

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-909

MEDICAL REVIEW

DIVISION DIRECTOR DECISIONAL REVIEW

Date: July 26, 2007

To: NDA 21-909

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy products, CDER, FDA

Product: Allegra (fexofenadine hydrochloride) ODT (orally disintegrating tablets)
30 mg

Applicant: sanofi-aventis

Administrative and Introduction

Sanofi-aventis submitted a 505(b)(1) new drug application (NDA 21-909) on September 28, 2006, (received on September 29, 2006, CDER stamp date) for use of Allegra (fexofenadine hydrochloride) ODT (orally disintegrating tablets) 30 mg for relief of symptoms associated with seasonal allergic rhinitis (SAR) and treatment of uncomplicated skin manifestations of chronic idiopathic urticaria (CIU) in patients 6 to 11 years of age. The PDUFA due date for this application is July 29, 2007. Sanofi-aventis submitted necessary data that support approval of this application. In subsequent sections of this document brief comments are made on findings that have direct bearing on the approvability decision of this application and labeling of this product. For details the reader is referred to Dr. Fadiran's cross-disciplinary summary review, and various primary and secondary discipline reviews.

Background and Regulatory History

Allegra was first approved for marketing in the United States as 60 mg oral capsules in 1996 (NDA 20-625). Subsequently Allegra has been approved for marketing as 30 mg, 60 mg, and 180 mg tablets (NDA 20-625, NDA 20-872), and as 30 mg/5 mL oral suspension (NDA 21-963) as single ingredient products, and as combination products (Allegra-D) with 120 mg or 240 mg pseudoephedrine. Fexofenadine is approved for marketing in various countries around the world. Allegra ODT is not approved in any country. The putative advantage of the ODT dosage form is that it disintegrates in the mouth immediately following administration and therefore it can be taken with or without water. The 30 mg dosage strength and the tablet dosage form limit its use to patients 6 to 11 years of age.

Chemistry, Manufacturing, and Controls

Allegra ODT tablets contain 30 mg fexofenadine hydrochloride and various compendial excipients. The drug substance is manufactured by Aventis Pharma in Frankfurt, Germany, and the drug product is manufactured by CIMA Labs Inc, in Minnesota, United

States. All DMFs associated with this application are acceptable. All manufacturing and testing facilities associated with this drug product have acceptable EER status. The CMC review team has found the submitted material adequate to support approval.

There was an issue with the use of the ODT terminology for this product because the size of this product crosses the 500 mg threshold and the disintegration time crossed the 30 second threshold expected of such a product. This issue was raised with sanofi-aventis at the End-of-Phase 2 meeting, Pre-NDA meeting, and during review of the NDA. During review of this application sanofi-aventis submitted data showing that using USP method the disintegration time for Allegra ODT was 29 second. The remaining item for the ODT terminology was size of the tablet. The Agency ultimately allowed the use of ODT terminology for this product because the size and disintegration time threshold was only proposed by the Agency only recently, and there are other recently approved ODT products that also missed the size threshold by margins similar to this product. The deliberation that led to this conclusion is detailed in CMC discipline primary review of Dr. M. Haber, and supervisory reviews of Dr. Ali Al-Hakim, and Dr. Fraser.

Nonclinical Pharmacology and Toxicology

Nonclinical pharmacology and toxicology assessment is primarily based on findings for other dosage forms of fexofenadine (NDA 20-625, NDA 20-872). No new non-clinical toxicology studies were required or performed for this application.

Clinical Pharmacology

Fexofenadine is an antihistamine with selective H1-receptor antagonist activity. The oral bioavailability of fexofenadine is decreased with high fat meal. High fat meal decreased AUC and Cmax by approximately 40% and 60%, respectively, for the ODT formulation. Therefore, this product is labeled to be taken on empty stomach. Water had no effect on bioavailability of Allegra ODT. Fexofenadine is not extensively metabolized by the liver. After oral dosing approximately 5% of the total dose was eliminated by hepatic metabolism. The major route of elimination is through urine and feces.

Fexofenadine has interaction with antacids, erythromycin, ketoconazole, and fruit juices. Aluminum and magnesium containing antacids decrease fexofenadine AUC by 41% and Cmax by 43%. Co-administration of fexofenadine with erythromycin or with ketoconazole increases fexofenadine AUC by 109% and 164%, respectively. Fruit juices, such as grapefruit, orange, and apple, reduce fexofenadine exposure. These interactions are possibly due to transported-related effects.

The QT/QTc effect of fexofenadine has been extensively studied in the past and it has been concluded that fexofenadine does not have an effect on QT/QTc.

Sanofi-aventis conducted three pivotal clinical pharmacology studies to support approval of the ODT product. These studies included a food effect study to characterize the

bioavailability of four prototype ODT fexofenadine formulations (study M016455H/1004), a bioequivalence study to compare the bioavailability of the ODT formulation to a marketed tablet formulation in fasted condition (study M016455H/1007), and a bioavailability study to assess the effect of dosing with and without water under fasted condition (study M016455H/1008). Study 1004 showed that food decreased the rate and extent of exposure of fexofenadine, which is expected for fexofenadine. Based on this study, sanofi-aventis carried one formulation further to the other two studies. Study 1007 showed that Allegra ODT is bioequivalent to Allegra Tablets (Table 1), and study 1008 showed that the bioavailability of Allegra ODT is not affected by water (Table 2).

Table 1. Mean PK parameters for fexofenadine, Study 1007

	Fexofenadine Tablets 30 mg single dose (n=52)	Fexofenadine ODT 30 mg single dose (n=52)	Ratio (90% CI)
AUC 0-inf, ng.hr.mL	637	635	98.9 (92.3, 106)
Cmax, ng/mL	93.8	888.0	93.2 (85.3, 102)
Tmax, hr	2.0	2.0	

Table 2. Mean PK parameters for fexofenadine, Study 1008

	Fexofenadine ODT 30 mg single dose With water (n=53)	Fexofenadine ODT 30 mg single dose Without water (n=53)	Ratio (90% CI)
AUC 0-inf, ng.hr.mL	628	699	112 (102, 122)
Cmax, ng/mL	86.3	96.5	113 (100, 127)
Tmax, hr	2.0	2.0	

Clinical and Statistical

No clinical studies were required or conducted to support this application. The entire program was based on clinical pharmacology studies as mentioned above. The general efficacy and safety findings from other dosage forms of fexofenadine are applicable to this product.

Data Quality, Integrity, and Financial Disclosure

DSI conducted an audit of the study center and the analytical site involved in the pivotal clinical pharmacology studies. The inspection did not reveal any significant deficiencies. During review of the submission no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with accepted clinical standards. The applicant submitted acceptable financial disclosure statements.

Pediatric Considerations

Sanofi-aventis requested deferral of pediatric studies for Allegra ODT for children 2 years to <6 years of age and a waiver for children below 2 years of age. This request is reasonable and will be granted. Allegra is already approved for SAR in patients 2 years of age and older, and for CIU in patients 6 months of age and older. The Division has previously concluded that the lower age bound for these indications are reasonable and appropriate. Allegra is also approved as an oral suspension, which is an appropriate dosage form for very young children. Therefore, conducting pediatric studies with the ODT formulation even below 6 years of age is not essential.

Labeling

Sanofi-aventis submitted a label in the Physician's Labeling Rule format that included new data generated with the ODT formulation and contained the existing information from the currently approved Allegra product label. Single ingredient fexofenadine has one unified label where all dosage forms are covered. The proposed label covers the Tablets, ODT, and Oral Suspension formulations, but not the Capsules. Sanofi-aventis made a business decision in 2002 not to manufacture and market Allegra Capsules in the United States, and in a letter dated July 26, 2007, submitted to NDA 20-625 sanofi-aventis confirmed it does not plan to market Allegra Capsule in the United States anymore, and will submit a request to have the capsule formulation listed as "discontinued" in the Orange book. This decision is based on commercial and marketing reasons and not due to safety reasons.

The proposed label was reviewed by various disciplines of this Division, and on consult by OSE. Various changes to different sections of the label were done to harmonize this label with other antihistamines as much as possible, and to accurately and truthfully communicate the findings to health care providers. The indications and usage section was changed to remove reference to specific symptoms. The Division and sanofi-aventis have agreed to the final version of the label.

Product Name

The proposed trade name Allegra ODT was acceptable to the Division and to OSE. The root name, Allegra, is already in use for fexofenadine containing products, and the ODT extension is appropriate for this dosage form.

Action

Sanofi-aventis has submitted adequate data to support approval of Allegra ODT 30 mg for relief of symptoms associated with SAR and treatment of uncomplicated skin manifestations of CIU in patients 6 to 11 years of age. The action on this application will be Approval.

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

/s/

Badrul Chowdhury
7/26/2007 01:57:34 PM
MEDICAL OFFICER

Appears This Way
On Original

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-909
Submission Code	N-000
Letter Date	9/28/06
Stamp Date	9/29/06
PDUFA Goal Date	7/29/07
Reviewer Name	Charles E. Lee, M.D.
Review Completion Date	5/11/07
Established Name	Fexofenadine HCl
(Proposed) Trade Name	Allegra (fexofenadine HCl) ODT (Orally Disintegrating Tablets), 30 mg
Therapeutic Class	H ₁ -receptor antagonist, antihistamine
Applicant	Sanofi-Aventis US, LLC
Priority Designation	S
Formulation	Oral disintegrating tablet
Dosing Regimen	1 tablet (30 mg) twice daily
Indication	Relief of symptoms associated with seasonal allergic rhinitis Treatment of uncomplicated skin manifestations of chronic idiopathic urticaria
Intended Population	Children, 6 to 11 years of age

Table of Contents

1 EXECUTIVE SUMMARY	5
1 EXECUTIVE SUMMARY	5
1.1 RECOMMENDATION ON REGULATORY ACTION	5
1.2 RECOMMENDATION ON POSTMARKETING ACTIONS	5
1.2.1 Risk Management Activity.....	5
1.2.2 Required Phase 4 Commitments	5
1.2.3 Other Phase 4 Requests	5
1.3 SUMMARY OF CLINICAL FINDINGS.....	5
1.3.1 Brief Overview of Clinical Program	5
1.3.2 Efficacy	6
1.3.3 Safety	6
1.3.4 Dosing Regimen and Administration	7
1.3.5 Drug-Drug Interactions	7
1.3.6 Special Populations	8
2 INTRODUCTION AND BACKGROUND.....	9
2.1 PRODUCT INFORMATION	9
2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS.....	9
2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES	10
2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS	10
2.5 PRESUBMISSION REGULATORY ACTIVITY	10
3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES.....	11
3.1 CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE)	11
3.2 ANIMAL PHARMACOLOGY/TOXICOLOGY	13
4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY	13
4.1 SOURCES OF CLINICAL DATA.....	13
4.2 TABLES OF CLINICAL STUDIES.....	14
4.3 REVIEW STRATEGY	15
4.4 DATA QUALITY AND INTEGRITY	15
4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES	16
4.6 FINANCIAL DISCLOSURES	16
5 CLINICAL PHARMACOLOGY.....	16
6 INTEGRATED REVIEW OF EFFICACY.....	19
6.1 INDICATION.....	20
7 INTEGRATED REVIEW OF SAFETY.....	21
7.1 METHODS AND FINDINGS.....	22
7.1.1 Deaths	22
7.1.2 Other Serious Adverse Events.....	22
7.1.3 Dropouts and Other Significant Adverse Events.....	22
7.1.5 Common Adverse Events.....	23
7.1.6 Less Common Adverse Events	25
7.1.7 Laboratory Findings.....	25
7.1.8 Vital Signs.....	26
7.1.9 Electrocardiograms (ECGs).....	27
7.1.13 Withdrawal Phenomena and/or Abuse Potential.....	28
7.1.14 Human Reproduction and Pregnancy Data	29

7.1.16	Overdose Experience	29
7.1.17	Postmarketing Experience.....	29
7.2	ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS	33
7.2.1	Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety	33
7.2.2	Description of Secondary Clinical Data Sources Used to Evaluate Safety	35
7.2.3	Adequacy of Overall Clinical Experience.....	36
7.2.9	Additional Submissions, Including Safety Update.....	36
7.3	SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS	36
8	ADDITIONAL CLINICAL ISSUES.....	37
8.1	DOSING REGIMEN AND ADMINISTRATION.....	37
8.2	DRUG-DRUG INTERACTIONS	38
8.3	SPECIAL POPULATIONS	38
8.4	PEDIATRICS	39
8.6	LITERATURE REVIEW	40
8.7	POSTMARKETING RISK MANAGEMENT PLAN.....	40
9	OVERALL ASSESSMENT	40
9.1	CONCLUSIONS.....	40
9.2	RECOMMENDATION ON REGULATORY ACTION	41
9.4	LABELING REVIEW.....	41

Appears This Way
On Original

Table of Tables

Table 1 Pivotal clinical pharmacology studies, NDA 21-909.....	14
Table 2 Mean PK parameters for fexofenadine, fasting and fed conditions, Study M016455H/1004	17
Table 3 Mean PK parameters for fexofenadine, Study M016455H/1007.....	18
Table 4 Mean PK parameters for fexofenadine, Study M016455H/1008.....	19
Table 5 Adverse events in the pooled pivotal clinical pharmacology studies in adult subjects (M016455I/1004, M016455I/1007, and M016455I/1008)	23
Table 6 Most frequently reported (10 or more) postmarketing spontaneous adverse events for fexofenadine HCl in patients less than 12 years of age, or 30 mg dose, or 60 mg total daily dose.....	30
Table 7 Most frequently reported (3 or more) postmarketing spontaneous adverse events for fexofenadine HCl in patients less than 6 years of age.....	31
Table 8 Most frequently reported (5 or more) postmarketing spontaneous adverse events for fexofenadine HCl in patients 6 to less than 12 years of age.....	32
Table 9 Most frequently reported postmarketing spontaneous adverse events for fexofenadine HCl in patients with age unspecified but taking a 30 mg dose or a 60 mg total daily dose.....	32
Table 10 Summary of pivotal clinical pharmacology studies providing safety information, NDA 21-909.	34
Table 11 Demographics in pivotal clinical pharmacology studies in adult subjects.....	34

Appears This Way
On Original

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends an "Approval" action. The application supports the efficacy and safety of Allegra ODT (Orally Disintegrating Tablets) for the treatment of symptoms of seasonal allergic rhinitis (SAR) and chronic idiopathic urticaria (CIU) in children 6 to less than 12 years of age.

The ODT nomenclature for the dosage form of this product has been under discussion during the review cycle. The disintegration time for the product meets the 30 second ONDQA specification, but the tablet exceeds the 500 mg size limit. These specifications were published on April 6, 2007, in the draft Guidance for Industry: Orally Disintegrating Tablets, approximately five months after this NDA was submitted. It is this reviewer's opinion that the proposed ODT nomenclature is acceptable, given that the ODT draft guidance was not available in public form prior to the filing of the application, that the FDA has approved ODTs in larger sizes than the proposed product, and because the applicant has provided information from the medical literature to support the safety of the product in this population. At the time of this review, ONDQA has not decided if the ODT nomenclature is acceptable.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There is no risk management plan or activity required for this application.

1.2.2 Required Phase 4 Commitments

There are no phase 4 commitments required for this application.

