

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-963

MEDICAL REVIEW(S)

Clinical Team Leader Review Memorandum

Date : Friday October 13, 2006

To : NDA 21-963

From: Lydia I. Gilbert-McClain, MD, FCCP
Medical team leader, Division of Pulmonary and Allergy Products

Through: Badrul A. Chowdhury, MD PhD
Director, Division of Pulmonary and Allergy Products

Product: Fexofenadine hydrochloride oral suspension

Applicant: Sanofi-Aventis

Background/Administrative

NDA 21-963 Was submitted on December 15, 2005 under 505 (b) of the FD &C Act to obtain marketing approval for fexofenadine hydrochloride oral suspension for the treatment of symptoms associated with seasonal allergic rhinitis (SAR) and chronic idiopathic urticaria (CIU) in children 6 months to 11 years of age. The PDUFA goal date for this application is October 15, 2006.

Fexofenadine hydrochloride (ALLEGRA) is currently approved as tablets (NDA 20-872) and capsules (NDA 20-625) for the treatment of symptoms of SAR and CIU in adults and children 6 years of age and older. The Applicant previously conducted pharmacokinetic and safety studies in children > 6 months to 6 years of age in response to a Written Request. The Applicant developed a clinical formulation in order to conduct the studies to comply with the written request, but did not develop a formulation for marketing. Therefore, although the Division had adequate efficacy and safety information to approve fexofenadine hydrochloride for use in children down to 6 months of age, such approval was withheld because there was no age-appropriate formulation for children under 6 years of age at the time.

The Applicant has since developed an oral suspension with the primary objective of providing an age-appropriate formulation for pediatric patients less than 6 years of age. Given that safety and pharmacokinetic information is already available in patients 6 months of age and older, and efficacy for the treatment of symptoms of SAR and CIU has been established in adults and children 6 to 11 years of age, a bioequivalence program that compared the rate and extent of exposure of the fexofenadine hydrochloride suspension to fexofenadine hydrochloride tablets or capsules (the same dose of the tablet and the capsules are bioequivalent to each other) is all that would be needed from a clinical standpoint to support the efficacy of the oral suspension product. The development program was conducted under IND 51, 709 and the marketed fexofenadine hydrochloride 30 mg tablet was used as the reference product.

Safety information is obtained from the clinical pharmacology studies and the other safety and clinical pharmacology studies conducted previously in patients 6 months to < 6 years of age.

Chemistry, Manufacturing and Controls

The product is formulated as an oral suspension containing 6mg/ml of fexofenadine hydrochloride as the active ingredient. The formulation also includes sucrose and xylitol as sweeteners and an artificial raspberry cream flavor and several other excipients that have been previously used in other oral formulations. The product is packaged in [REDACTED] and 300 ml amber polyethylene terephthalate (PET) plastic bottles with a [REDACTED] seal.

During development of the suspension, an FDA field inspection conducted in November 2004, cited [REDACTED] the site where the analytical portion of the clinical pharmacology study was conducted for failed resuspension specifications. The FDA CMC review team upon evaluation of the field inspection report determined that the method used to assess resuspension of the formulation (the density assay) was not appropriate. The appropriate assay to use should have been the active assay method and with this method, the product had acceptable resuspension specifications. Of note, the density method to assess resuspension was subsequently abandoned at the [REDACTED] manufacturing site.

Clinical Pharmacology

Three pharmacokinetic studies were conducted (2 in adults and one in children 2 to 5 years of age) to evaluate the bioavailability, bioequivalence and food effect on the oral suspension formulation. The two studies in adults were conducted in male and female healthy volunteers 18 -45 years of age, and one bioavailability study was conducted in pediatric patients 2 – 5 years of age. The pediatric patients were those whose physician determined were candidates for antihistamine therapy for the treatment of allergic rhinitis. All three clinical pharmacology studies were single-dose open label studies and are summarized in the table below.

Study	Design	Population	N	*Results			
M016455I/ 1004	Open-label, randomized, single-dose, 2-treatment, 2-period crossover design comparing fexofenadine oral suspension 30 mg dose (6mg/ml) to Allegra® tablet 30 mg dose Objective: Bioequivalence	Male and female volunteers 18- 42 years	54		A	B	Ratio (CI)
				AUC _(0-∞)	680	638	93.8 (84.3 -104)
				C _{max}	97.2	103	106 (93.5 -119)
M016455I/ 1003	Same design as #1004 under fed and fasted conditions Objective: Food effect	Male and female volunteers 18-45 years	54		Fasted	Fed	
				AUC _(0-∞)	638	445	

				C_{max}	98.2	51.9
M)164551/ 1005	Open-label, single-dose (oral suspension 30 mg [6mg/ml]), multicenter study. Objective: Safety and PK	Pediatric patients 2 – 5 years eligible for antihistamine therapy	50	Mean C_{max} 224 ng/ml Mean $AUC_{(0-last)}$ =898 ng.h/ml Median t_{max} = 1 hr		
The results of the adult studies are reported as LS geometric means, and the results for the pediatric study are reported as means. Treatment A = Single dose 30 mg Fexofenadine HCl tablet (Reference) Treatment B = Single dose 30 mg fexofenadine as 5 l of 6 mg/ml suspension (test)						

Fexofenadine oral suspension 30 mg (6mg/ml) is bioequivalent to the fexofenadine 30 mg tablet in that the CI for the ratio of both the C_{max} and the $AUC_{(0-\infty)}$ for the oral suspension and the tablet is within 80 – 125%. There is a food effect noted following a high-fat breakfast with a 30% reduction in $AUC_{(0-\infty)}$ and 47% reduction in C_{max} .

From previous clinical pharmacology studies in pediatric patients 6 months to less than 6 years of age, and pharmacokinetic analysis from PK data in adults and pediatric subjects 6 to 11 years of age it was found that body weight and age affected the oral clearance and plasma concentrations of fexofenadine in pediatric subjects. Age was found to be the most significant factor for the PK in children. The most accurate dosing for patients 6 months to 2 years of age would take both age and body weight (in kg) into account however, given the extensive safety profile of fexofenadine and the complexity of a dosing regimen based on age and weight, the FDA clinical pharmacology team determined that the most appropriate dose would be 15 mg for children 6 months to < 2 years of age and 30 mg for children 2 to 5 years of age with normal renal function. In patients with decreased renal function, the dose should be halved.

Clinical Safety

Review of the safety data in the clinical pharmacology studies did not reveal any new safety signals with this product. A total of 50 pediatric subjects 2 -5years of age participated in the single-dose oral bioavailability study. There were no deaths, serious adverse events or withdrawals due to adverse events. Additional safety information in children 6 months to < 6 years of age is obtained from 534 pediatric patients 6 months to < 6 years of age in other clinical pharmacology and safety studies. The safety data from these studies did not reveal any safety signals.

Non-clinical Pharmacology and Toxicology

No additional pharmacology/toxicology information was required for this application.

Data Quality, Integrity, and Financial Disclosure

The clinical pharmacology studies were conducted in keeping with good clinical practice and in accordance with the appropriate regulations for human subjects protection. A Division of Scientific Investigation (DSI) audit of the analytical portion of study M0164551/1004 was conducted. The DSI inspection found discrepancies in 8 samples

from 4 subjects and also noted in their report that a study to demonstrate the lack of matrix effect in the fexofenadine assay was not conducted. DSI explained the problem with the 8 samples as follows: They noted that following the original analysis, the site ([REDACTED]) found that there were 63 samples with results above the limit of quantitation (i.e. > 150 ng/ml). Consequently, all these samples were re-assayed after a 3-fold dilution. The re-assay values of 55 of these 63 samples were found to be within 30% of the original values and 8 samples were significantly different (>30%) of the original values factoring in the 3-fold dilution. Based on this finding, DSI recommended that the 8 samples be re-assayed if feasible or be excluded from the analysis. The Applicant excluded the samples from the analysis and bioequivalence was still demonstrated with the excluded samples. Regarding the matrix effect, the Applicant responded to DSI's comment stating their intent to submit the required study report by August 30, 2006. This issue is not an approvability issue for the application and the applicant had already submitted validation data in the original NDA submission.

