625 annual update, 2002	

On initial overview of the NDA application: There are no outstanding pharmacology/toxicology issues identified at this time in the pharmacology/toxicology section.

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		This submission is a 505(b)(2) NDA application.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by			Not Applicable (N/A)

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
	the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			N/A
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			N/A
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			N/A
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m <sup>2</sup> or comparative serum/plasma levels) and in accordance with 201.57?			N/A
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			N/A
11	Has the applicant addressed any abuse potential issues in the submission?	X		
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?	X		This submission is a 505(b)(2) NDA.

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes**

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

*At present, no issues have been identified and need to be forwarded in the 74-day letter.*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201373	ORIG-1	SANOFI AVENTIS US LLC	FEXOFENADINE HCL

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/s/

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XINGUANG LI  
05/19/2010

PAUL C BROWN  
05/20/2010