1.2.3 Other Phase 4 Requests

There are no phase 4 requests for this application.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

There are three pivotal studies in the applicant's drug development program for the proposed ODT formulation. These studies were designed to support the efficacy of the fexofenadine HCl ODT 30 mg tablet by assessing its relative bioavailability to the approved and currently marketed

30 mg Allegra Tablets. The pivotal studies are summarized below in Table 1, Pivotal Clinical Pharmacology Studies, NDA 21-909, Section 4.2 Tables of Clinical Studies.

The safety of the product was supported by safety information from pivotal adult clinical pharmacology studies M016455H/1004, M016455H/1007, and M016455H/1008. In addition, safety was supported by data from the applicant's safety database for postmarketing and spontaneous adverse event reports for fexofenadine HCl and a search of the medical literature for information relevant to fexofenadine HCl 30 mg and the safety of fexofenadine HCl in general.

1.3.2 Efficacy

This application supports the efficacy of Allegra ODT for the treatment of symptoms of SAR and CIU in children 6 to less than 12 years of age. This application relies on a comparison of the bioavailability and bioequivalence of the proposed new drug to that of an approved reference product, Allegra (fexofenadine HCl) Tablets, 30 mg. No clinical efficacy studies were required to support this application. The clinical pharmacology studies in this application confirmed that under fasting conditions, the proposed product is bioequivalent to the reference product for rate and extent of exposure. Ratios of the $AUC_{0-\infty}$ and C_{max} values for fexofenadine for the proposed and reference products fell within 80% to 125% limits. Administration of fexofenadine HCl ODT with food decreased both the extent and rate of absorption. Labeling appropriately notes the decrease in bioavailability of fexofenadine in the fed state. Absorption of the ODT formulation is comparable when taken with and without water and the product may be labeled accordingly.

1.3.3 Safety

The safety data in this application support the safety of the applicant's product. Safety data from the pivotal clinical pharmacology studies in adult subjects did not identify a safety signal. There were no deaths in the pivotal clinical pharmacology studies in adult subjects. Serious adverse events and dropouts due to adverse events in the pivotal clinical pharmacology studies in adult subjects did not reveal a safety signal. Headache and nausea were the most frequent adverse events in the pooled pivotal clinical pharmacology studies in adult subjects. Data from the pooled pivotal clinical pharmacology studies in adult subjects did not suggest an association of adverse events and gender or race. Subgroup analysis by age was not performed because all subjects were 18-45 years of age. Laboratory studies, vital signs, and ECGs in pooled pivotal clinical pharmacology studies in adult subjects showed no meaningful changes or differences between demographic subgroups and did not identify a safety signal.

Postmarketing adverse events in patients less than 12 years of age were consistent with those previously reported for fexofenadine HCl. There were fairly few postmarketing reports or serious adverse events in this age group. Given the extensive exposure to fexofenadine HCl, the postmarketing adverse events in patients less than 12 years of age did not raise concerns regarding a safety signal. No new safety concern or safety signal could be identified on the basis of reports of drug abuse or misuse of fexofenadine HCl, human reproduction and pregnancy data, or overdose. The applicant's search of the medical literature for safety information related to

fexofenadine HCl identified no deaths, serious adverse events, or new safety signal for adverse events and the safety update identified no safety signal.

1.3.4 Dosing Regimen and Administration

The application is for an ODT formulation of fexofenadine HCl. The application does not propose to change the current indications for Allegra. The current indications are relief of symptoms associated with SAR in adults and children 2 years of age and older and treatment of uncomplicated skin manifestations of CIU in adults and children 6 months of age and older. This application does not propose to change the currently approved dose of fexofenadine HCl. The dose of Allegra ODT for the treatment of symptoms of SAR and CIU in children 6 to 11 years of age is 30 mg twice daily. A dose of 30 mg once daily is recommended as the starting dose in pediatric patients with decreased renal function.

Co-administration of fexofenadine HCl with food results in a decreased rate of absorption and a decreased extent of absorption of fexofenadine. Food caused a 59% decrease in C_{max} value and 40% decrease in AUC_{0-inf} estimates for the ODT relative to its fasted state. Food also increased the mean $t_{1/2}$ value for the proposed formulation relative to that for the fasted state.

The 30 mg fexofenadine HCl ODT administered without water was bioequivalent to the tablet administered with water with respect to AUC_{0-inf} , but the upper limit of C_{max} was slightly outside of the bioequivalence bounds (90% CI: 100 to 127). The point estimates for AUC_{0-inf} and C_{max} were approximately 13% higher for the test treatment than for reference. The rate and extent of absorption of the proposed ODT formulation with and without water are comparable. The slight increases in AUC and C_{max} noted when the product is administered without water do not represent safety concerns because of the safety profile for this drug and its large therapeutic index.

Co-administration of fexofenadine with grapefruit, orange, and apple juices reduce the bioavailability of fexofenadine. The applicant's current and proposed labeling recommend that the products be taken with water. The current and proposed labeling appropriately address this interaction.

1.3.5 Drug-Drug Interactions

The bioavailability of fexofenadine is decreased if administered within 15 minutes of aluminum and magnesium-containing antacids. Administration of 120 mg of fexofenadine hydrochloride (2 x 60 mg capsule) within 15 minutes of an aluminum and magnesium containing antacid (Maalox) decreased fexofenadine AUC by 41% and C_{max} by 43%. The applicant's current labeling for Allegra Capsules, Tablets, Oral Suspension and the proposed labeling for Allegra ODT state that the products should not be taken closely in time with aluminum and magnesium containing antacids. The current and proposed labeling appropriately address this drug-drug interaction.

Co-administration of fexofenadine hydrochloride with either ketoconazole or erythromycin results in increased plasma concentrations of fexofenadine in healthy adult subjects.

Fexofenadine has no effect on the pharmacokinetics of either erythromycin or ketoconazole. No differences in adverse events or QTc interval were observed when subjects were administered fexofenadine hydrochloride alone or in combination with either erythromycin or ketoconazole. The changes in plasma levels were within the range of plasma levels achieved in adequate and well-controlled clinical trials. The current and proposed labeling appropriately address this drug-drug interaction.

1.3.6 Special Populations

In subjects with renal impairment, peak plasma levels of fexofenadine are greater and mean elimination half-lives are longer than observed in healthy volunteers. Based on increases in bioavailability and half-life, current labeling recommends a dose of 60 mg once daily in adults and children 12 years of age and older with decreased renal function and 30 mg once daily in children 6 to 11 years of age. Accordingly, the proposed dose of Allegra ODT in children 6 to 11 years of age with SAR or CIU and decreased renal function is of 30 mg once daily.

Appears This Way
On Original

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The applicant has developed an orally disintegrating tablet (ODT) formulation of fexofenadine HCl. Fexofenadine HCl is an antihistamine with H1-receptor antagonist activity. The ODT product is intended for use is for relief of symptoms associated with SAR and treatment of uncomplicated skin manifestations of CIU in children 6 to less than 12 years of age [labeling\proposed.pdf, page 6]. Currently fexofenadine HCl is approved in a 30 mg tablet formulation for the same indications and populations [labeling\current.pdf, page 13].

2.2 Currently Available Treatment for Indications

Antihistamines are the first-line drugs for the treatment of allergic rhinitis. Multiple antihistamines are available as Over-the-Counter (OTC) products, as specified by the OTC Monograph for Antihistamine Drug Products [21 CFR 341.72] and are approved as prescription drug products under NDAs and ANDAs. These products are available in capsule, tablet, suspension, and solution formulations and are indicated in children as young as 6 months of age. Other classes of medications are also available for the treatment of allergic rhinitis, including intranasal sodium cromolyn (an OTC product), intranasal ipratropium Br for the treatment of rhinorrhea associated with SAR, intranasal azelastine HCl for the treatment of SAR, and intranasal corticosteroids for the treatment of perennial allergic rhinitis (PAR) and SAR.

Various prescription antihistamines are also first-line drugs for the treatment of CIU. One OTC antihistamine, Claritin (loratadine), has been approved for the treatment of hives, which is the term used in the OTC setting for this condition. These prescription and OTC antihistamines are also available in capsule, tablet, suspension, and solution formulations, and are indicated in children as young as 6 months of age.

Fexofenadine HCl 60 mg twice daily and fexofenadine HCl 180 mg once daily were approved for marketing in the United States for the treatment of symptoms of SAR in adults and children 12 years of age and older as Allegra Capsules (NDA 20-625) on July 25, 1996 and as Allegra Tablets (NDA 20-872) on February 25, 2000, respectively. Fexofenadine HCl 30 mg twice daily was approved for marketing in the United States for treatment of symptoms of SAR and CIU in children 6 to 11 years of age as Allegra Tablets (NDA 20-872) on February 25, 2000. Fexofenadine HCl 60 mg twice daily was approved for marketing in the United States for the treatment of manifestations of CIU in adults and children 12 years of age and older as Allegra Capsules (NDA 20-625) on July 25, 1996 and as Allegra Tablets (NDA 20-872) on February 25, 2000, respectively. Fexofenadine HCl 180 mg once daily was approved in the United States for the CIU indication on October 13, 2005. Fexofenadine HCl suspension 30 mg/5 mL was approved for marketing in the United States for treatment of symptoms of SAR in children 2 to 11 years of age and CIU in children 6 months to 11 years of age as Allegra Oral Suspension (NDA 21-963) on October 16, 2006.

Fexofenadine HCl 30 mg tablets are approved in 74 countries other than the US, including countries in North, Central, and South America, the Caribbean, Asia, and Australia and New Zealand [clinstat\clinsum.pdf, pages 66-67].

Fexofenadine HCl ODT 30 mg is not approved in any country. Fexofenadine HCl 30 mg tablets are approved in 59 countries other than the US, including countries in North, Central, and South America, the Caribbean, Asia, and Australia and New Zealand [clinstat\clinsum.pdf, pages 81-83].

2.3 Availability of Proposed Active Ingredient in the United States

Allegra (fexofenadine HCl) is currently approved in the United States in capsule (NDA 20-625), tablet (NDA 20-872), and oral suspension formulations. The capsule formulation is not currently marketed. The products are approved for the following indications and in the following age groups:

- Allegra 180 mg po once daily and Allegra 60 mg po twice daily in seasonal allergic rhinitis (SAR) and chronic idiopathic urticaria (CIU) for adults and children 12 years of age and older
- Allegra 30 mg po twice daily in SAR and CIU for children 6 to 11 years of age
- Allegra 15 mg po twice daily in CIU for children 6 months to less than 2 years of age

Fexofenadine HCl is also approved in the United States as a generic drug in tablet formulations by various manufacturers (~~_____~~ ANDA 76-447, Teva Pharmaceutical Industries, and ANDA 77-081, Mylan Pharmaceuticals). b(4)

2.4 Important Issues With Pharmacologically Related Products

Fexofenadine is an antihistamine with H₁-receptor antagonist activity. It is a newer antihistamine that does not produce sedation, compared with currently available older antihistamines, many of which are available as OTC drug products.

Co-administration of fexofenadine HCl with food results in a decreased rate of absorption and decreased extent of absorption of fexofenadine. In addition, the bioavailability of fexofenadine is decreased if administered within 15 minutes of aluminum and magnesium-containing antacid. Grapefruit, orange, and apple juices reduce the bioavailability of fexofenadine when co-administered with these juices [labeling\approved.pdf, page 7].

2.5 Presubmission Regulatory Activity

An End-of-Phase 2 meeting was held between the Division and the applicant on January 10, 2003. Clinical comments were provided and the Division concurred with the applicant's proposed clinical pharmacology/bioequivalence approach to supporting the efficacy and safety of their product. The Division noted that the proposed tablet weighed ~~_____~~ and raised concerns b(4)

that it might represent a choking hazard in children less than 4 years of age [Meeting minutes and Medical Officer Review, IND 62,912, N-017 MR, 11/1/02].

Comments on the applicant's Pre-NDA meeting package were faxed to the applicant on March 7, 2005 and a teleconference was held with the applicant on March 8, 2005. The applicant was advised that their proposed NDA Table of Contents was not acceptable. They were advised to include a clinical data section and a safety update. As part of the clinical data section, in the Integrated Summary of Safety (ISS), the applicant was advised to include post-marketing adverse events for fexofenadine, covering the period of time since the approval of Allegra-D 24 Hour Tablets. Additionally, the applicant was advised to include a review of information from the published medical literature relevant to the safety of fexofenadine in the ISS. The review was to cover the period of time since the approval of Allegra-D 24 Hour Tablets. The applicant was also advised that the ISS should also address the safety of fexofenadine in subgroups, including children and the elderly, by gender, by race, and in patients with renal and hepatic impairment [Medical Officer Review, Charles E. Lee, M.D., IND 62,912, N-028 MP, 2/3/05; Teleconference Minutes, IMTS# 14569, IND 62,912, 3/8/05]. The applicant provided a revised Table of Contents in response to the Division's comments that was acceptable [Medical Officer Review, Charles E. Lee, M.D., IND 62,912, N-029 GC, 3/18/05].

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Fexofenadine HCl Orally Disintegrating Tablets (ODT), 30 mg were formulated to provide an immediate-release orally disintegrating tablet of a 30 mg dose of fexofenadine HCl. Film-coated tablets containing fexofenadine HCl are approved at the 30 mg dosage strength using twice daily dosing for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria in children 6 to 11 years of age (NDA 20-872, submitted July 17, 1998, approved February 25, 2000). The ODT formulation is to provide an alternative dosage form to the currently approved pediatric product/dosage strength.

~~_____~~ [summary\summary.pdf, page 36]. An aluminum foil/aluminum foil blister container closure system will be used for the commercial packaging of the drug product [summary\summary.pdf, page 49].

Drug substance is manufactured by Aventis Pharma, Frankfurt, Germany [summary\summary.pdf, page 40]. Drug product is manufactured by CIMA Labs Inc., Eden Prairie, Minnesota, United States [summary\summary.pdf, page 86].

The excipients in the proposed formulation include microcrystalline cellulose, sodium starch glycolate, povidone K-30, ~~_____~~, magnesium stearate, mannitol, crospovidone, sodium bicarbonate, citric acid anhydrous, aspartame, natural and artificial orange flavor, and artificial cream flavor [summary\summary.pdf, page 49].

The final drug product formulation was used in all pivotal clinical trials [summary\summary.pdf, page 49; CMC\product\3.2.p-drug product.pdf, page 36].

The Division raised concerns at the End-of-Phase 2 and Pre-NDA meetings about using the ODT nomenclature because of the product's size and disintegration time [IND 62,912, End-of-Phase 2 Meeting Minutes, 1/10/03; Pre-NDA Meeting Minutes, 3/8/05]. At the Pre-NDA meeting, the Division noted that the Agency's current thinking was that an ODT should be less than 500 mg in weight and should disintegrate within 30 seconds. The applicant acknowledged the Agency's opinion, but noted that reformulation would not be feasible. The Division stated that the ODT nomenclature and standards were currently under discussion in the Agency, and that decisions would be made on a case-by-case basis for products that had already been submitted or were close to being submitted to the Agency. The Division could not definitively say that the product was not an ODT and stated these concerns would be a review issue that would be answered at the end of the NDA review cycle [Pre-NDA Meeting Minutes, 3/8/05].