Pediatric Considerations

No additional pediatric studies are required since the Applicant already has conducted studies down to age 6 months (as part of a Written Request) and studies in pediatric patients less than 6 months of age are not appropriate since the diseases for which the drug is indicated do not exist in patients 0 – 6 months of age. Therefore, under PREA, the Applicant should be granted a waiver for studies in pediatric patients 0 - < 6 months of age.

Nomenclature

The Applicant proposed the name "Allegra® [REDACTED] Suspension." The inclusion of the term [REDACTED] Suspension" with the name was rejected by the DMETS reviewer because the term is not a recognized dosage form in the U.S. pharmacopeia. Moreover, although the suspension [REDACTED] DMETS recommended that the term [REDACTED] suspension" be changed Oral Suspension and the Applicant has agreed to this. Thus the product name would read "Allegra® Oral Suspension."

Labeling

The product package insert did not require a lot of changes. The clinical pharmacology section was updated to include the new information about the oral suspension including the food effect findings. The Applicant had proposed a weight-based dosing regimen for the patients 6 months to less than 2 years of age but given the wide safety margin for fexofenadine, the variability in the PK findings with age and weight and the complexity of the age/weight-based dosing recommendations, the clinical pharmacology team recommended that the dosing recommendation be 15 mg twice daily in patients 6 months to 2 years of age and 30 mg twice daily in patients 2 to 11 years of age. Half the dose is recommended for patients with decreased renal function. With respect to the container labels DMETS recommended that the concentration be written as 30 mg/5ml instead of [REDACTED]. They noted that since the dosage recommendation is 15 mg or 30 mg, the format of 30 mg/5ml would reduce the chances of dosing calculation errors. Additionally, they note that the concentration of most oral liquid pharmaceutical

preparations is expressed in 5 ml. The Applicant has responded and agreed to the Agency's labeling recommendations.

Summary/Recommendation

The Applicant has established bioequivalence of fexofenadine oral suspension 30 mg to the 30 mg fexofenadine tablet. The safety of the fexofenadine HCl in patients 6 months to 11 years of age is supported by the clinical safety studies, the extensive post-marketing safety information of fexofenadine in adults and older pediatric patients, and the pharmacokinetic data. The Applicant has addressed the issues identified in the DSI audit and there are no outstanding issues from other review disciplines.

Action

The regulatory action on this application will be APPROVAL.

**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/

Lydia McClain
10/13/2006 10:16:59 AM
MEDICAL OFFICER

Badrul Chowdhury
10/13/2006 11:34:08 AM
MEDICAL OFFICER
I concur

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-963
Submission Code	N-000
Letter Date	12/15/05
Stamp Date	12/16/05
PDUFA Goal Date	10/16/06
Reviewer Name	Charles E. Lee, M.D.
Review Completion Date	8/7/06
Established Name	Fexofenadine HCl
(Proposed) Trade Name	Allegra [REDACTED] Suspension
Therapeutic Class	H ₁ -Receptor Antagonist, Antihistamine
Applicant	Sanofi Aventis US
Priority Designation	S
Formulation	Suspension, 30 mg/5 mL (6 mg/mL)
Dosing Regimen	Seasonal allergic rhinitis, children 2 to [REDACTED] : 30 mg twice daily Chronic idiopathic urticaria, children 6 months to less than 2 years: 15 mg twice daily Chronic idiopathic urticaria, children 2 to [REDACTED] : 30 mg twice daily
Indication	Relief of symptoms associated with seasonal allergic rhinitis in children 2 to [REDACTED] of age Treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in children 6 months to [REDACTED]
Intended Population	Seasonal allergic rhinitis, children 2 to [REDACTED] Chronic idiopathic urticaria, children 6 months to [REDACTED] of age

Table of Contents

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	6
1.3.1 Brief Overview of Clinical Program	6
1.3.2 Efficacy	6
1.3.3 Safety	7
1.3.4 Dosing Regimen and Administration	8
1.3.5 Drug-Drug Interactions	9
1.3.6 Special Populations	9
2 INTRODUCTION AND BACKGROUND	10
2.1 PRODUCT INFORMATION	10
2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS	10
2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES	11
2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS	11
2.5 PRESUBMISSION REGULATORY ACTIVITY	11
3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES	12
3.1 CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE)	12
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	21
7.1.1 Deaths	22
7.1.2 Other Serious Adverse Events	22
7.1.3 Dropouts and Other Significant Adverse Events	23
7.1.5 Common Adverse Events	24
7.1.6 Less Common Adverse Events	29
7.1.7 Laboratory Findings	29
7.1.8 Vital Signs	31
7.1.9 Electrocardiograms (ECGs)	32
7.1.13 Withdrawal Phenomena and/or Abuse Potential	33
7.1.14 Human Reproduction and Pregnancy Data	34
7.1.16 Overdose Experience	34

Clinical Review
Charles E. Lee, M.D.
NDA 21-963, N-000, 12/15/05
Allegra (fexofenadine HCl) Suspension 30/ mg/5 mL (6 mg/mL)

7.1.17 Postmarketing Experience	34
7.2 ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS	38
7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety	38
7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety	42
7.2.3 Adequacy of Overall Clinical Experience	43
7.2.9 Additional Submissions, Including Safety Update	44
7.3 SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS	44
8 ADDITIONAL CLINICAL ISSUES	44
8.1 DOSING REGIMEN AND ADMINISTRATION	44
8.2 DRUG-DRUG INTERACTIONS	46
8.3 SPECIAL POPULATIONS	46
8.4 PEDIATRICS	47
8.6 LITERATURE REVIEW	47
8.7 POSTMARKETING RISK MANAGEMENT PLAN	47
9.4 LABELING REVIEW	47
9.5 COMMENTS TO APPLICANT	49

Table of Tables

Table 1 Pivotal clinical pharmacology studies, NDA 21-963 [clinstat\clinsum.pdf, pages 38-40].	14
Table 2. Mean PK parameters for fexofenadine, fasting and fed conditions, Study M0164551/1003 [hpbio\hupharm\1003.pdf, page 4]	17
Table 3. Mean PK parameters for fexofenadine, Study M0164551/1004 [hpbio\hupharm\1004.pdf, page 4]	18
Table 4. PK parameters for fexofenadine, patients 2-5 years of age, Study M0164551/1005 [hpbio\hupharm\1005.pdf, page 4]	19
Table 5. Adverse events leading to discontinuation, pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age (M0164551/1005, M0164551/1114, M0164551/3112, M016455T/1123, M016455T/3001, M016455T/3002) [clinstat\iss\iss.pdf, page 72].	24
Table 6. Adverse events in the pooled pivotal clinical pharmacology studies in adult subjects (M0164551/1003 and M0164551/1004) [clinstat\iss\iss.pdf, page 57].	25
Table 7. Adverse events occurring in pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age (M0164551/1005, M0164551/1114, M0164551/3112, M016455T/1123, M016455T/3001, M016455T/3002) [clinstat\iss\iss.pdf, page 60].	26
Table 8. Adverse events occurring at a frequency of 2% in pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age (M0164551/1005, M0164551/1114, M0164551/3112, M016455T/1123, M016455T/3001, M016455T/3002) [clinstat\iss\iss.pdf, page 60].	28
Table 9 Most frequently reported 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 82].	35
Table 10 Most frequently reported postmarketing spontaneous adverse events for fexofenadine HCl in patients less than 6 years of age [clinstat\iss\iss.pdf, page 84].	36
Table 11 Most frequently reported postmarketing spontaneous adverse events for fexofenadine HCl in patients 6 to less than 12 years of age [clinstat\iss\iss.pdf, page 87].	37
Table 12 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 91].	38
Table 13 Summary of pivotal clinical pharmacology studies providing safety information, NDA 21-963 [clinstat\clinsum.pdf, pages 38-40].	39
Table 14 Demographics in pivotal clinical pharmacology studies in adult subjects [clinstat\iss\iss.pdf, page 51].	40
Table 15 Demographics in pivotal clinical pharmacology studies in pediatric patients 6 to 11 years of age [clinstat\iss\iss.pdf, pages 51-52; clinstat\iss\isstable.pdf, pages 353, 355, 358].	41
Table 16 Demographics in supporting studies in pediatric patients 6 months to 5 years of age [clinstat\iss\iss.pdf, page 52].	41
Table 17 Extent of exposure in pediatric patients 6 to 11 years of age [clinstat\iss\iss.pdf, pages 48-49].	42
Table 18 Extent of exposure in pediatric patients 6 months to 5 years of age [clinstat\iss\iss.pdf, page 49].	42

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends an “Approval” action for this application, pending resolution of discrepancies found in a routine DSI audit of one of the pivotal clinical pharmacology studies.

The clinical pharmacology studies in this application support the efficacy of the applicant’s product. DSI audit revealed discrepancies between two assays of eight samples that had original levels above the upper limit of quantitation (>150 ng/mL) in study M0164551/1004. The applicant has re-assayed these samples and will be submitting a reanalysis of the data from this study. The Office of Clinical Pharmacology review team will be reviewing the reanalysis. 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 suspension with food decreased both the extent and rate of absorption. Labeling appropriately notes this significant decrease in bioavailability of fexofenadine in the fed state. Administration of fexofenadine HCl suspension to children from 2 to less than 6 years of age resulted in systemic exposures that were comparable to the 30 mg dose in children 6 to less than 12 years of age and the 60 mg dose in adults and children 12 years of age and older.

Safety data in this application support the safety of the proposed product. Safety data consisted of information from pivotal and supportive clinical pharmacology pivotal studies, 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.

1.2 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 were three pivotal bioavailability and bioequivalence studies in this application, Study M016455I/1003, Study M016455I/1004, and Study M016455I/1005. These studies were designed to support the efficacy of fexofenadine HCl suspension 30 mg/5 mL by assessing its relative bioavailability to the approved and currently marketed 30 mg Allegra Tablets and to determine if systemic exposures of fexofenadine in children were comparable to those in adults.

Safety of the product was supported by safety information from adult clinical pharmacology pivotal studies M016455I/1003 and M016455I/1004, and from pooled pediatric studies, including pivotal study M016455I/1005 and supportive studies M016455I/1005, M016455I/1114, M016455I/3112, M016455T/1123, M016455T/3001, and M016455T/3002. 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

The clinical pharmacology studies in this application support the efficacy of the applicant's product. DSI audit revealed discrepancies between two assays of eight samples that had original levels above the upper limit of quantitation (>150 ng/mL) in study M016455I/1004, however. The applicant has re-assayed these samples and will be submitting a reanalysis of the data from this study. The Office of Clinical Pharmacology review team will be reviewing the reanalysis.

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 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 product fell within 80% to 125% limits. Administration of fexofenadine HCl suspension with food decreased both the extent and rate of absorption. Labeling appropriately notes this significant decrease in bioavailability of fexofenadine in the fed state. Administration of fexofenadine HCl suspension to children from 2 to less than 6 years of age resulted in systemic exposures that were comparable to the 30 mg dose in children 6 to less than 12 years of age and the 60 mg dose in adults and children 12 years of age and older.

1.3.3 Safety

Safety data in this application support the safety of the proposed product.

The applicant's Integrated Summary of Safety consisted of a summary of safety information from adult clinical pharmacology pivotal studies M0164551/1003 and M0164551/1004, and from pooled pediatric studies, including pivotal study M0164551/1005 and supportive studies M0164551/1005, M0164551/1114, M0164551/3112, M016455T/1123, M016455T/3001, and M016455T/3002. 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. The database includes cases from clinical trials, postmarketing surveillance studies, spontaneous notifications, cases from regulatory authorities, and the published literature. The search was designed to capture all cases received through September 30, 2005 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, and patients with age unspecified but taking a 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 also 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."

There were no deaths in the pivotal clinical pharmacology studies in adult subjects or in the pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age. There were no serious adverse events in the pivotal clinical pharmacology studies in adult subjects. A total of four patients experienced serious adverse events in the pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age. No single serious adverse event was reported by more than one patient. These data did not identify a safety signal. Dropouts due to adverse events in the pivotal clinical pharmacology studies in adult subjects and in the pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age did not reveal a safety signal.

Dizziness and headache were the most frequent adverse events in the pooled pivotal clinical pharmacology studies in adult subjects. Adverse events occurring in pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age were fairly frequent and occurred at a higher frequency among patients in the placebo group (49.5%, 213/430) than in the fexofenadine HCl 15 mg (39.8%, 43/108) and fexofenadine HCl 30 mg (40.9%, 174/426) groups. The most common adverse events in patients in the fexofenadine HCl 15 mg group were vomiting, diarrhea, otitis media, and somnolence. The most common adverse events in patients in the fexofenadine HCl 30 mg group were vomiting, pyrexia, cough, otitis media, and diarrhea.

There was no dose ordering noted. Data from pooled pivotal clinical pharmacology studies in adult subjects and pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age did not suggest an association of adverse events and gender, race, or age.

Laboratory studies, vital signs, and ECGs in pooled pivotal clinical pharmacology studies in adult subjects and pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age showed no meaningful differences between treatment groups or among demographic subgroups and did not identify 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 data.

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. 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 proposed dose of Allegra Suspension for the treatment of symptoms of seasonal allergic rhinitis (SAR) in children 2 to years of age is 30 mg twice daily. A dose of 30 mg (5 mL) once daily is recommended as the starting dose in pediatric patients with decreased renal function.

The proposed dose of Allegra Suspension for the treatment of symptoms of chronic idiopathic urticaria (CIU) is 30 mg (5 mL) twice daily for patients . For pediatric patients with decreased renal function, the proposed starting doses are 30 mg (5 mL) once daily for patients

(see CLINICAL PHARMACOLOGY). The bottle is to be shaken well, before each use [labeling\proposed.pdf, pages 14-15].

Dosing of fexofenadine HCl in the pediatric population was previously addressed in an earlier NDA supplement. In order to determine the optimal dose for children 6 months to less than 2 years of age, a population PK analysis was performed based on data from adult subjects and pediatric patients. The modeling revealed that age and body weight are significant predictors of variability in fexofenadine pharmacokinetics in pediatrics. The model indicated that age is the most significant factor for the PK of fexofenadine in children. The Office of Clinical Pharmacology reviewer, Dr. Shinja Kim, determined that the appropriate dose for children 6 months to less than 2 years of age is 15 mg, and the appropriate dose in children 2 to 5 years of age (and up to less than 12 years old) is 30 mg, based on simplicity of dosing recommendation and the relative safety of fexofenadine.

The proposed dose should therefore be revised as follows:

The recommended dose of Allegra Suspension for the treatment of symptoms of SAR in children 2 to 11 years of age is 30 mg twice daily. A dose of 30 mg (5 mL) once daily is recommended as the starting dose in pediatric patients with decreased renal function.

The recommended dose of Allegra Suspension for the treatment of symptoms of CIU is 15 mg (2.5 mL) twice daily for patients 6 months to less than 2 years of age and 30 mg (5 mL) twice daily for patients 2 to 11 years of age. For pediatric patients 6 months to less than 2 years of age with decreased renal function, the proposed starting doses is 15 mg (2.5 mL) once daily and 30 mg (5 mL), once daily for 2 to 11 years of age.

Co-administration of fexofenadine HCl with food results in a decreased rate of absorption and a decreased extent of absorption of fexofenadine. 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 and appropriately address these issues.

1.3.5 Drug-Drug Interactions

The bioavailability of fexofenadine is decreased if administered within 15 minutes of aluminum and magnesium-containing antacids. The applicant's current labeling for Allegra Capsules and Tablets and the proposed labeling for Allegra Suspension state that the products should not be taken closely in time with aluminum and magnesium containing antacids. 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.

The proposed dose in pediatric patients with SAR and decreased renal function is of 30 mg (5 mL) once daily. The proposed dose for pediatric patients with CIU and decreased renal function

_____ To simplify dosing recommendations, the appropriate dose for children 6 months to less than 2 years of age is 15 mg, and the appropriate dose in children 2 _____ is 30 mg. These doses are to be administered once daily in children of these age groups with decreased renal function, consistent

with the recommendations of Dr. Shinja Kim and the Clinical Pharmacology and Biopharmaceutics review team.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The applicant has developed a suspension formulation of fexofenadine HCl 30 mg/5 mL (6 mg/mL). Fexofenadine hydrochloride is an antihistamine with selective H1-receptor antagonist activity. The application is for a suspension formulation of fexofenadine HCl and proposes to expand the current indication for relief of symptoms associated with SAR to include children 2 years of age and treatment of uncomplicated skin manifestations of CIU to include children 6 months of age [labeling\proposed.pdf, page 6]. The current indication is relief of symptoms associated with SAR in adults and children 6 years of age and older and treatment of uncomplicated skin manifestations of CIU in adults and children 6 years of age and older [labeling\approved.pdf, page 6].