In the NDA filing communication, the applicant was advised that the product did not meet the requirements of an ODT [NDA 21-909, Filing Communication, 12/12/06]. A teleconference was held with the applicant on January 23, 2007 regarding the ODT nomenclature for the dosage form. The applicant pointed out that FDA had approved other ODTs with weights greater than 500 mg, with one approval occurring in the last year. In addition, they pointed out that when the USP method is used, disintegration times were approximately 29 seconds.

The CMC review for this NDA indications that the tablet weight and disintegration time are acceptable [ONDQA Review, M. Haber, Ph.D., NDA 21-909, N-000, 9/28/06], but at the time of the review, ONDQA has not decided if the ODT nomenclature is acceptable.

The applicant provided information from the medical literature from two articles to support the safety of chewable and ODT dosage forms in children [NDA 21-909, N-000 BC, 2/8/07]. The first article was a literature review of articles addressing foreign-body injuries related to chewable tablet formulations. The article identified 68 different chewable tablet formulations that are approved for children in the United States. In the larger case series included in this review, from National Electronic Injury Surveillance System, a part of the Consumer Product Safety Commission, there were 1130 foreign injury cases in children noted with 41 deaths due to aspiration. Only 12% of these deaths were due to "medications such as pills." In another case series this review, there was only one medicine tablet among 234 tracheobronchial foreign bodies removed from patients younger than 16 years of age.¹ Another article investigated how children 3 to 5 years of age handle a placebo lozenge in the oral cavity when they were instructed on how to use it. In this study of 65 children, approximately 60% of the children could keep parts of the lozenge in the mouth for at least 10 minutes. Approximately 80% could keep parts of the lozenge in the mouth for at least 5 minutes.² The applicant noted that the tablets in this article, 400 mg and 800 mg, were similar in size to their proposed ODT.

¹ Michele TM, et. al. J. Asthma, 39(5):391-403, 2002.

² Leksell E and Mejare M. Swed Dent J, 18(4):149-153, 1994.

Reviewer comment:

The draft Guidance for Industry: Orally Disintegrating Tablets was published in public form on April 6, 2007, approximately five months after this NDA was submitted. As the applicant has pointed out, the Agency has approved several ODTs greater than 500 mg in weight, including one in the last year.

The applicant has provided clinical data from the literature that suggest that use of chewable or ODT tablets do not represent a serious safety concern in children 6 to less than 12 years of age. This reviewer does not believe that the proposed ODT formulation represents a serious safety concern for this population.

It is this reviewer's opinion that the proposed ODT nomenclature is acceptable, given that the ODT draft guidance was not available in public form prior to the filing of the application, that the FDA has approved ODTs in larger sizes than the proposed product, and because the applicant has provided information from the medical literature to support the safety of the product in this population.

A detailed review of the CMC portion of the application may be found in Dr. Martin Haber's ONDQA review [ONDQA Review, M. Haber, Ph.D., NDA 21-909, N-000, 9/28/06].

3.2 Animal Pharmacology/Toxicology

Fexofenadine HCl has been reviewed and found to be safe and efficacious at doses up to 180 mg and is supported by data in NDA 20-625 and NDA 20-872. No new non-clinical toxicology studies were required or performed for this application.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

There are three pivotal studies in the applicant's drug development program for the proposed ODT formulation. These studies were designed to support the efficacy of fexofenadine HCl ODT 30 mg tablet by assessing their relative bioavailability to the approved and currently marketed 30 mg Allegra Tablets. The pivotal studies are summarized below in Table 1, Section 4.2 Tables of Clinical Studies.

The safety of the product was supported by safety information from adult clinical pharmacology pivotal studies M016455H/1004, M016455H/1007, and M016455H/1008. In addition, safety was supported by data from the applicant's safety database for postmarketing and spontaneous adverse event reports for fexofenadine HCl and a search of the medical literature for information relevant to fexofenadine HCl 30 mg and the safety of fexofenadine HCl in general.

Clinical Review
 Charles E. Lee, M.D.
 NDA 21-909, N-000, 9/28/06
 Allegra (fexofenadine HCl) Orally Disintegrating Tablets

4.2 Tables of Clinical Studies

The three pivotal clinical pharmacology studies in this application are summarized below in Table 1.

Table 1 Pivotal clinical pharmacology studies, NDA 21-909 [clinstat/clinsum.pdf, pages 27-29].

Study Number	Study Type	Treatment Groups	Treatment duration	Design	Number of subjects	Diagnosis, age of subjects	Materials submitted in this application
M106455H/1004	Pivotal food effect study	Marketed F 30 mg tablet, single dose, fasted conditions Proposed F 30 mg ODT, single dose, fasted and fed conditions Other prototype 30 mg ODTs, single dose, fasted and fed conditions, some without water	Single dose	Single center, randomized, open label, eight treatment, four-period, incomplete crossover	54	Healthy men and women, 18-45 years	Protocol Study report Tabulations No case report forms necessary
M106455H/1007	Pivotal bioequivalence study	Marketed F 30 mg tablet, single dose, fasted conditions Proposed F 30 mg ODT, single dose, fasted and fed conditions	Single dose	Single center, randomized, open label, two period, two-way crossover	54	Healthy men and women, 18-45 years	Protocol Study report Tabulations Case report form
M106455H/1008	Pivotal bioavailability study	Proposed F 30 mg ODT, single dose, fasted conditions with water Proposed F 30 mg ODT, single dose, fasted conditions without water	Single dose	Single center, randomized, open label, two period, two-way crossover	54	Healthy men and women, 18-45 years	Protocol Study report Tabulations Case report form

F = fexofenadine HCl

Appears This Way
 On Original

4.3 Review Strategy

The pharmacokinetics results of the three pivotal clinical pharmacology studies in this application were briefly reviewed and summarized in Section 5 Clinical Pharmacology. This review includes an abbreviated Section 6 Integrated Review of Efficacy because the drug development program was based on clinical pharmacology studies and because there were no new clinical studies required to support this application.

Safety data supporting this application was reviewed in depth and is presented in Section 7 Integrated Review of Safety. The applicant's Integrated Summary of Safety consisted of a summary of safety information from adult clinical pharmacology pivotal studies M016455H/1004, and M016455H/1007, and M016455H/1008. The safety information from these studies included adverse event data, laboratory data, vital signs data, and ECG data. In addition, the applicant searched their ClinTrace safety database for postmarketing and spontaneous adverse event reports for fexofenadine HCl and a search of the medical literature for information relevant to fexofenadine HCl 30 mg and the safety of fexofenadine HCl in general. Review of these data are also presented in presented in Section 7 Integrated Review of Safety.

4.4 Data Quality and Integrity

DSI clinical audit was not requested because no efficacy or safety studies were included in the development program for this drug product.

There was one study center and analytical site in the United States for the three pivotal clinical pharmacology studies in this application, Studies M016455H/1004, M016455H/1007, and M016455H/1008. DSI audit of the center performing the studies was requested. Study M016455H/1007 was audited. This was a pivotal single-dose bioequivalence study performed in adults under fasting and conditions.

The principal investigator was:

Dennis N. Morrison, D.O.
Bio-Kinetic Clinical Applications
1816 West Mount Vernon
Springfield, MO 65802
Telephone: (417) 831-0456
Fax: (417) 831-0778
[hpbio\hupharm\1007.pdf, pages 1, 246]

The analytical site was:

b(4)

[hpbio\hupharm\1007.pdf, page 174]

DSI audit did not reveal any significant deficiencies at the clinical and analytical sites [DSI Review, J. Parepally, Ph.D., NDA 21-909, N-000, 9/28/06].

4.5 Compliance with Good Clinical Practices

The three pivotal clinical pharmacology studies in this application were conducted in accordance with Good Clinical Practice [hpbio\hupharm\1004.pdf, pages 1, 17; hpbio\hupharm\1007.pdf, pages 1, 20; hpbio\hupharm\1008.pdf, pages 1, 19]. The applicant certified that they did not use and would not use in any capacity the services of any person debarred under to Section 306(a) and 306(b) of the Federal Food, Drug, and Cosmetic Act in connection with their application [other\debar.pdf, page 1].

4.6 Financial Disclosures

The applicant certified that there was no financial arrangement with the clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study. The applicant stated that the clinical investigators in the pivotal studies in this application certified that they did not have a proprietary interest in the proposed product or a significant equity in the applicant. The clinical investigators also certified that they were not a recipient of significant payments [other\financial.pdf, pages 1-2].

5 CLINICAL PHARMACOLOGY

There were three pivotal bioavailability and bioequivalence studies in this application, Study M016455H/1004, Study M016455H/1007, and Study M016455H/1008. They are described briefly below. A detailed review of the results may be found in Dr. Sayed Al Habet's clinical pharmacology and biopharmaceutics review [Clinical Pharmacology and Biopharmaceutics Review, S. Al Habet, Ph.D., NDA 21-909, N-000, 9/28/06].

Study M016455H/1004 was a pivotal bioavailability and food effect study designed to characterize the bioavailability of four prototype ODT formulations of fexofenadine HCl 30 mg under fed and fasted conditions. This study identified the one ODT formulation to be further developed and provided information on the effect of food on its bioavailability. It was an open-label, randomized, single-dose, four-period, eight-treatment, partially balanced, incomplete crossover study conducted in 35 healthy male and female adult subjects between 18 and 45 years of age [clinstat\clinsum.pdf, page 18; hpbio\hupharm\1004.pdf, pages 001-005, 027]. Study treatments included the marketed 30 mg fexofenadine HCl tablet administered under fasted conditions, two prototype oral disintegrating tablet formulations (I and II) of fexofenadine HCl 30 mg administered under fasted and fed conditions, two additional prototype oral disintegrating tablet formulations of fexofenadine HCl 30 mg (IV and V) administered under fasted conditions, and a prototype oral disintegrating tablet formulations (I) of fexofenadine HCl 30 mg administered under fasted conditions and without water [hpbio\hupharm\1004.pdf, pages 3-4]. Samples were taken immediately before dosing (0 hours) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36, and 48 hours during each study period for plasma fexofenadine levels. Subjects were confined at the study site from check-in on Day -1 until Day 3 [hpbio\hupharm\1004.pdf, page

22]. Safety endpoints included adverse events, vital signs, physical examinations, clinical laboratory studies, and ECGs [hpbio\hupharm\1004.pdf, page 4]. There was one patient who withdrew from the study for personal reasons. There were no withdrawals from the study due to adverse events and there were no serious adverse events [hpbio\hupharm\1004.pdf, page 51]. Results for the selected prototype formulation (II) are summarized below in Table 2.

Table 2 Mean PK parameters for fexofenadine, fasting and fed conditions, Study M016455H/1004
 [hpbio\hupharm\1003.pdf, pages 45-46, 60]

PK Parameter	Treatment A	Treatment D	Treatment E	Pair	Ratio, % (90% CI)	
	Fexofenadine HCl tablet 30 mg Single dose Reference Fasting State	Fexofenadine HCl ODT 30 mg Single dose Prototype II Fasted State	Fexofenadine HCl ODT 30 mg Single dose Prototype II Fed State			
AUC _{0-inf} , ng.hr/mL (n)	672 (33)	655 (17)	391 (16)	D/A	102	(90.9, 115.7)
				E/D	60.4	(53.0, 68.7)
C _{max} , ng/mL (n)	101 (35)	96.6 (17)	38.1 (17)	D/A	100	(84.6, 118.2)
				E/D	50.0	(34.2, 49.0)
T _{max} , h (n)	2.1 (35)	2.0 (17)	3.7 (17)	--	--	--
t _{1/2} (n)	14.2 (32)	17.1 (17)	17.6 (16)	--	--	--

Formulation II appeared to demonstrated adequate bioavailability based on AUC_{0-inf} and C_{max} ratios relative to the marketed reference (lactose free tablet) and in compliance with the bioequivalence criteria of 80 – 125%. Food caused a 59% decrease in C_{max} value and 40% decrease in AUC_{0-inf} estimates for the proposed formulations (II) relative to its fasted state [hpbio\hupharm\1004.pdf, page 51]. Food also increased the mean t_{1/2} value for the proposed formulation relative to that for the fasted state. Other prototypes did not meet bioequivalence criteria.

Reviewer comment:

Formulation II was appropriately chosen as the formulation to be developed.

Study M016455H/1007 was a pivotal bioequivalence study designed to compare the bioavailability of the proposed ODT formulation to the marketed 30 mg fexofenadine tablet under fasted conditions with 240 mL of water. It was an open label, randomized, single dose, two-period, two-way crossover study conducted in were 54 healthy adult male and female subjects, 18 to 45 years of age, enrolled in the study. Study treatments included the marketed 30 mg fexofenadine HCl tablet and the selected prototype oral disintegrating tablet formulation (II) of fexofenadine HCl 30 mg administered under fasted conditions [clinstat\clinsum.pdf, pages 18-19; hpbio\hupharm\1007.pdf, page 3]. Serial blood samples were collected over a 48-hour period after each treatment. There was a six-day washout between study periods. Samples were taken at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36, and 48 hours post-dose [hpbio\hupharm\1007.pdf, page 4]. Subjects were housed at the study site from check-in on Day -1 until Day 3 [hpbio\hupharm\1007.pdf, pages 31-32]. Safety endpoints included adverse

events, vital signs, physical examinations, laboratory studies, and ECGs [hpbio\hupharm\1007.pdf, page 3]. There was one subject who withdrew from the study because of personal reasons. One person experienced a headache withdrew from the study because of this adverse event. There were no serious adverse events [hpbio\hupharm\1007.pdf, pages 4, 54, 58]. The applicant concluded that the fexofenadine HCl 30 mg ODT formulation was bioequivalent to the marketed 30 mg tablet in healthy adult subjects under fasted conditions. Results for the selected prototype formulation (II) are summarized below in Table 3.

Table 3 Mean PK parameters for fexofenadine, Study M016455H/1007 [hpbio\hupharm\1007.pdf, pages 52, 71-72]

PK Parameter	Fexofenadine HCl tablet 30 mg Single dose Treatment A N = 52	Fexofenadine HCl ODT 30 mg Single dose Treatment B N = 52	Ratio, % (90% CI) B/A
AUC _{0-inf} , ng.hr/mL	637	635	98.9 (92.3, 106)
C _{max} , ng/mL	93.8	888.0	93.2 (85.3, 102)
T _{max} , h	2.0	2.0	--
t _{1/2}	11.6	11.8	--

The proposed ODT formulation was bioequivalent to Allegra Tablets, 30 mg. The 90% confidence intervals for ratios for C_{max} and AUC_{0-inf} were within the bioequivalence criteria of 80-125%.

Reviewer comment:

The two formulations studied were bioequivalent.