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 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 BID and fexofenadine HCl 180 mg QD were approved for marketing in the United States for the treatment of symptoms of SAR in adults and children 12 years of age and over 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 BID 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 BID 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 QD was approved in the United States for the CIU indication on October 13, 2005.

Fexofenadine HCl suspension 30 mg/5 mL 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) and tablet formulations (NDA 20-872). 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 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 6-11 years of age

Fexofenadine HCl is also approved in the United States as a generic drug in tablet formulations by various manufacturers (ANDA 76-191, Barr Laboratories, ANDA 76-502, Dr. Reddy's Laboratories, and ANDA 76-447, Teva Pharmaceutical Industries).

2.4 Important Issues With Pharmacologically Related Products

Fexofenadine is an antihistamine with selective H₁-receptor antagonist activity. It is a "second generation" antihistamine with much lower potential for producing sedation than currently available "first generation" 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 [labeling\approved.pdf, page 7]. Grapefruit, orange, and apple juices reduce the bioavailability of fexofenadine when co-administered with these juices. The applicant's proposed labeling addresses these issues [labeling\proposed.pdf, pages 2, 8, 14].

2.5 Presubmission Regulatory Activity

Comments on the applicant's End of Phase 2 meeting package were faxed to the applicant on March 29, 2005 and a teleconference was held with the applicant on March 30, 2005 [Meeting minutes and Medical Officer Review, IND 51,709, N-092 MP, 2/24/05]. 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.

Comments on the applicant's Pre-NDA meeting package were faxed to the applicant on August 2, 2005 and a teleconference was held with the applicant on August 3, 2005. The Division

addressed the proposed INDICATIONS AND USAGE section. The Division concurred with the proposed content for the Integrated Summary of Efficacy and Integrated Summary of Safety. Although a separate package insert, as proposed by the applicant, was acceptable to the Division, the Division advised the applicant that a single package insert for all of the Allegra products would be preferable [Meeting minutes and Medical Officer Review, IND 51,709, N-099 MP, 7/1/05].

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Fexofenadine HCl 30 mg/5 mL Suspension, Oral is a buffered, white, aqueous suspension with a raspberry cream flavor. This product was developed to provide an oral dosage form of fexofenadine HCl suitable for pediatric applications. The oral suspension dosage form was selected because of improved taste (due to the low aqueous solubility of the active ingredient) and improved stability relative to solution formulations that were evaluated during development [summary\summary.pdf, page 45].

Fexofenadine HCl suspension is an immediate release oral suspension intended for twice-a-day oral dosing. Each 5-mL (1 teaspoon) dose contains 30 mg of fexofenadine HCl. The suspension is packaged in — amber polyethylene terephthalate (PET) plastic bottles

—
Drug substance is manufactured by Aventis Pharma, Frankfurt, Germany [summary\summary.pdf, page 50]. Drug product is manufactured by Sanofi Aventis Pharmaceuticals, Inc, Kansas City, Missouri [CMC\product\3.2.p-drug product.pdf, page 195].

The excipients in the proposed formulation include — glycol, edentate disodium, propylparaben, butylparaben, xanthan gum, poloxamer 407, titanium dioxide, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, artificial raspberry cream flavor, sucrose, xylitol, and purified water [CMC\product\3.2.p-drug product.pdf, page 002].

The final drug product formulation was used in all pivotal clinical trials [CMC\product\3.2.p-drug product.pdf, page 14].

As noted in the review of the End-of-Phase 2 meeting package, the Kansas City District Office of FDA issued a seven item FDA-483, Inspectional Observations, after an inspection performed on November 15-29, 2004 —, the manufacturer of Sanofi Aventis's fexofenadine suspension product [Establishment Inspection Report, —, Daniel S. Hutchison, Investigator; Medical Officer Review, Charles E. Lee, M.D., IND 51,709, N-092 MP, 2/24/05]. The FDA-483 reported that drug products that failed specifications were not rejected and that these products were shipped to a clinical trial. The report also indicates that the fexofenadine suspension drug product resuspended poorly as it aged. Mechanical shaking of the product for 30 to 60 minutes was required to sufficiently mix the sample for analysis. The inspection report

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 21-963 [clinstatclinsum.pdf, pages 38-40].

Study Number	Study Type	Treatment Groups	Treatment duration	Design	Number of subjects/patients	Diagnosis, age of subjects
M016455I/1003	Pivotal food effect study	F 5 mL of 30 mg/5 mL suspension, single dose, fasting conditions F 5 mL of 30 mg/5 mL suspension, single dose, fed conditions	Single dose	Single center, randomized, open label, two period, two-way crossover	54	Healthy men and women, 18-42 years
M016455I/1004	Pivotal bioavailability and bioequivalence study	F 5 mL of 30 mg/5 mL suspension, single dose, fasting conditions F 30 mg marketed tablet	Single dose	Single center, randomized, open label, two period, two-way crossover	54	Healthy men and women, 18-45 years
M016455EB/1005	Pivotal bioavailability study	F 5 mL of 30 mg/5 mL suspension, single dose, fasting conditions	Single dose	Multiple center, open label, no control, single period	50	Pediatric patients, 2-5 years, candidates for or history of antihistamine therapy

F = fexofenadine HCl

literature for information relevant to fexofenadine HCl 30 mg and the safety of fexofenadine HCl in general.

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 M016455I/1003 and M016455I/1004, and from pooled pediatric studies, including pivotal study M016455I/1005 and supportive studies M016455I/1005, M016455I/1114, M016455I/3112, M016455T/1123, M016455T/3001, and M016455T/3002. 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

There was one study center and analytical site in the United States for both clinical pharmacology studies in adults in this application, Studies M016455I/1003 and M016455I/1004. Pediatric study M016455I/1005 was conducted at six sites in the United States. DSI audit of the center performing the adult studies was requested. Study M016455I/1004 was audited. This was a pivotal single-dose bioequivalence study performed in adults under fasting conditions. There were no efficacy or safety studies in the development program for this drug product.

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\1004.pdf, pages 1, 240]

The analytical site was:

DSI audit revealed discrepancies between two assays of eight samples that had original levels above the upper limit of quantitation (>150 ng/mL) and that there was no study performed to show lack of matrix effect in the assay [Division of Scientific Investigations Review, Martin Yau, Ph.D., NDA 21-963, N-000, 12/15/05]. The applicant has re-assayed these samples and will be submitting a reanalysis of the data from this study. The Office of Clinical Pharmacology review team will be reviewing the reanalysis.

4.5 Compliance with Good Clinical Practices

The three pivotal clinical pharmacology studies in this application were conducted in accordance with Good Clinical Practices [hpbio\hupharm\1003.pdf, pages 001, 018; hpbio\hupharm\1004.pdf, pages 001, 019; hpbio\hupharm\1005.pdf, pages 001, 020]. The applicant certified that they did not use and would not use 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 1-17].

5 CLINICAL PHARMACOLOGY

There were three pivotal bioavailability and bioequivalence studies in this application, Study M0164551/1003, Study M0164551/1004, and Study M0164551/1005. They are described briefly below. A detailed review of the results may be found in Dr. Shinja Kim's clinical pharmacology and biopharmaceutics review [Clinical Pharmacology and Biopharmaceutics Review, S. Kim, Ph.D., NDA 21-963, N-000, 12/15/05].

Study M0164551/1003 was a pivotal clinical pharmacology study that compared the bioavailability of the to-be-marketed fexofenadine suspension under fed and fasted conditions. It was an open-label, randomized, single-dose, two-way, two-period, complete crossover study conducted in 54 healthy male and female adult subjects between 18 and 45 years of age [hpbio\hupharm\1003.pdf, pages 001-005, 027]. Study treatments were 5 mL of the 30 mg/5 mL

Clinical Review

Charles E. Lee, M.D.

NDA 21-963, N-000, 12/15/05

Allegra (fexofenadine HCl) Suspension 30/ mg/5 mL (6 mg/mL)

fexofenadine HCl suspension administered under fasting conditions and 5 mL of the 30 mg/5 mL fexofenadine HCl suspension administered after a high fat breakfast [hpbio\hupharm\1003.pdf, pages 027-028]. 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\1003.pdf, page 023]. Safety endpoints included adverse events, vital signs, physical examinations, clinical laboratory studies, and ECGs [hpbio\hupharm\1003.pdf, page 034]. There were five withdrawals from the study. There were four subjects who withdrew consent and one patient who withdrew due to adverse event of abdominal pain, headache, dysgeusia, and nausea [hpbio\hupharm\1003.pdf, page 004]. There were no serious adverse events [hpbio\hupharm\1003.pdf, page 055]. Results of Study M0164551/1003 are summarized below in Table 2.

Table 2. Mean PK parameters for fexofenadine, fasting and fed conditions, Study M0164551/1003
[hpbio\hupharm\1003.pdf, page 4]

PK Parameter	Fexofenadine HCl suspension, 30 mg/5 mL Single dose, 5 mL = 30 mg	Fexofenadine HCl suspension, 30 mg/5 mL Single dose, 5 mL = 30 mg	Ratio, % (90% CI) Fed/Fasted
	Fasting State	Fed State	
AUC _{0-inf} , ng.hr/mL (n = 47)	638	445	69.7 (64.0, 76.0)
C _{max} , ng/mL (n = 50)	98.2	51.9	52.9 (47.9, 58.3)
T _{max} , h (n = 50)	1.0	2.5	--
t _{1/2} (n = 48)	12.2	13.7	--

Administration of fexofenadine HCl suspension with food decreased both the extent and rate of absorption.

Reviewer comment:

The degree of food effect is greater than that noted for Allegra Tablets, 180 mg, where the extent of absorption was decreased by 21% and the rate of absorption was decreased by 20% [labeling\approved.pdf, page 2]. The food effect for the suspension has been added to the proposed label. The Information for Patients subsection of the approved labeling and proposed labeling note this interaction [labeling\approved.pdf, page 7, 13; labeling\proposed.pdf, pages 8, 14].

M0164551/1004 was an open label, randomized, single dose, two-period, two-way crossover study designed to establish the bioequivalence of 30 mg fexofenadine when administered as the to-be-marketed suspension relative to the marketed 30 mg fexofenadine tablet under fasting conditions. There were 54 healthy adult male and female subjects, 18 to 45 years of age, enrolled in the study. Study treatments were 5 mL of the 30 mg/5 mL fexofenadine HCl suspension and one 30 mg marketed fexofenadine HCl tablet [hpbio\hupharm\1004.pdf, pages 27-28]. 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. Subjects were housed at the study site from check-in on Day -1 until Day 3 [hpbio\hupharm\1004.pdf, page 031]. Safety endpoints included adverse events, vital signs, physical examinations, laboratory studies, and ECGs [hpbio\hupharm\1004.pdf, pages 033-034]. There was one subject who was lost to follow-up. There were no withdrawals from the

study due to adverse events and no serious adverse events [hpbio\hupharm\1004.pdf, pages 004-005]. Results of Study M016455I/1004 are summarized below in Table 3.

Table 3. Mean PK parameters for fexofenadine, Study M016455I/1004 [hpbio\hupharm\1004.pdf, page 4]

PK Parameter	Fexofenadine HCl 30 mg tablet Single dose	Fexofenadine HCl suspension, 30 mg/5 mL Single dose, 5 mL = 30 mg	Ratio, % (90% CI) B/A
	Treatment A N = 53	Treatment B N = 53	
AUC _{0-inf} , ng.hr/mL	680	638	93.8 (84.3, 104)
C _{max} , ng/mL	97.2	103	106 (93.5, 119)
T _{max} , h	1.5	1.0	--
t _{1/2}	11.0	11.0	--

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

Reviewer comment:

The two formulations studied were bioequivalent. However, DSI audit revealed discrepancies between two assays of eight samples that had original levels above the upper limit of quantitation (>150 ng/mL) and that there was no study performed to show lack of matrix effect in the assay [Division of Scientific Investigations Review, Martin Yau, Ph.D., NDA 21-963, N-000, 12/15/05]. The applicant has re-assayed these samples and will be submitting a reanalysis of the data from this study. The Office of Clinical Pharmacology review team will be reviewing the reanalysis.

Study M016455I/1005 was a phase 1, open label, single period, single dose, multicenter study designed to characterize the pharmacokinetics of 30 mg fexofenadine when administered as a to-be-marketed suspension under fasted conditions in pediatric patients 2 to 5 years of age. The secondary objective of the study was to evaluate the safety and tolerability of fexofenadine suspension in these patients. There were 50 male and female patients, 2 to 5 years of age, enrolled in the study. There were six study sites, all in the United States. Patients had been determined by their physician to be a candidate for antihistamine therapy for the treatment of allergic rhinitis or to have tolerated a therapeutic course of antihistamine therapy for allergic rhinitis without adverse effects. Study treatment was 5 mL of the 30 mg/5 mL fexofenadine HCl suspension [hpbio\hupharm\1005.pdf, page 028]. Serial blood samples were collected at pre-dose, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose [hpbio\hupharm\1005.pdf, pages 036-037]. Safety endpoints included adverse events, vital signs, physical examinations, laboratory studies, and ECGs [hpbio\hupharm\1005.pdf, pages 001-004]. There were no withdrawals from the study and no serious adverse events [hpbio\hupharm\1005.pdf, page 004]. Results of Study M016455I/1005 are summarized below in Table 4.

Table 4. PK parameters for fexofenadine, patients 2-5 years of age, Study M0164551/1005 [hpbio/hupharm\1005.pdf, page 4]

PK Parameter	Fexofenadine HCl suspension, 30 mg/5 mL Single dose, 5 mL = 30 mg N = 50
AUC _{0-last} , ng.hr/mL	898
C _{max} , ng/mL	224
T _{max} , h	1.0

Reviewer comment:

PK parameters for the fexofenadine suspension were fairly similar to PK parameter estimates based on population PK modeling and obtained using 30 mg fexofenadine granulation powder, where the AUC was 845 ng.h/mL and the C_{max} was 145 ng/mL [Clinical Pharmacology and Biopharmaceutics Review, Shinja Kim, Ph.D., NDA 20-872, SE8-011, 11/18/02].

In summary, these results support the efficacy of fexofenadine suspension, 30 mg/5 mL in the treatment of symptoms of SAR in children 2 to less than 6 years of age and CIU in children 6 months to less than 6 years of age. The suspension was bioequivalent to the marketed 30 mg Allegra Tablets and the proposed 30 mg dose in this age group resulted in systemic exposures that were comparable to the 30 mg dose in children 6 to less than 12 years of age and the 60 mg dose in adults and children 12 years of age and older. DSI audit revealed discrepancies between two assays of eight samples that had original levels above the upper limit of quantitation (>150 ng/mL) in study M0164551/1004. The applicant has re-assayed these samples and will be submitting a reanalysis of the data from this study. The Office of Clinical Pharmacology review team will be reviewing the reanalysis.

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 product fell within 80% to 125% limits. Administration of fexofenadine HCl suspension with food decreased both the extent and rate of absorption. Labeling appropriately notes this significant decrease in bioavailability of fexofenadine in the fed state. Administration of fexofenadine HCl suspension to children from 2 to less than 6 years of age resulted in systemic exposures that were comparable to the 30 mg dose in children 6 to less than 12 years of age and the 60 mg dose in adults and children 12 years of age and older.

It should be noted that DSI audit revealed discrepancies between two assays of eight samples that had original levels above the upper limit of quantitation (>150 ng/mL) in study M0164551/1004. As noted above, the applicant has re-assayed these samples and will be submitting a reanalysis of the data from this study. The Office of Clinical Pharmacology review team will be reviewing the reanalysis.

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. Shinja Kim's clinical pharmacology review [Clinical Pharmacology and Biopharmaceutics Review, S. Kim, Ph.D., NDA 21-963, N-000, 12/15/05].