Study M016455H/1008, a pivotal bioavailability study designed to compare the pharmacokinetics of the proposed ODT formulation administered under fasted conditions, both with and without water. It was a phase 1, open label, randomized, single-dose, two-period, two treatment, complete crossover study conducted in 54 healthy male and female patients, 18-45 years of age. Study treatments included the proposed oral disintegrating tablet formulation of fexofenadine HCl 30 mg administered under fasted conditions with 240 mL of water and the proposed oral disintegrating tablet formulation of fexofenadine HCl 30 mg administered under fasted conditions without water. Serial blood samples were collected over a 48-hour period after each treatment. There was a six-day washout between study periods [clinstat\clinsum.pdf, page 19; hpbio\hupharm\1008.pdf, pages 2-4]. Samples were taken at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36, and 48 hours post-dose [hpbio\hupharm\1008.pdf, page 3]. Subjects were housed at the study site from check-in on Day -1 until Day 3 [hpbio\hupharm\1008.pdf, pages 30-31]. Safety endpoints included adverse events, vital signs, physical examinations, laboratory studies, and ECGs [hpbio\hupharm\1008.pdf, page 3]. There were two subjects that discontinued the study prematurely due to adverse events. There was one serious adverse event, a subject that experienced a thermal burn and respiratory fume inhalation disorder [hpbio\hupharm\1008.pdf, page 5]. The applicant concluded that the 30 mg fexofenadine orally disintegrating tablet administered without water was bioequivalent to the tablet administered with water with respect to AUC_{0-inf}, but the upper limit of C_{max} was slightly outside of the bioequivalence bounds (90%

CI: 100 to 127) [hpbio\hupharm\1008.pdf, page 58]. Results of Study M016455H/1008 are summarized below in Table 4.

Table 4 Mean PK parameters for fexofenadine, Study M016455H/1008 [hpbio\hupharm\1008.pdf, pages 51, 72]

PK Parameter	Fexofenadine HCl ODT 30 mg Single dose With water Reference Treatment A N = 53	Fexofenadine HCl ODT 30 mg Single dose Without water Test Treatment B N = 53	Ratio, % (90% CI) B/A
AUC _{0-inf} , ng.hr/mL	628	699	112 (102, 122)
C _{max} , ng/mL	86.3	96.5	113 (100-127)
T _{max} , h	2.0	2.0	--
t _{1/2}	12.8	12.0	--

Reviewer comment:

The upper 90% confidence interval for the ratio for C_{max} fell slightly outside bioequivalence limits and the point estimate AUC_{0-inf} and C_{max} were approximately 13% higher for the test treatment than for reference. The rate and extent of absorption of the proposed ODT formulation with and without water are comparable. The slight increases in AUC and C_{max} noted when the product is administered without water do not represent safety concerns because of the safety profile for this drug and its large therapeutic index.

In summary, these results support the efficacy of fexofenadine HCl ODT, 30 mg in the treatment of symptoms of SAR and CIU in children 2 to less than 11 years of age. The ODT was bioequivalent to the reference drug product, the currently marketed 30 mg Allegra Tablets. Administration of fexofenadine HCl suspension with food decreased both the extent and rate of absorption of the ODT. Labeling appropriately notes this significant decrease in bioavailability of fexofenadine in the fed state. Absorption of the ODT formulation is comparable when taken with and without water and the product may be labeled accordingly.

6 INTEGRATED REVIEW OF EFFICACY

This application is supported by comparison of the bioavailability and bioequivalence of the proposed new drug to that of an approved reference product. The reference product for the clinical pharmacology studies in this application was the Sanofi Aventis product, Allegra (fexofenadine HCl) Tablets, 30 mg. No clinical efficacy studies were required to support this application.

The clinical pharmacology studies in this application support the efficacy of the applicant's product. The clinical pharmacology studies in this application confirmed that under fasting conditions, the proposed product is bioequivalent to the reference product for rate and extent of exposure. Ratios of the AUC_{0-inf} and C_{max} values for fexofenadine for the proposed and reference products fell within 80% to 125% limits. Administration of fexofenadine HCl ODT with food decreased both the extent and rate of absorption. Labeling appropriately notes this significant

decrease in bioavailability of fexofenadine in the fed state. Absorption of the ODT formulation is comparable when taken with and without water and the product may be labeled accordingly.

A summary of the clinical pharmacology data supporting this application is found in Section 5 of this review, and additional detail may be found in Dr. Sayed Al Habet's clinical pharmacology review [Clinical Pharmacology and Biopharmaceutics Review, S. Al Habet, Ph.D., NDA 21-909, N-000, 9/28/06].

6.1 Indication

There are no proposed changes to the current indication for Allegra. The current indication for Allegra is as follows:

Seasonal Allergic Rhinitis

ALLEGRA tablets are indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 6 years of age and older.

ALLEGRA Pediatric Suspension is indicated for the relief of symptoms associated with seasonal allergic rhinitis in children 2 to 11 years of age.

Symptoms treated effectively were sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes.

Chronic Idiopathic Urticaria

ALLEGRA tablets are indicated for treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 years of age and older.

ALLEGRA Pediatric Suspension is indicated for treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in children 6 months to 11 years of age.

Fexofenadine hydrochloride significantly reduces pruritus and the number of wheals.

In January 2006, the Agency published a final rule ("Physician's Labeling Rule" or "PLR") that amended the requirements for the content and format of labeling for human prescription and biological products. The revision of labeling to meet these requirements allows an opportunity to update labeling claims. The Division considers the following statements _____

_____ and _____ to be inappropriate for the INDICATIONS section of the labeling. The Division is requiring sponsors of other products of the same class for the same or similar indications to remove these claims from their labeling. The Division considers information addressing the effect of a drug on individual symptoms of allergic rhinitis and chronic idiopathic urticaria to be appropriate for the CLINICAL STUDIES section of the label. The applicant will be asked to delete these statements from INDICATIONS.

b(4)

7 INTEGRATED REVIEW OF SAFETY

The applicant's Integrated Summary of Safety consisted of a summary of safety information from adult clinical pharmacology pivotal studies M016455H/1004, M016455H/1007, and M016455H/1008. The safety information from these studies included adverse event data, laboratory data, vital signs data, and ECG data.

The applicant searched their ClinTrace safety database for postmarketing and spontaneous adverse event reports for fexofenadine HCl. The database includes cases from clinical trials, postmarketing surveillance studies, spontaneous notifications, cases from regulatory authorities, and the published literature [clinstat\iss\iss.pdf, page 62]. The search was designed to capture all cases received through June 15, 2006 where the age was reported to be less than 12 years. The applicant also provided analyses of postmarketing non-serious and serious adverse events for patients less than 6 years of age, patients 6 to less than 12 years of age, patients with age unspecified but taking 30 mg dose or 60 mg total daily dose. The applicant submitted analyses of postmarketing non-serious and serious adverse events for fexofenadine HCl in patients less than 12 years of age or who were taking a 30 mg dose or 60 mg total daily dose.

The applicant performed a search of the medical literature for information relevant to fexofenadine HCl 30 mg and the safety of fexofenadine HCl in general. The search covered the period of time since the approval of NDA 21-704, Allegra-D 24 Hour Tablets. The dates covered were from October 2003 until December 31, 2005. The search was conducted with the Medline, Embase, and Dialog Datastar databases using the keywords "fexofenadine," "Allegra," and "Telfast."

There were no deaths in the pivotal clinical pharmacology studies in adult subjects. One subject experienced a serious adverse event in the pivotal clinical pharmacology studies in adult subjects. This subject experienced a thermal burn and respiratory fume inhalation disorder as a result of a house fire on Day 4 of the study. These data did not identify a safety signal. Dropouts due to adverse events in the pivotal clinical pharmacology studies in adult subjects did not reveal a safety signal. Headache and nausea were the most frequent adverse events in the pooled pivotal clinical pharmacology studies in adult subjects. Data from pooled pivotal clinical pharmacology studies in adult subjects did not suggest an association of adverse events and gender or race. Subgroup analysis for age was not performed because all subjects were 18-45 years of age. Laboratory studies, vital signs, and ECGs in pooled pivotal clinical pharmacology studies in adult subjects showed no meaningful changes or differences between demographic subgroups and did not identify a safety signal.

Postmarketing adverse events in patients less than 12 years of age were consistent with those previously reported for fexofenadine HCl. There were fairly few postmarketing reports or serious adverse events in this age group. Given the extensive exposure to fexofenadine HCl, postmarketing adverse events in patients less than 12 years of age did not raise concerns regarding a safety signal. No new safety concern or safety signal could be identified on the basis of reports of drug abuse or misuse of fexofenadine HCl, human reproduction and pregnancy data, or overdose.

The applicant's search of the medical literature for safety information related to fexofenadine HCl identified no deaths, serious adverse events, or new safety signal for adverse events and the safety update identified no safety signal.

A detailed review of the applicant's Integrated Summary of Safety follows below.

7.1 Methods and Findings

7.1.1 Deaths

There were no deaths in the pivotal clinical pharmacology studies in adult subjects [clinstat\iss\iss.pdf, page 55]. There was one death identified by the applicant's search of their postmarketing adverse events database, a one-day old male infant with pulmonary artery stenosis, hypospadias, fetal growth retardation, and a single umbilical artery. The infant's mother had been treated with fexofenadine and loratadine for allergic rhinitis from day 10 to day 23 of her pregnancy [clinstat\iss\iss.pdf, page 81; clinstat\iss\isscioms.pdf, pages 15-18]. The applicant's search of the medical literature for safety information related to fexofenadine HCl identified no deaths [clinstat\other\literature_table.pdf, pages 1-43]. The applicant's safety update identified no deaths [NDA 21-909, N-000 SU, 1/27/07, update\update.pdf, page 11].

Reviewer comment:

These data do not identify a safety signal.

7.1.2 Other Serious Adverse Events

One subject experienced a serious adverse event in the pivotal clinical pharmacology studies in adult subjects (M016455H/1004, M016455H/1007, and M016455H/1008). Subject 0001/1024, a 42-year old white male in M016455H/1008 experienced a thermal burn and respiratory fume inhalation disorder as a result of a house fire on Day 4 of the study. The event required hospitalization and was considered not to be related to study medication [clinstat\iss\iss.pdf, page 57]. The applicant's search of the medical literature for safety information related to fexofenadine HCl identified no serious adverse events [clinstat\other\literature_table.pdf, pages 1-43]. The applicant's safety update identified no serious adverse events [NDA 21-909, N-000 SU, 1/27/07, update\update.pdf, page 8].

Reviewer comment:

These data do not identify a safety signal.

7.1.3 Dropouts and Other Significant Adverse Events

There were three dropouts from the pivotal clinical pharmacology studies in adult subjects due to adverse events. All three patients were receiving fexofenadine 30 mg as study treatment. In study M016455H/1007, subject 0001/1045 discontinued due to headache. In study M016455H/1008, subject 0001/1024, discontinued because of a thermal burn and respiratory fume inhalation

disorder as a result of a house fire. In study M016455H/1008, subject 0001/1028, discontinued because of a headache [clinstat\iss\iss.pdf, page 55].

The applicant's search of the medical literature for safety information related to fexofenadine HCl identified no other significant adverse events [clinstat\other\literature_table.pdf, pages 1-43]. The applicant's safety update identified no other significant adverse events [NDA 21-909, N-000 SU, 1/27/07, update\update.pdf, page 8].

Reviewer comment:

These data do not identify a safety signal.

7.1.5 Common Adverse Events

Common adverse events are discussed in the following section.

7.1.5.1 Eliciting adverse events data in the development program

Subjects were continuously monitored for general well-being and adverse events in the pivotal clinical pharmacology studies conducted in adult subjects. Subjects were instructed to report any adverse events that occurred [hpbio\hupharm\1004.pdf, page 27; hpbio\hupharm\1007.pdf, page 33; hpbio\hupharm\1008.pdf, page 32].

Adverse events for the pivotal clinical pharmacology studies were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 5.0 (M016455H/1004) and Version 7.1 (M016455H/1007 and M016455H/1008), but were reported in MedDRA Version 9.0 in the applicant's ISS [clinstat\iss\iss.pdf, page 44].

7.1.5.3 Incidence of common adverse events

Adverse events in the pooled pivotal clinical pharmacology studies in adult subjects are summarized in Table 5. Headache was the most frequent adverse event in these studies. Headache, nausea, and upper respiratory tract infection were the only adverse events that occurred in more than one subject [clinstat\iss\iss.pdf, page 45].

Table 5 Adverse events in the pooled pivotal clinical pharmacology studies in adult subjects (M016455I/1004, M016455I/1007, and M016455I/1008) [clinstat\iss\iss.pdf, page 45].

Adverse event	Fexofenadine HCl 30 mg N = 139	
All subjects with adverse events	23	(16.6)
Headache	9	(6.5)
Nausea	4	(2.9)
Upper respiratory tract infection	2	(1.4)
Back pain	1	(0.7)
Cough	1	(0.7)
Diarrhea	1	(0.7)
Dry mouth	1	(0.7)
Dysgeusia	1	(0.7)
Dysmenorrhea	1	(0.7)
Fatigue	1	(0.7)
Gastroesophageal reflux disease	1	(0.7)

Clinical Review
Charles E. Lee, M.D.
NDA 21-909, N-000, 9/28/06
Allegra (fexofenadine HCl) Orally Disintegrating Tablets

Adverse event	Fexofenadine HCl 30 mg N = 139	
Hot flush	1	(0.7)
Malaise	1	(0.7)
Nasopharyngitis	1	(0.7)
Respiratory fume inhalation disorder	1	(0.7)
Thermal burn	1	(0.7)
Vision blurred	1	(0.7)

The applicant's search of the medical literature for safety information related to fexofenadine HCl identified no safety signal for adverse events [clinstat\other\literature_table.pdf, pages 1-43]. The applicant's safety update identified no safety signal for adverse events [NDA 21-909, N-000 SU, 1/27/07, update\update.pdf, page 8].

Reviewer comment:

Adverse event data do not identify a safety signal.

7.1.5.3.1 Incidence of adverse events in subgroups—Gender

In the pooled pivotal clinical pharmacology studies in adult subjects, there was a higher proportion of females (20.3%, 15/74) that reported adverse events than males (12.3%, 8/65). The most commonly reported adverse event reported by patients of both genders was headache, which was reported by 6.8% (5/74) of female subjects and by 6.2% (4/65) of male subjects. Nausea was reported by 5.4% (4/74) of female subjects and by no male subjects. The remaining adverse events were reported by one subject each in either gender subgroup [clinstat\iss\iss.pdf, page 50].

Reviewer comments:

The safety data for the pivotal clinical pharmacology studies in adults do not suggest an association of adverse events and gender.

7.1.5.3.2 Incidence of adverse events in subgroups—Race

The majority of subjects in clinical pharmacology studies in adult subjects were white (87.1%, 121/139). It was not possible for the applicant to draw meaningful conclusion regarding the distribution of adverse events by race [clinstat\iss\iss.pdf, page 51].

Reviewer comments:

It is not possible to draw conclusions on the association of adverse events with race in the pivotal clinical pharmacology studies in adults because of the small number of non-white subjects.

7.1.5.3.2 Incidence of adverse events in subgroups—Age

No subgroup analyses based on age were performed in the pivotal clinical pharmacology studies in adult subjects because all subjects were 18 to 45 years of age [clinstat\iss\iss.pdf, page 53].

Reviewer comments:

It is not possible to draw conclusions on the association of adverse events and age.

7.1.5.4 Common adverse event tables

The contents of the ADVERSE REACTIONS section of the proposed label are the same as in the recently approved label for Allegra Oral Suspension (NDA 21-963, N-000, 12/15/05). The applicant has proposed no changes to the adverse event tables in the label. Adverse events in the pooled pivotal clinical pharmacology studies in adult subjects are not included in proposed labeling for the product [clinstat\iss\iss.pdf, page 11].