6.1 Indication

The current indication for Allegra is as follows:

Seasonal Allergic Rhinitis

ALLEGRA is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 6 years of age and older. Symptoms treated effectively were sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes.

Chronic Idiopathic Urticaria

ALLEGRA is indicated for treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children 6 years of age and older. It significantly reduces pruritus and the number of wheals.

The applicant proposes to revise the indication to read:

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 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 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.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The applicant's Integrated Summary of Safety consisted of a summary of safety information from adult clinical pharmacology pivotal studies M016455I/1003 and M016455I/1004, and from pooled pediatric studies, including pivotal study M016455I/1005 and supportive studies M016455I/1005, M016455I/1114, M016455I/3112, M016455T/1123, M016455T/3001, and M016455T/3002. 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. The database includes cases from clinical trials, postmarketing surveillance studies, spontaneous notifications, cases from regulatory authorities, and the published literature. The search was designed to capture all cases received through September 30, 2005 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, and patients with age unspecified but taking a 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 also 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."

There were no deaths in the pivotal clinical pharmacology studies in adult subjects or in the pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age. There were no serious adverse events in the pivotal clinical pharmacology studies in adult subjects. A total of four patients experienced serious adverse events in the pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age. No single serious adverse event was reported by more than one patient. These data did not identify a safety signal. Dropouts due to adverse events in the pivotal clinical pharmacology studies in adult subjects and in the pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age did not reveal a safety signal.

Dizziness and headache were the most frequent adverse events in the pooled pivotal clinical pharmacology studies in adult subjects. Adverse events occurring in pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age were fairly frequent and occurred at a higher frequency among patients in the placebo group (49.5%, 213/430) than in the fexofenadine HCl 15 mg (39.8%, 43/108) and fexofenadine HCl 30 mg (40.9%, 174/426) groups. The most common adverse events in patients in the fexofenadine HCl 15 mg group were vomiting, diarrhea, otitis media, and somnolence. The most common adverse events in patients

in the fexofenadine HCl 30 mg group were vomiting, pyrexia, cough, otitis media, and diarrhea. There was no dose ordering noted. Data from pooled pivotal clinical pharmacology studies in adult subjects and pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age did not suggest an association of adverse events and gender, race, or age.

Laboratory studies, vital signs, and ECGs in pooled pivotal clinical pharmacology studies in adult subjects and pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age showed no meaningful differences between treatment groups or among demographic subgroups and did not identify 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 data.

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.

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.

7.1.1 Deaths

There were no deaths in the pivotal clinical pharmacology studies in adult subjects or in the pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age [clinstat\iss\iss.pdf, page 70]. The applicant's search of the medical literature for safety information related to fexofenadine HCl identified no deaths [clinstat\other\literature_table.pdf, pages 1-40]. The applicant's safety update identified no deaths [NDA 21-963, N-000 SU, 4/13/06, update\update.pdf, page 7].

Reviewer comment:

These data do not identify a safety signal.

7.1.2 Other Serious Adverse Events

There were no serious adverse events in the pivotal clinical pharmacology studies in adult subjects (M016455I/1003 and M016455I/1004) [clinstat\iss\iss.pdf, page 72].

A total of four patients experienced serious adverse events in the pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age. No single serious adverse event was reported by more than one patient. The frequency of serious adverse events was 0.5% (2/430) for

placebo, 0% (0/108) for fexofenadine HCl 15 mg, and 0.5% (2/426) for fexofenadine HCl 30 mg. These serious adverse events are briefly summarized below [clinstat\iss\iss.pdf, pages 74-75]:

1. Bronchospasm requiring hospitalization in a 14-month old male (Patient 0109/00004) with a history of reactive airways disease. The patient wheezing started three days before receiving a single dose of fexofenadine HCl 30 mg.
2. Worsening of preexisting asthma requiring hospitalization in a 4 year old female (Patient 1374/00009) who was receiving fexofenadine HCl 30 mg twice daily
3. Hypersensitivity reaction with generalized itching, sneezing, facial flushing, coughing, and wheezing, in a three year old male five minutes after receiving the first dose of placebo study treatment. The patient's symptoms were treated with oral cetirizine. The patient continued study medication until two days later.
4. Respiratory syncytial virus infection requiring hospitalization in a 9 month old male treated with placebo study treatment.

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 1-40]. The applicant's safety update identified one serious adverse event, a male patient of unknown age who developed nephrotic syndrome. This patient was taking two medications for benign prostate hypertrophy and is likely to have not been a pediatric patient [NDA 21-963, N-000 SU, 4/13/06, update\update.pdf, page 9].

Reviewer comment:

These data do not identify a safety signal.

7.1.3 Dropouts and Other Significant Adverse Events

There was one dropout from the pivotal clinical pharmacology studies in adult subjects due to an adverse event. The subject (Patient 00001/1053) was an 18-year old male who discontinued because of nausea. The patient also had abdominal pain and headache. No treatment was necessary and the events resolved spontaneously [clinstat\iss\iss.pdf, page 70].

Adverse events leading to discontinuation in pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age are summarized in Table 5 below. The frequency of discontinuation due to adverse events in patients treated with placebo (6.0%, 26/430) was greater than that in patients treated with fexofenadine HCl 15 mg (2.8%, 3/108) or fexofenadine HCl 30 mg (3.5%, 15/426) [clinstat\iss\iss.pdf, page 72].

Table 5. Adverse events leading to discontinuation, pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age (M016455I/1005, M016455I/1114, M016455I/3112, M016455T/1123, M016455T/3001, M016455T/3002) [clinstatlissliss.pdf, page 72].

Adverse event	Placebo N = 430		Fexofenadine HCl 15 mg N = 108		Fexofenadine HCl 30 mg N = 426		Fexofenadine HCl Total N = 534	
	n	(%)	n	(%)	n	(%)	n	(%)
All patients with adverse events	26	(6.1)	3	(2.8)	15	(3.5)	18	(3.4)
Gastroenteritis viral	0	(0)	1	(0.9)	5	(0.5)	3	(0.6)
Otitis media	3	(0.7)	1	(0.9)	2	(0.5)	3	(0.6)
Asthma	2	(0.5)	0	(0)	2	(0.5)	2	(0.4)
Cough	2	(0.5)	1	(0.9)	0	(0)	1	(0.2)
Viral infection	2	(0.5)	0	(0)	1	(0.2)	1	(0.2)
Upper respiratory tract infection	5	(1.2)	0	(0)	0	(0)	0	(0)
No adverse event	2	(0.5)	0	(0)	0	(0)	0	(0)
Urticaria	5	(0.5)	0	(0)	0	(0)	0	(0)

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 1-40]. The applicant's safety update identified no other significant adverse events [NDA 21-963, N-000 SU, 4/13/06, 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

In the pivotal clinical pharmacology studies conducted in adult subjects, the investigator observed subjects for adverse events (local or systemic) and instructed subjects to report any events that occurred during the study. [hpbio\hupharm\1003.pdf, page 32; hpbio\hupharm\1004.pdf, page 32]

Elicitation of adverse event data in the pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age is described below. The investigator observed subjects for adverse events (local or systemic) and instructed subjects and their legally authorized representatives to report any events that occurred during the study in study M016455I/1005 [hpbio\hupharm\1005.pdf, page 34]. Adverse events were monitored throughout the single dose clinical pharmacology studies M016455I/1114 and M016455T/1123 [hpbio\hupharm\m016455i_1114_synopsis.pdf, page 2; Medical Officer Review, Charles E. Lee, M.D., NDA 20-872, SE8-003, 7/12/00; hpbio\hupharm\m016455i_1123_synopsis.pdf, page 2]. Adverse events were monitored, but were not recorded in patient diaries in clinical safety and efficacy study M016455I/3112 [clinstat\3112synopsis.pdf, page 2; Medical Officer Review, Charles E. Lee, M.D., NDA 20-872, SE8-003, 7/12/00]. Adverse events were recorded in a diary

record in safety and efficacy studies M016455T/3001 and M016455T/3002 [clinstat\3001synopsis.pdf, page 2; Medical Officer Review, Charles E. Lee, M.D., NDA 20-625, SE8-012, 11/20/02; clinstat\3002synopsis.pdf, page 2; Medical Officer Review, Charles E. Lee, M.D., NDA 20-625, SE8-012, 11/20/02].

Adverse events for pivotal clinical pharmacology studies M016455I/1004 and M016455I/1003 in adult subjects were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 7.1. Pivotal clinical pharmacology study M016455I/1005 in pediatric subjects was coded using MedDRA Version 8.0 [clinstat\iss\iss.pdf, page 56].

Adverse events analyzed in studies M016455I/1005, M016455I/1114, M016455I/3112, M016455T/1123, M016455T/3001, and M016455T/3002 were coded using the Hoechst Adverse Reaction Terminology System (HARTS) dictionary. HARTS is primarily a modified version of the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) dictionary [clinstat\iss\iss.pdf, page 56].

Adverse event data in studies not originally coded using MedDRA recoded using MedDRA. All adverse events for the studies analyzed in the applicant's Integrated Summary of Safety were reported in MedDRA Version 8.0 [clinstat\iss\iss.pdf, page 56].

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 6. Dizziness was the most frequent adverse event in these studies and all cases of dizziness and the one case of syncope occurred in Period 1 of study M016455I/1004. The applicant notes that scheduled dosing was delayed from 7:00 AM until 8:00 AM due to late delivery of study drug and that the longer fasting interval may have contributed to the reports of dizziness and syncope (fainting) [clinstat\iss\iss.pdf, pages 56-57].

Table 6. Adverse events in the pooled pivotal clinical pharmacology studies in adult subjects (M016455I/1003 and M016455I/1004) [clinstat\iss\iss.pdf, page 57].

Adverse event	Fexofenadine HCl 30 mg	
	N = 107	
All subjects with adverse events	10	(9.4)
Dizziness	6	(5.6)
Headache	2	(1.9)
Abdominal pain	1	(0.9)
Dysgeusia	1	(0.9)
Nausea	1	(0.9)
Syncope	1	(0.9)

Adverse events occurring in pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age are summarized in Table 7 below. Adverse events were fairly frequent and occurred at a higher frequency among patients in the placebo group (49.5%, 213/430) than in the fexofenadine HCl 15 mg (39.8%, 43/108) and fexofenadine HCl 30 mg (40.9%, 174/426) groups. The most common adverse events in patients in the fexofenadine HCl 15 mg group were vomiting, diarrhea, otitis media, and somnolence. The most common adverse events in patients

in the fexofenadine HCl 30 mg group were vomiting, pyrexia, cough, otitis media, and diarrhea. There was no dose ordering noted [clinstat\iss\iss.pdf, pages 59-60].

Table 7. Adverse events occurring in pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age (M016455I/1005, M016455I/1114, M016455I/3112, M016455T/1123, M016455T/3001, M016455T/3002) [clinstat\iss\iss.pdf, page 60].

Adverse event	Placebo N = 430		Fexofenadine HCl 15 mg N = 108		Fexofenadine HCl 30 mg N = 426		Fexofenadine HCl Total N = 534	
	n	(%)	n	(%)	n	(%)	n	(%)
All patients with adverse events	213	(49.5)	43	(39.8)	174	(40.9)	217	(40.6)
Vomiting	37	(8.6)	13	(12.0)	18	(4.2)	31	(5.8)
Pyrexia	30	(7.0)	2	(1.9)	19	(4.5)	21	(3.9)
Cough	14	(3.3)	2	(1.9)	17	(4.0)	19	(3.6)
Otitis media	14	(3.3)	3	(2.8)	16	(3.8)	19	(3.6)
Diarrhea	11	(2.6)	4	(3.7)	12	(2.8)	16	(3.0)
Rhinorrhea	4	(0.9)	1	(0.9)	9	(2.1)	10	(1.9)
Upper respiratory tract infection	17	(4.0)	1	(0.9)	9	(2.1)	10	(1.9)
Viral infection	12	(2.8)	1	(0.9)	8	(1.9)	9	(1.7)
Nasopharyngitis	6	(1.4)	1	(0.9)	7	(1.6)	8	(1.5)
Rhinitis allergic	3	(0.7)	2	(1.9)	6	(1.4)	8	(1.5)
Headache	9	(2.1)	0	(0)	7	(1.6)	7	(1.3)
Abdominal pain upper	6	(1.4)	0	(0)	6	(1.4)	6	(1.1)
Sinusitis	2	(0.5)	2	(1.9)	4	(0.9)	6	(1.1)
Somnolence	1	(0.2)	3	(2.8)	3	(0.7)	6	(1.1)
Excoriation	1	(0.2)	0	(0)	5	(1.2)	5	(0.9)

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 1-40]. The applicant's safety update identified no safety signal for adverse events [NDA 21-963, N-000 SU, 4/13/06, 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 (10.5%, 4/38) that reported adverse events than males (8.7%, 6/69). The most commonly reported adverse event reported by patients of both genders was dizziness, which was reported by 7.9% (3/38) of female subjects and by 4.35% (3/69) of male subjects. The remaining adverse events were reported by one subject each in either gender subgroup [clinstat\iss\iss.pdf, page 62].

In pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age, female patients had a higher frequency of adverse events (placebo 50.5%, 99/196; fexofenadine HCl 40.3%, 94/233) than males (placebo 48.7%, 114/234; fexofenadine HCl 40.9%, 123/301). Vomiting was the most frequent adverse event reported for females (placebo 8.7%, 17/196; fexofenadine HCl 45.2%, 12/233) than in males (placebo 8.6%, 20/234; fexofenadine HCl 6.3%, 19/301). The frequencies of adverse events among male and female patients treated with

fexofenadine were fairly similar and within the range of variation expected with small numbers of patients [clinstat\iss\iss.pdf, page 63].

Reviewer comments:

The safety data for these open label and uncontrolled clinical pharmacology studies in adults do not suggest an association of adverse events and gender.

The safety data for the pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age 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 (89.7%, 96/107). It was not possible for the applicant to draw meaningful conclusion regarding the distribution of adverse events by race [clinstat\iss\iss.pdf, page 64].

In pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age, the frequencies of patients with adverse events were higher for patients receiving placebo than for patients receiving fexofenadine HCl in all racial subgroups—White, Black, and Other. The frequencies of adverse events in patients of White, Black, and Other races who were treated with fexofenadine were fairly similar and within the range of variation expected with small numbers of patients [clinstat\iss\iss.pdf, pages 65-66].

Reviewer comments:

These safety data do not suggest an association of adverse events and race.

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 67].

In the pivotal and supportive studies in pediatric patients, the frequencies of adverse events were higher for subjects receiving placebo than for subjects receiving fexofenadine HCl in patients 6 months to less than 2 years of age and in patients 2 years to 5 years of age.

For patients 6 months to less than 2 years of age, the most frequently reported adverse event was vomiting for both the placebo group and the fexofenadine HCl treatment groups. For patients 2 to 5 years of age, pyrexia was the most frequently reported adverse event in both placebo and fexofenadine HCl treatment groups. Incidences of adverse events in patients treated with fexofenadine in the two age groups were fairly similar and within the range of variation expected with small numbers of patients [clinstat\iss\iss.pdf, pages 67-68].

Reviewer comments:

These safety data do not suggest an association of adverse events and age.

7.1.5.4 Common adverse event tables

This section addresses the proposed adverse event table to be added to the ADVERSE REACTIONS section of the label. Adverse events in the pooled pivotal clinical pharmacology studies in adult subjects is not included in proposed labeling for the product.

Adverse events occurring at a frequency of greater than 2% in pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age are summarized in Table 8 below. The most common adverse events for fexofenadine HCl overall were vomiting, pyrexia, diarrhea, cough, otitis media, diarrhea, rhinorrhea, upper respiratory tract infections, and somnolence. Adverse events occurring more commonly for fexofenadine overall than for placebo included cough, otitis media, diarrhea, rhinorrhea, and somnolence. Frequencies of these adverse events were fairly similar, however, and as noted above, there was no dose ordering [clinstat\iss\iss.pdf, pages 59-60].

Table 8. Adverse events occurring at a frequency of 2% in pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age (M016455I/1005, M016455I/1114, M016455I/3112, M016455T/1123, M016455T/3001, M016455T/3002) [clinstat\iss\iss.pdf, page 60].