7.1.5.5 Identifying common and drug-related adverse events

The applicant states that fexofenadine HCl was well tolerated in pivotal clinical pharmacology studies M016455H/1004, M016455H/1007, and M016455H/1008 in adult subjects. The overall frequencies of adverse events were low; the most commonly reported adverse event was headache, which is consistent with the known safety profile of fexofenadine HCl. The applicant drew no other conclusions on causality of adverse events [clinstat\iss\iss.pdf, page 60].

Reviewer comment:

These data do not suggest a safety signal attributable to fexofenadine HCl.

7.1.6 Less Common Adverse Events

All adverse events occurring in the pivotal clinical pharmacology studies in adults are reviewed in Section 7.1.5.3 Incidence of common adverse events.

7.1.7 Laboratory Findings

Laboratory findings are discussed in the following sections of this review.

7.1.7.1 Overview of laboratory testing in the development program

The applicant analyzed data from hematology evaluations and clinical chemistry evaluations performed in the pooled pivotal clinical pharmacology studies in adult subjects, studies M016455H/1004, M016455H/1007, and M016455H/1008 [clinstat\iss\iss.pdf, pages 11, 83].

7.1.7.3 Standard analyses and explorations of laboratory data

The applicant performed analyses focused on measures of central tendency and analyses focused on outliers or shifts from normal to abnormal. These analyses of laboratory data are discussed below.

7.1.7.3.1 Analyses focused on measures of central tendency

The mean change from baseline in hematology and serum chemistry values in the pooled pivotal clinical pharmacology studies in adult subjects were small [clinstat\iss\iss.pdf, pages 85-86].

The applicant performed analyses of mean change from baseline in hematology and serum chemistry values by demographic subgroups for the pooled pivotal clinical pharmacology studies

in adult subjects. These analyses did not reveal any risks associated with the use of fexofenadine HCl for any gender or race [clinstat\iss\iss.pdf, pages 91-95]. All subjects were adults from 18 to 45 years of age and subgroup analysis by age could not be performed [clinstat\iss\iss.pdf, page 95].

Reviewer comment:

Mean changes from baseline in hematology and serum chemistry values show no meaningful changes and no meaningful differences between demographic subgroups. These data do not identify a safety signal.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

The frequencies of subjects with laboratory values meeting the criteria for PCA, LPCA, or CSA were low. There was one subject in the pooled pivotal clinical pharmacology studies in adults who had a clinically significant abnormal (CSA) laboratory value. Subject 0001/1013 was a 28-year-old Black female in M016455H/1007 who had an absolute neutrophil value of $2.10 \times 10^9/L$ at baseline that decrease to $1.40 \times 10^9/L$ at post-study. This change met both CSA and predefined change abnormal (PCA) criteria. The remaining hematology values were within normal limits at post-study and no follow-up evaluations were performed [clinstat\iss\iss.pdf, page 88].

The applicant performed analyses of data of subjects and patients with CSA values by demographic subgroups for the pooled pivotal clinical pharmacology studies in adult subjects. These analyses did not reveal any risks associated with the use of fexofenadine HCl for any gender or race [clinstat\iss\iss.pdf, pages 91-96]. All subjects were adults from 18 to 45 years of age and subgroup analysis by age could not be performed [clinstat\iss\iss.pdf, page 96].

Reviewer comment:

These laboratory data show no meaningful changes or meaningful differences between demographic subgroups. These data do not identify a safety signal.

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

There were no outliers with markedly abnormal laboratory values in the pooled pivotal clinical pharmacology studies in adults [clinstat\iss\isstable.pdf, pages 105-107]. There were no dropouts in the pooled pivotal clinical pharmacology studies in adults [clinstat\iss\iss.pdf, page 55].

7.1.8 Vital Signs

Vital signs data are discussed in the following sections of this review.

7.1.8.1 Overview of vital signs testing in the development program

The applicant analyzed systolic blood pressure, diastolic blood pressure, and heart rate data from the pooled pivotal clinical pharmacology studies in adult subjects, studies M016455H/1004, M016455H/1007, and M016455H/1008 [clinstat\iss\iss.pdf, page 111].

7.1.8.3 Standard analyses and explorations of vital signs data

The applicant performed analyses focused on measures of central tendency and on outliers. These analyses of vital signs data are discussed below.

7.1.8.3.1 Analyses focused on measures of central tendencies

The applicant notes that there were no meaningful changes in heart rate, systolic blood pressure, or diastolic blood pressure from baseline to the end of the studies in the clinical pharmacology studies in adult subjects [clinstat\iss\iss.pdf, page 113]. The applicant states that analyses of vital signs data by demographic subgroups for the pooled pivotal clinical pharmacology studies in adult subjects did not reveal any risks associated with the use of fexofenadine HCl for any gender or race. Subgroup analysis by age was not performed because all subjects were healthy men and women 18-45 years of age [clinstat\iss\iss.pdf, page 116-118].

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

In the pivotal clinical pharmacology studies in adult subjects, there were no vital signs values that met criteria for PCA, predefined change abnormal at last evaluation (LPCA), or CSA [clinstat\iss\iss.pdf, page 115]. Subgroup analysis by age was not performed there were no vital signs values that met criteria for PCA, LPCA, or CSA [clinstat\iss\iss.pdf, page 116-118].

Reviewer comment:

These vital signs data show no meaningful changes and do not identify a safety signal. There are no meaningful differences in vital signs data among demographic subgroups.

7.1.9 Electrocardiograms (ECGs)

ECG data are discussed in the following sections of this review.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

The applicant analyzed ECG data from the pooled pivotal clinical pharmacology studies in adult subjects, studies M016455H/1004, M016455H/1007, and M016455H/1008 [clinstat\iss\iss.pdf, page 102].

Preclinical cardiovascular safety data are summarized in the currently approved label for Allegra (fexofenadine HCl). The label states that in dogs (30 mg/kg/orally twice daily for 5 days) and rabbits (10 mg/kg, intravenously over 1 hour), fexofenadine hydrochloride did not prolong QTc. In dogs, the plasma fexofenadine concentration was approximately 9 times the therapeutic plasma concentrations in adults receiving the maximum recommended human daily oral dose of 180 mg. In rabbits, the plasma fexofenadine concentration was approximately 20 times the therapeutic plasma concentration in adults receiving the maximum recommended human daily oral dose of 180 mg. No effect was observed on calcium channel current, delayed K⁺ channel current, or action potential duration in guinea pig myocytes, Na⁺ current in rat neonatal myocytes, or on the delayed rectifier K⁺ channel cloned from human heart at concentrations up to 1 x 10⁻⁵ M of fexofenadine [labeling\approved.pdf, pages 3-4].

7.1.9.3 Standard analyses and explorations of ECG data

The applicant performed analyses focused on measures of central tendency and on outliers. These analyses of ECG data are discussed below.

7.1.9.3.1 Analyses focused on measures of central tendency

The applicant evaluated mean changes from baseline for the ECG intervals PR, QRS, QT, QTcB, and QTcF in the pooled pivotal clinical pharmacology studies in adult subjects. The applicant noted no meaningful changes in any of the ECG intervals [clinstat\iss\iss.pdf, pages 104-105].

There were no meaningful differences between genders and races in the subgroup analysis of ECG for the pivotal clinical pharmacology studies. Because the subjects in these studies were to be healthy male or female subjects of any race between the ages of 18 and 45 years, no subgroup analyses based on age were performed.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

In the pivotal clinical pharmacology studies in adult subjects, there were no ECG values that met criteria for PCA, LPCA, or CSA [clinstat\iss\iss.pdf, page 107].

There were no meaningful differences between genders and races in the subgroup analysis of ECGs for the pivotal clinical pharmacology studies. Because the subjects in these studies were to be healthy male or female subjects of any race between the ages of 18 and 45 years, no subgroup analyses based on age were performed [clinstat\iss\iss.pdf, pages 107-110].

Reviewer comment:

These ECG data show no meaningful changes and do not identify a safety signal. There are no meaningful differences in ECG data among demographic subgroups.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The applicant notes that there have been no studies conducted on withdrawal effects following treatment with fexofenadine HCl, but that no withdrawal effects have been observed [clinstat\iss\iss.pdf, page 125].

As of June 15, 2006, the applicant reported that there was one spontaneous report of drug abuse with fexofenadine HCl. The case of drug abuse involved several teenagers that were attempting to "get high" by taking four or five fexofenadine HCl 180 mg tablets.

The applicant also reported that as of June 15, 2006, there were 33 spontaneous reports of drug misuse with fexofenadine HCl. Many of the cases were pediatric patients who received the drug despite being younger than 6 years of age, older children who received a larger than indicated dose, or use of the drug for off-label indications. One of the 31 cases was associated with a serious adverse event; the other events were not serious. The serious adverse event was a 3-year old male who received a single 30 mg dose of fexofenadine HCl for atopy and experienced

anaphylaxis. The patient was hospitalized and recovered [clinstat\other\drugabuse.pdf, pages 6-12].

Reviewer comment:

This reviewer concurs with the applicant's conclusion that no new safety concern or safety signal could be identified on the basis of reports of drug abuse or misuse of fexofenadine HCl.

7.1.14 Human Reproduction and Pregnancy Data

The applicant identified 15 postmarketing adverse events associated with drug exposure during pregnancy. These events included talipes, fetal distress, limb malformation, multiple congenital abnormalities, peritonitis, restlessness, muscle spasms and twitching, cerebral artery occlusion and convulsion, prematurity, constipation, and prematurity/small for dates. The applicant concluded that the data did not suggest a safety signal based on the lack of consistent pattern of malformation, insufficient clinical details, and confounding factors [clinstat\iss\iss.pdf, pages 81-82].

Reviewer comment:

This reviewer evaluated the applicant's human reproduction and pregnancy data and concurs with the applicant that there is no evidence of a safety signal.

7.1.16 Overdose Experience

The applicant searched their postmarketing adverse event database for cases of overdose. As of June 15, 2006, the applicant identified 28 spontaneous reports of overdose. Doses of fexofenadine HCl in these reports ranged from 30 mg to 1680 mg. Of these 28 reports, three were reported as being serious and 25 were non-serious. Eighteen of the 28 reports, with doses ranging from 30 mg to 1680 mg, were not associated with any adverse event. The three serious cases included (1) a 8-year old male patient who experienced hallucination, increased lacrimation, mydriasis, ocular hyperemia, and urinary incontinence after receiving an unknown dose of fexofenadine for an unknown indication, (2) a 9-year old female patient that experienced urticaria after receiving 60 mg fexofenadine HCl for bronchitis, and (3) a 20-month old male who ingested approximately 10 tablets of 120 mg fexofenadine HCl. There was no adverse reaction to the study medication [clinstat\other\drugabuse.pdf, pages 10-12].

Reviewer comment:

The applicant noted that fexofenadine HCl has demonstrates a very favorable benefit/risk profile, even in cases with documented significant overdoses and that no new safety signal could be detected after review of the overdose data for fexofenadine HCl. This reviewer concurs with the applicant's conclusion.

7.1.17 Postmarketing Experience

The applicant searched their ClinTrace safety database for postmarketing and spontaneous adverse event reports for fexofenadine HCl. The database includes cases from clinical trials, postmarketing surveillance studies, spontaneous notifications, cases from regulatory authorities,

and the published literature [clinstat\iss\iss.pdf, page 62]. The search was designed to capture all cases received through June 15, 2006 where the age was reported to be less than 12 years.

The applicant provided analyses of postmarketing non-serious and serious adverse events for fexofenadine HCl in the following group:

- Patients less than 12 years of age or 30 mg dose or 60 mg total daily dose

The applicant also provided analyses of postmarketing non-serious and serious adverse events for these subgroups [clinstat\iss\iss.pdf, pages 67-78]

- Patients less than 6 years of age
- Patients 6 to less than 12 years of age
- Patients with age unspecified but taking 30 mg dose or 60 mg total daily dose

Postmarketing adverse events, in general, were consistent with those previously reported for fexofenadine HCl. There were fairly few serious adverse events. Given the extensive exposure to fexofenadine HCl in patients less than 12 years of age, postmarketing adverse event, do not raise concerns regarding a safety signal in this age group.

A review of the analyses of postmarketing safety data follows below.

7.1.17.1 Patients less than 12 years of age or 30 mg dose or 60 mg total daily dose

There were 601 spontaneous adverse events reported in patients less than 12 years of age, or a 30 mg dose, or a 60 mg total daily dose. The majority of the events were non-serious (92.0%, 553/601). The most frequent spontaneous adverse events in this group are summarized in Table 6 below. The applicant states that the most frequently reported adverse events were consistent with the known safety profile of fexofenadine HCl [clinstat\iss\iss.pdf, page 66].

Table 6 Most frequently reported (10 or more) postmarketing spontaneous adverse events for fexofenadine HCl in patients less than 12 years of age, or 30 mg dose, or 60 mg total daily dose [clinstat\iss\iss.pdf, page 66].

Adverse event	Number of events
Drug ineffective	69
Headache	29
Back pain	18
Somnolence	16
Overdose	12
Insomnia	12
Hypersensitivity	11
Medication error	11
Psychomotor hyperactivity	10

Appears This Way
On Original

There were 48 serious adverse events (8.0%, 48/601) in patients less than 12 years of age, or who were taking a 30 mg dose or a 60 mg total daily dose. There were only four serious adverse events reported in more than one patient; convulsion, fetal growth retardation, loss of consciousness, and premature labor were each reported twice. There was one death due to fetal growth retardation and multiple congenital anomalies, which is described in Section 7.1.1 Deaths of this review [clinstat\iss\iss.pdf, pages 66-67].

Reviewer comment:

Postmarketing adverse events in this group were infrequent and were consistent with those previously reported for fexofenadine HCl. There were similar numbers of reports of somnolence, insomnia, and psychomotor hyperactivity. Serious adverse events were infrequent and, given the extensive exposure to the drug, do not raise concerns regarding a safety signal. The applicant estimates that post-marketing exposure to fexofenadine HCl 30 mg from June 2000 through March 2006 is estimated to be approximately 127 million patient treatment days or approximately 348,200 patient years [clinstat\iss\iss.pdf, page 64].

7.1.17.2 Patients less than 6 years of age

There were 92 postmarketing adverse events reported for patients less than 6 years of age. The majority of adverse events were non-serious (76.1%, 70/92). The most frequent spontaneous adverse events in this group are summarized in Table 7 below.

Table 7 Most frequently reported (3 or more) postmarketing spontaneous adverse events for fexofenadine HCl in patients less than 6 years of age [clinstat\iss\iss.pdf, page 68].

Adverse event	Number of events
Accidental exposure	7
Medication error	5
Vomiting	4
Accidental overdose	3
Drug ineffective	3
No adverse event	3
Somnolence	3

There were 21 serious adverse events in nine patients (24.7%, 21/85). The applicant notes that there were confounding factors such as concomitant medication or illness in six of the nine patients. Eight of the patients were infants exposed to fexofenadine in utero. Serious adverse events reported in these patients included premature labor, small for gestational age, fetal growth retardation, and cardiac, musculoskeletal, CNS, and musculoskeletal anomalies. The applicant notes that there is no evidence of teratogenicity in preclinical studies of fexofenadine HCl [clinstat\iss\iss.pdf, pages 67-71; clinstat\iss\ae_tables.pdf, pages 73-74].

Reviewer comment:

Postmarketing adverse events in this group were infrequent. Fifteen of the events were related to accidental exposure, medication error, or accidental overdose. There are relatively few serious adverse events related to in utero exposure to fexofenadine HCl, given the extensive postmarketing exposure to the drug. No consistent pattern of congenital malformation was present in these few cases. Postmarketing adverse events and serious adverse events do not suggest a safety signal in patients less than 6 years of age.

7.1.17.3 Patients 6 to less than 12 years of age

There were 252 postmarketing adverse events reported for patients 6 years to less than 12 years of age. The majority of adverse events were non-serious (93.3%, 235/252). The most frequent spontaneous adverse events in this group are summarized in Table 8 below.

Table 8 Most frequently reported (5 or more) postmarketing spontaneous adverse events for fexofenadine HCl in patients 6 to less than 12 years of age [clinstat\iss\iss.pdf, page 72].

Adverse event	Number of events
Drug ineffective	27
Headache	12
Psychomotor hyperactivity	7
Hypersensitivity	6
Overdose	6
Anxiety	5
Back pain	5
Depression	5
Medication error	5
Somnolence	5

There were 17 serious adverse events occurred in eight patients (6.7 %, 17/252). There were two reports of hallucinations. There was one report of major depression and suicide attempt in an 11 year-old, one report of grand mal convulsion in an 11 year-old, and one report of increased liver enzymes in a 10-year old. The patient with depression and suicide attempt had a previous history of mild dysphoria and concomitant treatment with methylphenidate HCl. The patient with a convulsion had a previous history of seizure disorder. The patient with elevated liver enzymes had abdominal pain and vomiting prior to initiating treatment with fexofenadine HCl [clinstat\iss\iss.pdf, pages 72-75].

Reviewer comment:

Postmarketing adverse events in this group were infrequent. Concomitant illness or medication was present for many of the serious adverse event reports. Postmarketing adverse events and serious adverse events do not suggest a safety signal in patients 6 to less than 12 years of age.

7.1.17.4 Patients with age unspecified, but taking 30 mg per dose or a 60 mg total daily dose
 There were 257 postmarketing adverse events reported for patients with age unspecified but taking 30 mg dose or a 60 mg total daily dose. The most frequent spontaneous adverse events in this group are summarized in Table 9 below. The majority of adverse events were non-serious (96.5%, 248/257).

Table 9 Most frequently reported postmarketing spontaneous adverse events for fexofenadine HCl in patients with age unspecified but taking a 30 mg dose or a 60 mg total daily dose [clinstat\iss\iss.pdf, page 76].

Adverse event	Number of events
Drug ineffective	39
Headache	16
Back pain	13
Insomnia	9
Somnolence	8
Dizziness	7
Nausea	7
Pruritus	5

Clinical Review
Charles E. Lee, M.D.
NDA 21-909, N-000, 9/28/06
Allegra (fexofenadine HCl) Orally Disintegrating Tablets

Adverse event	Number of events
Rash	5
Urticaria	5

There were 9 serious adverse events occurred in 9 patients (3.4 %, 8/238). There were two reports of limb malformations in newborns, two reports of loss of consciousness, one report each of convulsion, atrioventricular block, hypersensitivity, generalized rash, and nephrotic syndrome. Both cases of limb malformations had a family history of similar malformations. The patient with atrioventricular block had a previous history of heart block and hypertension and was taking concomitant digoxin, carvedilol, and torasemide. There was little information accompanying the reports of loss of consciousness [clinstat\iss\iss.pdf, pages 75-78, clinstat\iss\ae_tables.pdf, pages 75-78].

Reviewer comment:

Non-serious adverse events were similar in character to those noted in children 6 to 12 years of age. Postmarketing adverse events and serious adverse events do not suggest a safety signal in patients with unspecified age taking a 30 mg dose or 60 mg total daily dose of fexofenadine HCl.

7.2 Adequacy of Patient Exposure and Safety Assessments

Adequacy of patient exposure and safety assessments is addressed below.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The applicant provided a summary of safety information, including subgroup analyses, from the pivotal clinical pharmacology studies M016455H/1004, M016455H/1007, and M016455H/1008 in adult subjects, supportive clinical pharmacology studies PJPR0037 and M016455I/1119 in pediatric subjects 6 to 12 years of age, pivotal efficacy and safety study PJPR0066/77 in pediatric subjects 6 to 11 years of age, supportive efficacy and safety study M016455C/3212 in pediatric subjects 6 to 11 years of age, and long-term safety studies PJPR0031 and PJPR0027 in adult subjects. The safety information from these studies included adverse event data, laboratory data, vital signs data, and ECG data [clinstat\iss\iss.pdf, page 011].

This review will address only the safety data from supportive clinical pharmacology studies from the pivotal clinical pharmacology studies M016455H/1004, M016455H/1007, and M016455H/1008 in adult subjects. The supportive studies have been previously submitted to NDA 20-625, NDA 20-872, or NDA 21-963 and have previously been reviewed.

7.2.1.1 Study type and design/patient enumeration

There are three pivotal studies in the applicant's drug development program for the proposed ODT formulation. These studies are described below and are summarized below in Table 10 [clinstat\clinsum.pdf, pages 18-19]:

- Study M016455H/1004, a pivotal bioavailability and food effect study designed to characterize the bioavailability of four prototype ODT formulations of fexofenadine HCl 30 mg under fed and fasted conditions. This study identified the one ODT formulation to be further developed and provided information on the effect of food on its bioavailability.
- Study M016455H/1007, a pivotal bioequivalence study designed to compare the bioavailability of the proposed ODT formulation to the marketed 30 mg fexofenadine tablet under fasted conditions with 240 mL of water
- Study M016455H/1008, a pivotal bioavailability study designed to compare the pharmacokinetics of the proposed ODT formulation administered under fasted conditions, both with and without water

Table 10 Summary of pivotal clinical pharmacology studies providing safety information, NDA 21-909 [clinstatclinsum.pdf, pages 27-29].

Study Number	Study Type	Treatment Groups	Treatment duration	Design	Number of subjects	Diagnosis, age of subjects
M106455H/1004	Pivotal food effect study	Marketed F 30 mg tablet, single dose, fasted conditions Proposed F 30 mg ODT, single dose, fasted and fed conditions Other prototype 30 mg ODTs, single dose, fasted and fed conditions, some without water	Single dose	Single center, randomized, open label, eight treatment, four-period, incomplete crossover	54	Healthy men and women, 18-45 years
M106455H/1007	Pivotal BE study	Marketed F 30 mg tablet, single dose, fasted conditions Proposed F 30 mg ODT, single dose, fasted and fed conditions	Single dose	Single center, randomized, open label, two period, two-way crossover	54	Healthy men and women, 18-45 years
M106455H/1008	Pivotal BA study	Proposed F 30 mg ODT, single dose, fasted conditions with water Proposed F 30 mg ODT, single dose, fasted conditions without water	Single dose	Single center, randomized, open label, two period, two-way crossover	54	Healthy men and women, 18-45 years

F = fexofenadine HCl

7.2.1.2 Demographics

Demographics in pivotal clinical pharmacology studies in adult subjects are summarized in Table 11 below. The majority of subjects were of female gender and White race. The mean age of subjects was 25.1 years [clinstat\iss\iss.pdf, page 41].

Table 11 Demographics in pivotal clinical pharmacology studies in adult subjects [clinstat\iss\iss.pdf, page 41].

Demographic characteristic	Fexofenadine HCl 30 mg	
	N = 139	
	n	(%)
Gender		
Female	74	(53.2)
Male	69	(46.8)

Clinical Review
 Charles E. Lee, M.D.
 NDA 21-909, N-000, 9/28/06
 Allegra (fexofenadine HCl) Orally Disintegrating Tablets

Demographic characteristic	Fexofenadine HCl 30 mg	
	n	(%)
Race		
White	121	(87.1)
Non-White	18	(12.9)
Age, years		
Mean ± SD	25.1 ± 6.87	
Range	18.0-45.0	

7.2.1.3 Extent of exposure (dose/duration)

A total of 139 subjects were exposed to fexofenadine HCl 30 mg in the pivotal clinical pharmacology studies in adult subjects. Patients were exposed from 1 to 37.0 days. The applicant's analysis included the washout periods between doses, even though some subjects may have only received single doses in each treatment period. The total estimated exposure is therefore overestimated. The mean duration of exposure was 13.1 days [clinstat\iss\iss.pdf, pages 38-39].

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Other clinical data sources used to evaluate safety are reviewed below.

7.2.2.2 Postmarketing experience

The applicant provided an analysis of adverse events from postmarketing safety information received on the fexofenadine HCl mono product and entered into their ClinTrace™ database on or before 15 June 2006. The search strategy was intended to capture all cases in the database for the fexofenadine HCl single-ingredient product from spontaneous sources received up to and including 15 June 2006 where the age was reported to be less than 12 years.

There were 383 cases identified; 222 cases were retrieved based on reported or calculated age less than 12 years and 161 cases were retrieved based on information from the dosing fields (i.e., 30 mg in any dose field or 60 mg in the Total Daily Dose field) where no age was reported nor could be calculated [clinstat\iss\iss.pdf, pages 61-62].

Fexofenadine HCl 30 mg is indicated as a twice-daily dose for SAR and CIU in patients 6 to 11 years of age. The applicant estimates that post-marketing patient exposure to fexofenadine HCl 30 mg from June 2000 through March 2006 is approximately 127 million patient treatment days or approximately 348,200 patient years [clinstat\iss\iss.pdf, page 64].

Reviewer comments:

The applicant's search strategy is acceptable and provides an acceptable approach to identify relevant safety information on the use of fexofenadine HCl 30 mg. Postmarketing exposure is adequate to provide an evaluation of the safety of the product.

7.2.2.3 Literature

The applicant performed a search of the medical literature for information relevant to fexofenadine HCl 30 mg and the safety of fexofenadine HCl in general. The search covered the period of time since the approval of NDA 21-704, Allegra-D 24 Hour Tablets. The dates covered were from October 2003 until December 31, 2005. The search was conducted with the Medline, Embase, and Dialog Datastar databases using the keywords "fexofenadine," "Allegra," and "Telfast." The search identified 90 references [clinstat\iss\iss.pdf, page 68; clinstat\other\literature_table.pdf]. Safety information relevant to the applicant's review of the medical literature is addressed in Sections 7.1.1, 7.1.2, 7.1.3, and 7.1.5.3 of this review.

Reviewer comments:

The applicant's search strategies and search terms are acceptable and provide an acceptable approach to identify relevant safety information on the use of fexofenadine HCl.

7.2.3 Adequacy of Overall Clinical Experience

The designs of studies in this application, as described in Section 7.2.1.1 Study type and design/patient enumeration, were adequate to allow for assessment of safety.

As noted in Section 7.2.1.3 Extent of exposure (dose/duration), the extent of exposure in this NDA supplement is fairly short. Although the duration of exposure is short, long term safety studies for fexofenadine HCl in NDA 20-625 (study PJPR0031) and NDA 20-872 (study PJPR0027) had treatment periods of 6 months and one year, respectively.

7.2.9 Additional Submissions, Including Safety Update

The applicant submitted the required 120-day safety update, dated January 25, 2007 [NDA 21-909, N-000 SU, 1/25/07]. During the period between submission of the NDA and the completion of the safety update, there were no clinical trials with fexofenadine HCl 30 mg ODT oral were conducted and there were no new data from animal studies. The safety update included worldwide postmarketing safety data for fexofenadine HCl 30 mg received during the period June 16, 2006 through October 31, 2006. The safety database query methodology used for the safety update was the same as that used for the original NDA submission, as described in Section 7.2.2.2 Postmarketing experience [NDA 21-909, N-000 SU, 1/25/07, cover.pdf, page 1]. Information from the safety update is addressed in Sections 7.1.1, 7.1.2, 7.1.3, and 7.1.5.3 of this review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The applicant seeks marketing approval of their fexofenadine HCl orally disintegrating tablet for treatment of symptoms of SAR in children from 2 to 5 years of age and uncomplicated skin manifestations of CIU in children from 6 months to 5 years of age. Adverse events occurring at a frequency of greater than 2% in pivotal clinical pharmacology studies in adult subjects included headache and nausea. No safety concerns were identified with review of vital signs, laboratory

study, or ECG data. No safety concerns were noted among demographic subgroups. The data from uncontrolled clinical pharmacology studies in adults do not reveal new safety concerns for fexofenadine HCl.

Postmarketing adverse events in patients less than 12 years of age were consistent with those previously reported for fexofenadine HCl. There were fairly few postmarketing reports or serious adverse events in this age group. Given the extensive exposure to fexofenadine HCl, postmarketing adverse events in patients less than 12 years of age did not raise concerns regarding a safety signal. There were no safety concerns identified with the applicant's search of the medical literature for information relevant to fexofenadine HCl 30 mg and the safety of fexofenadine HCl in general.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The application is for an ODT formulation of fexofenadine HCl. The application does not propose to change the current indications for Allegra [labeling\proposed.pdf, pages 1, 4]. The current indications are relief of symptoms associated with SAR in adults and children 2 years of age and older and treatment of uncomplicated skin manifestations of CIU in adults and children 6 months of age and older [labeling\approved.pdf, page 6].

Dosing of fexofenadine HCl in the pediatric population was previously addressed in earlier NDA supplements [Clinical Pharmacology and Biopharmaceutics Review, Shinja Kim, Ph.D., NDA 20-872, SE08-011, 11/18/02; Office of Clinical Pharmacology Review, Shinja Kim, Ph.D., NDA 21-963, N-000, 12/15/05]. This application seeks approval of a new dosage form and does not propose to change the currently approved dose of fexofenadine HCl. The proposed dose of Allegra ODT for the treatment of symptoms of SAR and CIU in children 6 to 11 years of age is 30 mg twice daily. A dose of 30 mg once daily is recommended as the starting dose in pediatric patients with decreased renal function [labeling\proposed.pdf, page 4].

Co-administration of fexofenadine HCl with food results in a decreased rate of absorption and a decreased extent of absorption of fexofenadine. Food caused a 59% decrease in C_{max} value and 40% decrease in AUC_{0-inf} estimates for the ODT relative to its fasted state [hpbio\hupharm\1004.pdf, page 51]. Food also increased the mean $t_{1/2}$ value for the proposed formulation relative to that for the fasted state.

The 30 mg fexofenadine HCl ODT administered without water was bioequivalent to the tablet administered with water with respect to AUC_{0-inf} , but the upper limit of C_{max} was slightly outside of the bioequivalence bounds (90% CI: 100 to 127) and the point estimate AUC_{0-inf} and C_{max} were approximately 13% higher for the test treatment than for reference [hpbio\hupharm\1008.pdf, page 58]. The rate and extent of absorption of the proposed ODT formulation with and without water are comparable. The slight increases in AUC and C_{max} noted

when the product is administered without water do not represent safety concerns because of the safety profile for this drug and its large therapeutic index.

Co-administration of fexofenadine with grapefruit, orange, and apple juices reduce the bioavailability of fexofenadine. The applicant's current and proposed labeling recommend that the products be taken with water. The current and proposed labeling appropriately address this interaction [labeling\approved.pdf, page 7; labeling\proposed.pdf, pages 9, 10].

8.2 Drug-Drug Interactions

The bioavailability of fexofenadine is decreased if administered within 15 minutes of aluminum and magnesium-containing antacids. Administration of 120 mg of fexofenadine hydrochloride (2 x 60 mg capsule) within 15 minutes of an aluminum and magnesium containing antacid (Maalox) decreased fexofenadine AUC by 41% and C_{max} by 43% [labeling\approved.pdf, page 7; labeling\proposed.pdf, page 8].

The applicant's current labeling for Allegra Capsules, Tablets, Oral Suspension and the proposed labeling for Allegra ODT state that the products should not be taken closely in time with aluminum and magnesium containing antacids [labeling\approved.pdf, page 7; labeling\proposed.pdf, page 8]. The current and proposed labeling appropriately address this drug-drug interaction.

Co-administration of fexofenadine hydrochloride with either ketoconazole or erythromycin results in increased plasma concentrations of fexofenadine in healthy adult subjects. Fexofenadine has no effect on the pharmacokinetics of either erythromycin or ketoconazole. In 2 separate studies in healthy adult subjects, fexofenadine hydrochloride 120 mg twice daily (240 mg total daily dose) was co-administered with either erythromycin 500 mg every 8 hours or ketoconazole 400 mg once daily under steady-state conditions to healthy adult subjects (n=24, each study). No differences in adverse events or QTc interval were observed when subjects were administered fexofenadine hydrochloride alone or in combination with either erythromycin or ketoconazole. The changes in plasma levels were within the range of plasma levels achieved in adequate and well-controlled clinical trials [labeling\approved.pdf, page 9; labeling\proposed.pdf, pages 3, 9].

8.3 Special Populations

In subjects with mild to moderate (creatinine clearance 41-80 mL/min) and severe (creatinine clearance 11-40 mL/min) renal impairment, peak plasma levels of fexofenadine were 87% and 111% greater, respectively, and mean elimination half-lives were 59% and 72% longer, respectively, than observed in healthy volunteers. Peak plasma levels in subjects on dialysis (creatinine clearance ≤ 10 mL/min) were 82% greater and half-life was 31% longer than observed in healthy volunteers. Based on increases in bioavailability and half-life, current labeling recommends a dose of 60 mg once daily in adults and children 12 years of age and older with decreased renal function and 30 mg once daily in children 6 to 11 years of age [labeling\approved.pdf, pages 3, 13]. Accordingly, the proposed dose of Allegra ODT in children

6 to 11 years of age with SAR or CIU and decreased renal function is of 30 mg once daily [labeling\proposed.pdf, pages 1, 4-5].

For children 2 to 11 years of age with SAR or CIU and decreased renal function, the recommended starting dose of Allegra Oral Suspension is 30 mg (5 mL) once daily. In children 6 months to less than 2 years of age with CIU and decreased renal function, the recommended dose of Allegra Oral Suspension is 15 mg (2.5 mL) once daily [labeling\proposed.pdf, pages 1, 4-5].

8.4 Pediatrics

Allegra ODT is proposed for use in children from 6 to 11 years of age and is the subject of this review. Accordingly, this section of this review will deal only with the applicant's requirements under the Pediatric Research Equity Act (PREA).

The applicant previously submitted studies designed to assess the effectiveness and safety of fexofenadine HCl in pediatric patients from 6 months to less than 6 years of age (NDA 20-872 SE8-011, 11/18/02, NDA 21-963, N-000, 12/15/05). In this application, the applicant requested a deferral of pediatric studies in patients less than 6 years of age for Allegra ODT [other\pedwaiver.pdf, page 4].

The Agency previously determined that the applicant fulfilled the requirements under PREA for patients 6 months of age and older. The requirement for pediatric studies for patients less than 6 months of age was waived because SAR does not exist in this age group and CIU is extremely rare and the drug does not represent a meaningful therapeutic benefit over existing therapies for this condition [NDA Acknowledgement Letter, dated 1/11/06, NDA 20-963, N-000, 12/15/05].

At the End-of-Phase 2 meeting on January 10, 2003, the Division advised the applicant that additional support from a study of the pharmacokinetics of the ODT would be required to support approval in children from 2 to less than 6 years of age. The data supporting the approval of NDA 21-963 included a study of the oral suspension formulation in children of this age group [Medical Officer Review, Charles E. Lee, M.D., NDA 21-963, N-000, 12/15/05]. Although we now have data on the bioavailability of fexofenadine administered without applesauce in this age group, we do not have data on the bioavailability of the ODT in this age group.

The applicant has requested a deferral of pediatric studies for the ODT formulation in children from 2 to less than 6 years of age. The proposed ODT formulation is not suitable for children less than 2 years of age and is not likely to be suitable for children from 2 to less than 6 years of age. An alternative fexofenadine HCl formulation (Allegra Oral Suspension) is currently marketed and liquid formulations of other antihistamines, both prescription and non-prescription, are available. The ODT dosage form of fexofenadine HCl does not represent a meaningful therapeutic benefit over existing therapies for this condition. It is this reviewer's opinion that pediatric studies for the ODT formulation should therefore be waived in children less than 6 years of age.

8.6 Literature Review

The applicant performed a search of the medical literature for information relevant to fexofenadine HCl 30 mg and the safety of fexofenadine HCl in general. The search was conducted with the Medline, Embase, and Dialog Datastar databases using the keywords "fexofenadine," "Allegra," and "Telfast." The search identified 90 references. Safety information relevant to the applicant's review of the medical literature is addressed in Sections 7.1.1, 7.1.2, 7.1.3, and 7.1.5.3 of this review.

8.7 Postmarketing Risk Management Plan

No postmarketing risk management plan is necessary

9 OVERALL ASSESSMENT

9.1 Conclusions

This application supports the efficacy and safety of Allegra ODT for the treatment of symptoms of SAR and CIU in children 6 to less than 12 years of age.

This application is supported by comparison of the bioavailability and bioequivalence of the proposed new drug to that of an approved reference product, Allegra (fexofenadine HCl) Tablets, 30 mg. No clinical efficacy studies were required to support this application. The clinical pharmacology studies in this application support the efficacy of the applicant's product. The clinical pharmacology studies in this application confirmed that under fasting conditions, the proposed product is bioequivalent to the reference product for rate and extent of exposure. Ratios of the AUC_{0-inf} and C_{max} values for fexofenadine for the proposed and reference product fell within 80% to 125% limits. Administration of fexofenadine HCl ODT with food decreased both the extent and rate of absorption. Labeling appropriately notes this significant decrease in bioavailability of fexofenadine in the fed state. Absorption of the ODT formulation is comparable when taken with and without water and the product may be labeled accordingly.

The safety data in this application support the safety of the applicant's product. Safety data from the pivotal clinical pharmacology studies in adult subjects did not identify a safety signal. Data from the pivotal clinical pharmacology studies in adult subjects did not suggest an association of adverse events and gender or race. Postmarketing adverse events in patients less than 12 years of age were consistent with those previously reported for fexofenadine HCl. Given the extensive exposure to fexofenadine HCl, postmarketing adverse events in patients less than 12 years of age did not raise concerns regarding a safety signal. No new safety concern or safety signal could be identified on the basis of reports of drug abuse or misuse of fexofenadine HCl, human reproduction and pregnancy data, or overdose. The applicant's search of the medical literature for safety information related to fexofenadine HCl identified no deaths, serious adverse events, or new safety signal for adverse events and the safety update identified no safety signal.

9.2 Recommendation on Regulatory Action

This reviewer recommends an "Approval" action.

9.4 Labeling Review

Detailed labeling review was performed. The labeling was submitted in Physician's Labeling Rule (PLR) format. Recommended changes in the proposed labeling are noted below in ~~strikeout~~ and underlined text. A complete ~~strikeout~~ version of proposed labeling with recommended changes will be sent to the applicant.

The major changes to the applicant's proposed labeling include the following:

- The statements ~~_____ and _____~~ were deleted for the INDICATIONS AND USAGE section of the labeling. The Division is requiring other products of the same class for the same or similar indications to remove these claims from labeling. The Division considers information addressing the effect of a drug on individual symptoms of allergic rhinitis and chronic idiopathic urticaria to be appropriate for the CLINICAL STUDIES section of the label, but not for the INDICATIONS section. b(4)
- The statement that "~~_____~~" in INDICATIONS AND USAGE was revised to "ALLEGRA is an H1-receptor antagonist" because of its promotional character b(4)
- Adverse reactions occurring at a frequency of $\geq 2\%$ and more commonly in drug than in placebo were included in the ADVERSE REACTIONS section of HIGHLIGHTS instead of those ~~_____~~
- A section describing the exposure to drug in clinical studies was added to the ADVERSE REACTIONS section of the label b(4)
- Adverse reaction rates were rounded to the closest integer
- A section on renal impairment was added to USE IN SPECIFIC POPULATIONS

A preliminary ~~strikeout~~ version of the proposed labeling follows below. Final labeling will be determined after negotiations with the applicant.

Appears This Way
On Original

23 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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

/s/

Charles Lee
5/29/2007 04:32:54 PM
MEDICAL OFFICER

Badrul Chowdhury
5/29/2007 04:40:44 PM
MEDICAL OFFICER
I concur

Appears This Way
On Original

1. GENERAL INFORMATION AND BACKGROUND

Allegra® (fexofenadine hydrochloride) is an antihistamine with selective H₁-receptor antagonist activity. Allegra is currently approved for the following indications and in the following age groups:

- Allegra 180 mg po QD and Allegra 60 mg po BID in seasonal allergic rhinitis (SAR) and chronic idiopathic urticaria (CIU) for adults and children 12 years of age and older
- Allegra 30 mg po BID in SAR and CIU for children 2 to 11 years of age
- Allegra 15 mg po BID in CIU for children 6 months to less than 2 years of age

The applicant has developed an orally disintegrating tablet (ODT) formulation of fexofenadine HCl 30 mg. The proposed indication is for the relief of symptoms associated with SAR in children 6 to 11 years of age and treatment of uncomplicated skin manifestations of CIU in children 6 to 11 years of age [Cover Letter; labeling\proposed.pdf, page 4].

The excipients in the proposed formulation include microcrystalline cellulose, sodium starch glycolate, povidone K-30, _____, magnesium stearate, alcohol _____, mannitol, crospovidone, sodium bicarbonate, citric acid, aspartame, natural and artificial orange flavor, and artificial cream flavor [CMC\product\3.2-p-drug product.pdf, page 2].

b(4)

The application is an electronic submission.

CLINICAL DEVELOPMENT PROGRAM

The applicant's program is based on a clinical pharmacology/bioequivalence approach. This application is supported by comparison of the bioavailability and bioequivalence of the proposed new drug to that of an approved reference product. The reference product for the clinical pharmacology studies in this application was the Sanofi Aventis product, Allegra (fexofenadine HCl) Tablets, 30 mg. No clinical efficacy studies were required to support this application.

There are three pivotal studies in the applicant's drug development program for the proposed ODT formulation. These studies are described below and summarized in greater depth later in this document [clinstat\clinsum.pdf, pages 18-19]:

- Study M016455H/1004, a pivotal bioavailability and food effect study designed to characterize the bioavailability of four prototype ODT formulations of fexofenadine HCl 30 mg under fed and fasted conditions. This study identified the one ODT formulation to be further developed and provided information on the effect of food on its bioavailability.
- Study M016455H/1007, a pivotal bioequivalence study designed to compare the bioavailability of the proposed ODT formulation to the marketed 30 mg fexofenadine tablet under fasted conditions with 240 mL of water
- Study M016455H/1008, a pivotal bioavailability study designed to compare the pharmacokinetics of the proposed ODT formulation administered under fasted conditions, both with and without water

There are a number of previously performed studies that the applicant considers to be supportive for the drug development program. These include clinical pharmacology studies, efficacy and safety studies, and safety studies. These studies have been previously submitted to IND 51,709,

NDA 20-625, or NDA 20-872 and have provided support for the approval of the capsule and tablet formulations of Allegra [clinstat\clinsum.pdf, pages 19-21]. These studies have previously been reviewed and will not be reviewed for this NDA.

2. FOREIGN MARKETING AND REGULATORY HISTORY

Fexofenadine HCl 30 mg tablets are approved in 74 countries other than the US, including countries in North, Central, and South America, the Caribbean, Asia, and Australia and New Zealand [clinstat\clinsum.pdf, pages 66-67].

Fexofenadine HCl 60 mg BID and fexofenadine HCl 180 mg QD were approved for marketing in the US for the treatment of symptoms of SAR in adults and children 12 years of age and over as Allegra® Capsules (NDA 20-625) on 25 July 1996 and as Allegra® Tablets (NDA 20-872) on 25 February 2000, respectively.

Fexofenadine HCl 30 mg BID was approved for marketing in the US for treatment of symptoms of SAR in children 6 to 11 years of age as Allegra® Tablets (NDA 20-872) on 25 February 2000. Fexofenadine HCl 60 mg BID was approved for marketing in the US for the treatment of manifestations of CIU in adults and children 12 years of age and older as Allegra® Capsules (NDA 20-625) on July 25, 1996 and as Allegra® Tablets (NDA 20-872) on February 25, 2000, respectively. Fexofenadine HCl 180 mg QD was approved in the US for the CIU indication on October 13, 2005. Fexofenadine HCl oral suspension 30 mg/5 mL (6 mg/mL, NDA 21-963) was approved for treatment of symptoms of SAR in children 2 to 5 years of age and manifestations of CIU in children 6 months to 5 years of age on October 16, 2006.

An End of Phase 2 meeting was held between the Division and the applicant on January 10, 2003. Clinical comments were provided and the Division concurred with the applicant's proposed clinical pharmacology/bioequivalence approach to supporting the efficacy and safety of their product. The Division noted that the proposed tablet weighed ~~_____~~ and raised concerns that it might represent a choking hazard in children less than 4 years of age [Meeting minutes and Medical Officer Review, IND 62,912, N-017 MR, 11/1/02].

b(4)

Comments on the applicant's Pre-NDA meeting package were faxed to the applicant on March 7, 2005 and a teleconference was held with the applicant on March 8, 2005. The sponsor was advised that their proposed NDA Table of Contents was not acceptable. They were advised to include a clinical data section and a safety update. As part of the clinical data section, in the Integrated Summary of Safety (ISS), the sponsor was advised to include post-marketing adverse events for fexofenadine, covering the period of time since the approval of Allegra-D 24 Hour Tablets. Additionally, the sponsor was advised to include a review of information from the published medical literature relevant to the safety of fexofenadine in the ISS. The review should cover the period of time since the approval of Allegra-D 24 Hour Tablets. The sponsor was also advised that the Integrated Summary of Safety should also address the safety of fexofenadine in subgroups, including children and the elderly, by gender, by race, and in patients with renal and hepatic impairment [Medical Officer Review, Charles E. Lee, M.D., IND 62,912, N-028 MP, 2/3/05; Teleconference Minutes, IMTS# 14569, IND 62,912, 3/8/05].

The sponsor provided a revised Table of Contents in response to the Division's comments that was acceptable. The applicant was advised that if they were not planning to seek changes to sections of the label other than INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION, the only information that is required for the Integrated Summary of Safety (ISS) would be safety information from the three pivotal clinical pharmacology studies, a review of postmarketing adverse events for fexofenadine, covering the period of time since the approval of Allegra-D 24 Hour Extended Release Tablets, and a review of information from the published medical literature relevant to the safety of fexofenadine. The review should cover the period of time since the approval of Allegra-D 24 Hour Extended Release Tablets [Medical Officer Review, Charles E. Lee, M.D., IND 62,912, N-029 GC, 3/18/05].

3. ITEMS REQUIRED FOR FILING AND REVIEWER COMMENTS (21 CFR 314.50)

The following items were included in this submission:

- Form FDA 356h [356h.pdf]
- Debarment certification [other\debar.pdf, page 1]
- Financial disclosure statement [other\financial.pdf, pages 1-2]
- Statements of Good Clinical Practice [hpbio\hupharm\1004.pdf, pages 1, 17; hpbio\hupharm\1007.pdf, pages 1, 20; hpbio\hupharm\1008.pdf, pages 1, 19]
- Integrated Summary of Efficacy [clinstat\ise\ise.pdf]
 - This application relies on the support of clinical pharmacology studies to demonstrate bioequivalence of the new formulation to an approved product. No clinical studies of the efficacy of the product or integrated summary of efficacy were required for this NDA. The sponsor provided a review and analysis of studies previously conducted to support the efficacy of fexofenadine capsules and tablets. These studies have previously been reviewed and will not be reviewed in this NDA
- Integrated Summary of Safety (ISS) [clinstat\iss\iss.pdf] included the following:
 - Summary of safety information, including subgroup analyses, from [clinstat\iss\iss.pdf, pages 14-60, 84-119]
 - ♦ Clinical pharmacology studies in this application, M106455H/1004, M106455H/1007, and M106455H/1008
 - ♦ Supportive clinical pharmacology studies PJPR0037 and M016455I/1119 in pediatric subjects 6 to 11 years of age
 - ♦ Pivotal efficacy and safety study PJPR0066/77 in pediatric subjects 6 to 11 years of age
 - ♦ Supportive efficacy and safety study M016455C/3212 in pediatric subjects 6 to 11 years of age
 - ♦ Long-term safety studies PJPR0031 and PJPR0027 in adult subjects
 - Postmarketing and spontaneous adverse event reports for fexofenadine HCl for patients less than 12 years of age for fexofenadine HCl 30 mg twice daily or 60 mg total daily dose [clinstat\iss\iss.pdf, pages 61-83]
 - Drug-drug, drug-demographic, and drug-disease interactions [clinstat\iss\iss.pdf, pages 120-125]
 - Withdrawal information [clinstat\iss\iss.pdf, page 125]
 - Drug abuse and overdose information [clinstat\other\drugabuse.pdf, pages 5-12]

- Publications related to fexofenadine from the medical literature [clinstat\clinsum.pdf, page 68; clinstat\other\literature_table.pdf]
- Proposed labeling and annotated labeling [labeling\proposed.pdf; labeling\contain\contain.pdf; summary\summary.pdf, pages 9-28].
- Case report forms for patients with serious adverse events or discontinuing studies [crf\1007\0001\subject1045.pdf; crf\1008\0001\subject1024.pdf]
- List of referenced DMFs [356h.pdf, page 2]
- Environmental assessment [cmc\3.2.r-environ.pdf, pages 2-8].
- Request for deferral of pediatric studies [other\pedwaiver.pdf, page 4]
 - The applicant is deferral of pediatric studies in patients less than 6 years of age for the ODT formulation

Reviewer comments:

The applicant notes that Aventis has developed an appropriate formulation (fexofendine HCl oral suspension, 6 mg/mL) for patients 6 months to 11 years of age with CIU and for patients from 2 to 11 years of age with SAR, which includes the age group of children younger than 6 years. The oral suspension formulation was recently approved on October 26, 2006.

It is reasonable to grant the deferral of pediatric studies for the ODT formulation in children from 2 to 5 years of age.

An ODT formulation is not suitable for children less than 2 years of age. Pediatric studies for this formulation should be waived in children less than 2 years of age.

At the End-of-Phase 2 meeting on January 10, 2003, the Division advised the applicant that the proposed clinical pharmacology studies would not provide sufficient support for the SAR and CIU indications in children 2 to 5 years of age. At that time, there was no data on the bioavailability of fexofenadine administered without applesauce in children less than 6 years of age and that the proposed ODT formulation was quite different from the approved tablet formulation. The Division advised the applicant that additional support from a study of the pharmacokinetics of the ODT would be required to support approval in this age group. The data supporting the approval of NDA 21-963 included a study of the oral suspension formulation in children 2 to 5 years of age (Study M016455B/1005) [Medical Officer Review, Charles E. Lee, M.D., NDA 21-963, N-000, 12/15/05]. Although we now have data on the bioavailability of fexofenadine administered without applesauce in this age group, we do not have data on the bioavailability of the ODT in this age group.

4. CLINICAL STUDIES

There are three pivotal bioavailability and bioequivalence studies in this application, Study M016455H/1004, Study M016455H/1007, and Study M016455H/1008.

The clinical review of this application will focus on the safety data from the three pivotal bioavailability and bioequivalence studies, Study M016455H/1004, Study M016455H/1007, and Study M016455H/1008.

The study reports and synopses for the three pivotal bioavailability and bioequivalence studies are appropriately indexed to allow review. These three studies are summarized below in Table 1. More detailed descriptions of these studies follow below.

4.1. Study M106455H/1004

Study M016455H/1004 was a pivotal bioavailability and food effect study designed to characterize the bioavailability of four prototype ODT formulations of fexofenadine HCl 30 mg under fed and fasted conditions. This study identified the one ODT formulation to be further developed and provided information on the effect of food on its bioavailability. It was an open-label, randomized, single-dose, four-period, eight-treatment, partially balanced, incomplete crossover study conducted in 35 healthy male and female adult subjects between 18 and 45 years of age [clinstat\clinsum.pdf, page 18; hpbio\hupharm\1004.pdf, pages 001-005, 027]. Study treatments included the marketed 30 mg fexofenadine HCl tablet administered under fasted conditions, two prototype oral disintegrating tablet formulations (I and II) of fexofenadine HCl 30 mg administered under fasted and fed conditions, two additional prototype oral disintegrating tablet formulations of fexofenadine HCl 30 mg (IV and V) administered under fasted conditions, and a prototype oral disintegrating tablet formulations (I) of fexofenadine HCl 30 mg administered under fasted conditions and without water [hpbio\hupharm\1004.pdf, pages 3-4]. Samples were taken immediately before dosing (0 hours) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36, and 48 hours during each study period for plasma fexofenadine levels. Subjects were housed at the study site from check-in on Day -1 until Day 3 [hpbio\hupharm\1004.pdf, page 22]. Safety endpoints included adverse events, vital signs, physical examinations, clinical laboratory studies, and ECGs [hpbio\hupharm\1004.pdf, page 4].

Formulation II appeared to demonstrated adequate bioavailability based on AUC(0-inf) and Cmax ratios relative to the marketed reference (lactose free tablet) and in compliance with the bioequivalence criteria of 80 – 125%. Food caused a 59% decrease in Cmax value and 40% decrease in AUC(0-inf) estimates for the proposed formulations (II) relative to its fasted state. There was one patient who withdrew from the study for personal reasons. There were no withdrawals from the study due to adverse events and there were no serious adverse events [hpbio\hupharm\1004.pdf, page 51].

4.2. Study M016455H/1007

Study M016455H/1007 was a pivotal bioequivalence study designed to compare the bioavailability of the proposed ODT formulation to the marketed 30 mg fexofenadine tablet under fasted conditions with 240 mL of water.

It was an open label, randomized, single dose, two-period, two-way crossover study conducted in were 54 healthy adult male and female subjects, 18 to 45 years of age, enrolled in the study. Study treatments included the marketed 30 mg fexofenadine HCl tablet and the selected prototype oral disintegrating tablet formulation (II) of fexofenadine HCl 30 mg administered under fasted conditions [clinstat\clinsum.pdf, pages 18-19; hpbio\hupharm\1007.pdf, page 3]. Serial blood samples were collected over a 48-hour period after each treatment. There was a six-day washout between study periods. Samples were taken at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36, and 48 hours post-dose [hpbio\hupharm\1007.pdf, page 4]. Subjects were housed at the study site from check-in on Day -1 until Day 3 [hpbio\hupharm\1007.pdf, pages 31-32].

Safety endpoints included adverse events, vital signs, physical examinations, laboratory studies, and ECGs [hpbio\hupharm\1007.pdf, page 3].

The applicant concluded that the fexofenadine HCl 30 mg ODT formulation was bioequivalent to the marketed 30 mg tablet in healthy adult subjects under fasted conditions. There was one subject who withdrew from the study because of personal reasons. One person experienced a headache withdrew from the study because of this adverse event. There were no serious adverse events [hpbio\hupharm\1007.pdf, pages 4, 54, 58].

4.3. Study M016455H/1008

Study M016455H/1008, a pivotal bioavailability study designed to compare the pharmacokinetics of the proposed ODT formulation administered under fasted conditions, both with and without water. It was a phase 1, open label, randomized, single-dose, two-period, two treatment, complete crossover study conducted in 54 healthy male and female patients, 18-45 years of age. Study treatments included the proposed oral disintegrating tablet formulation of fexofenadine HCl 30 mg administered under fasted conditions with 240 mL of water and the proposed oral disintegrating tablet formulation of fexofenadine HCl 30 mg administered under fasted conditions without water. Serial blood samples were collected over a 48-hour period after each treatment. There was a six-day washout between study periods [clinstat\clinsum.pdf, page 19; hpbio\hupharm\1008.pdf, pages 2-4]. Samples were taken at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36, and 48 hours post-dose [hpbio\hupharm\1008.pdf, page 3]. Subjects were housed at the study site from check-in on Day -1 until Day 3 [hpbio\hupharm\1008.pdf, pages 30-31]. Safety endpoints included adverse events, vital signs, physical examinations, laboratory studies, and ECGs [hpbio\hupharm\1008.pdf, page 3].

The applicant concluded that the 30 mg fexofenadine orally disintegrating tablet administered without water was bioequivalent to the tablet administered with water with respect to AUC(0-inf), but the upper limit of C_{max} was slightly outside of the bioequivalence bounds (90% CI: 100 to 127) [hpbio\hupharm\1008.pdf, page 58]. There were two subjects that discontinued the study prematurely due to adverse events. There was one serious adverse event, a subject that experienced a thermal burn and respiratory fume inhalation disorder [hpbio\hupharm\1008.pdf, page 5].

5. BRIEF REVIEW OF PROPOSED LABELING

Proposed package labeling has been included in this submission [labeling\proposed.pdf; labeling\contain.pdf; summary\summary.pdf, pages 9-31]. A brief review of proposed labeling was performed. Proposed labeling is similar in content to current labeling for Allegra Tablets and Allegra Oral Suspension. The labeling is provided in the format specified by the Physician Labeling Rule. A single package insert for Allegra Tablets, Allegra Oral Suspension, and Allegra Orally Disintegrating Tablets is proposed. Labeling comments are noted below.

The proposed labeling states that the product is designed to quickly disintegrate on the tongue,

Table 1. Summary of studies to receive clinical review, NDA 21-909 [clinstat/ci/insum.pdf, pages 27-29].

Study Number	Study Type	Treatment Groups	Treatment duration	Design	Number of subjects	Diagnosis, age of subjects	Materials submitted in this application
M106455H/1004	Pivotal food effect study	Marketed F 30 mg tablet, single dose, fasted conditions Proposed F 30 mg ODT, single dose, fasted and fed conditions Other prototype 30 mg ODTs, single dose, fasted and fed conditions, some without water	Single dose	Single center, randomized, open label, eight treatment, four-period, incomplete crossover	54	Healthy men and women, 18-45 years	Protocol Study report Tabulations No case report forms necessary
M106455H/1007	Pivotal bioequivalence study	Marketed F 30 mg tablet, single dose, fasted conditions Proposed F 30 mg ODT, single dose, fasted and fed conditions	Single dose	Single center, randomized, open label, two period, two-way crossover	54	Healthy men and women, 18-45 years	Protocol Study report Tabulations Case report form
M106455H/1008	Pivotal bioavailability study	Proposed F 30 mg ODT, single dose, fasted conditions with water Proposed F 30 mg ODT, single dose, fasted conditions without water	Single dose	Single center, randomized, open label, two period, two-way crossover	54	Healthy men and women, 18-45 years	Protocol Study report Tabulations Case report form

F = fexofenadine HCl

Appears This Way
 On Original

followed by swallowing with or without water. The label states that the product should be taken on an empty stomach and that it is not intended to be chewed. Labeling notes that the product may be taken with or without water.

Detailed label review will be performed later in the course of review of the NDA.

6. DSI REVIEW/AUDIT

DSI clinical audit will not be requested because no efficacy or safety studies were included in the development program for this drug product.

7. SUMMARY

This NDA is an application for an oral disintegrating tablet formulation of fexofenadine HCl. The applicant is Sanofi Aventis. The product contains fexofenadine HCl, 30 mg. The proposed indication is for the relief of symptoms associated with seasonal allergic rhinitis in children ~~and~~ and symptoms of CIU in children from ~~and~~. This application is an electronic submission. There are three pivotal clinical pharmacology studies submitted in support of this application. The studies are appropriately indexed and organized to allow review. The applicant has provided an Integrated Summary of Efficacy, Integrated Summary of Safety, copies of proposed labeling, and appropriate case report forms.

b(4)

The submission is adequate to allow clinical review. The submission is fileable.

8. TIME LINE FOR REVIEW

Write-up will be concomitant with the review process. The schedule for review is displayed in Table 2. Clinical review will focus primarily on safety and will be performed for each study before moving to the next study. Review of clinical pharmacology studies will be completed by March 16, 2007. The review of the ISS will take place next and will be complete by April 13, 2007. Label review will be complete by April 27, 2007. Draft review will be complete by May 11, 2007, approximately two weeks before the GRMP date for the completed and signed primary and secondary review.

Table 2. Proposed schedule for review of NDA 21-909.

Milestone	Target Date for Completion
Clinical pharmacology study M106455H/1004	2/16/07
Clinical pharmacology study M106455H/1007	3/2/07
Clinical pharmacology study M106455H/1007	3/16/07
ISS	4/13/07
Label Review	4/27/07
Draft Review Complete	5/11/07
Primary review complete and signed, GRMP date	5/29/07
Action Date, 10 months	7/29/07

9. COMMENTS FOR THE APPLICANT

There are no comments for the applicant.

Reviewed by:

Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Products

Badrul A. Chowdhury, M.D., Ph.D.
Director, Division of Pulmonary and Allergy Products

cc: Original NDA
HFD-570/Division File
HFD-570/Chowdhury/Division Director
HFD-570/Lee/Medical Reviewer
HFD-870/Roy/Clinical Pharmacology and Biopharmaceutics Reviewer
HFD-570/Peri/Chemist
HFD-570/Sancilio/Pharmacology Reviewer
HFD-570/L. Garcia/CSO

Appears This Way
On Original

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

/s/

Charles Lee
11/17/2006 08:46:27 AM
MEDICAL OFFICER

Badrul Chowdhury
11/17/2006 01:54:34 PM
MEDICAL OFFICER
I concur

Appears This Way
On Original