Adverse event	Placebo N = 430		Fexofenadine HCl 15 mg N = 108		Fexofenadine HCl 30 mg N = 426		Fexofenadine HCl Total N = 534	
	n	(%)	n	(%)	n	(%)	n	(%)
All patients with adverse events	213	(49.5)	43	(39.8)	174	(40.9)	217	(40.6)
Vomiting	37	(8.6)	13	(12.0)	18	(4.2)	31	(5.8)
Pyrexia	30	(7.0)	2	(1.9)	19	(4.5)	21	(3.9)
Cough	14	(3.3)	2	(1.9)	17	(4.0)	19	(3.6)
Otitis media	14	(3.3)	3	(2.8)	16	(3.8)	19	(3.6)
Diarrhea	11	(2.6)	4	(3.7)	12	(2.8)	16	(3.0)
Rhinorrhea	4	(0.9)	1	(0.9)	9	(2.1)	10	(1.9)
Upper respiratory tract infection	17	(4.0)	1	(0.9)	9	(2.1)	10	(1.9)
Somnolence	1	(0.2)	3	(2.8)	3	(0.7)	6	(1.1)

Reviewer comment:

This reviewer concurs with the applicant's summary of adverse events as represented in this table and its inclusion in the ADVERSE REACTIONS section of the product label.

7.1.5.5 Identifying common and drug-related adverse events

The applicant drew no conclusions on causality of the adverse events.

Reviewer comment:

The small differences in the frequencies of adverse events among treatment groups in these studies are not likely to be clinically meaningful. 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.

All adverse events occurring in pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age were examined by this reviewer. Adverse events occurring at frequencies of 2% or less in these studies were representative of what might be expected by chance in a group of infants and children of these ages. They included events such as constipation, rash, diaper dermatitis, teething, croup, gastroenteritis, otitis media, and respiratory tract congestion. These less common adverse events occurred at similar frequencies among the placebo and fexofenadine HCl treatment groups [clinstat\iss\isstable.pdf, pages 27-31].

Reviewer comment:

Data for less common adverse events do not suggest a safety signal attributable to fexofenadine HCl.

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, clinical chemistry evaluations, and urinalyses performed in the pooled pivotal clinical pharmacology studies in adult subjects, studies M016455I/1004 and M016455I/1003 and in pooled pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age, studies M016455I/1005, M016455I/1114, M016455I/3112, and M016455T/1123. Laboratory studies were not performed in supportive studies M016455T/3001 and M016455T/3002 in pediatric subjects 6 months to less than 2 years of age [clinstat\iss\iss.pdf, page 97].

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 100-101].

The mean change from baseline in hematology and serum chemistry values in pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age were small in the placebo and fexofenadine HCl treatment groups. There were no meaningful differences between the changes from baseline in the fexofenadine HCl group or between the fexofenadine HCl and placebo treatment groups [clinstat\iss\iss.pdf, pages 102-103].

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 and for the pooled pivotal and supportive studies in pediatric subjects 6 months to 5 years of age. These analyses did not reveal any risks associated with the use of fexofenadine HCl for any gender, race, or age group [clinastat\iss\iss.pdf, pages 111-125].

Reviewer comment:

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

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

There was one subject in the pooled pivotal clinical pharmacology studies in adults who had a clinically significant abnormal (CSA) laboratory value. Subject 0001/01019 was a 45-year-old White female in M016455I/1004 who had a SGPT value of 57.0 U/L at baseline that increased to 121.0 U/L at post-study. Other post-study laboratory findings for this subject were unremarkable. A follow-up evaluation performed 9 days after study conclusion indicated the SGPT value had returned to 50.0 U/L [clinstat\iss\iss.pdf, pages 105-106].

There were 10 patients in pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age with CSA LDH values (6.4%, 10/344), compared with no patients in the placebo groups (0%, 0/231). The applicant notes that all the patients with abnormal LDH values were from one study (M016455T/1123), which did not include a placebo group. Values at baseline already met the criterion for a CSA value (>675 IU/L) for all but one of these patients and, with the exception of 1 patient, changes at the end of study were small and therefore continued to meet the criteria for a CSA value. For absolute neutrophils, 6.5 % (4/62) patients in the placebo treatment group and 11.2% (19/170) of subjects in the total fexofenadine HCl treatment group had absolute neutrophil values that met CSA criteria ($<1.5 \times 10^9$ /L). Most of these patients had low neutrophil counts at baseline combined with relative increases of absolute lymphocyte counts, which indicated that the patients may have had viral infections [clinstat\iss\iss.pdf, pages 108-110].

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 and for the pooled pivotal and supportive studies in pediatric subjects 6 months to 5 years of age. These analyses did not reveal any risks associated with the use of fexofenadine HCl for any gender, race, or age group [clinstat\iss\iss.pdf, pages 125-143].

Reviewer comment:

Increased LDH values in pediatric patients at baseline and post-study were noted in study M016455T/1123. This finding is perplexing, but is not related to study drug. This was a single dose clinical pharmacology study performed in patients 6 months to less than 2 years of age. All patients were treated with fexofenadine HCl.

These laboratory data show no meaningful differences between treatment groups or among demographic subgroups and do not identify a safety signal.

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 (M016455I/1004 and M016455I/1003) and from the pooled pivotal and supportive studies in pediatric subjects 6 months to 5 years of age (M016455I/1005, M016455I/1114, M016455I/3112, M016455T/1123, M016455T/3001, and M016455T/3002) [clinstat\iss\iss.pdf, page 167].

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 in the pooled clinical pharmacology studies in adult subjects [clinstat\iss\iss.pdf, page 169].

The applicant notes that there were no meaningful changes in heart rate, systolic blood pressure, or diastolic blood pressure in pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age [clinstat\iss\iss.pdf, page 171].

These vital signs data show no meaningful differences between treatment groups and do not identify a safety signal.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

The applicant notes that there were no vital signs values that met criteria for CSA in the pooled clinical pharmacology studies in adult subjects [clinstat\iss\iss.pdf, page 172].

The applicant notes that there were no vital signs values that met criteria for CSA in pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age [clinstat\iss\iss.pdf, pages 173-174].

The applicant states that analyses of vital signs data by demographic subgroups for the pooled pivotal clinical pharmacology studies in adult subjects and for the pooled pivotal and supportive studies in pediatric subjects 6 months to 5 years of age did not reveal any risks associated with the use of fexofenadine HCl for any gender, race, or age group [clinstat\iss\iss.pdf, page 189].

These vital signs data show no meaningful differences between treatment groups 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 (M016455I/1004 and M016455I/1003) and from the pooled pivotal and supportive studies in pediatric subjects 6 months to 5 years of age (M016455I/1005, M016455I/3112, M016455T/1123, M016455T/3001, and M016455T/3002) [clinstat\iss\iss.pdf, page 167].

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 146-147].

The applicant's analysis of mean changes from baseline for the ECG intervals PR, QRS, QT, QTcB, and QTcF in the pooled pivotal and supportive studies in pediatric subjects 6 months to 5 years of age showed no meaningful changes in any of the ECG intervals [clinstat\iss\iss.pdf, pages 148-149].

Reviewer comment:

The ECG data show no meaningful differences between treatment groups and do not identify a safety signal.

7.1.9.3.2 *Analyses focused on outliers or shifts from normal to abnormal*

The applicant noted that there were no ECG values that met criteria for CSA in the pooled pivotal clinical pharmacology studies in adult subjects [clinstat\iss\iss.pdf, pages 148-149].

There were few patients in the pooled pivotal and supportive studies in pediatric subjects 6 months to 5 years of age who had CSA values for PR, and QTcB, intervals and the frequencies of CSA values were similar in the fexofenadine HCl and placebo groups. There were no patients with CSA values for QTcF in any treatment group. CSA values for QRS interval were noted in 4.0% (14/510) of fexofenadine HCl-treated patients and in 6.0% (16/430) of placebo-treated patients [clinstat\iss\iss.pdf, pages 150-515].

The applicant stated that their analyses of ECG 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 group. Subgroup analyses for the pooled pivotal and supportive studies in pediatric subjects 6 months to 5 years of age also did not reveal any risk associated with any particular gender, race, or age group [clinstat\iss\iss.pdf, page 167].

Reviewer comment:

The ECG data show no meaningful differences between treatment groups 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 196].

As of September 30, 2005, 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 reported that there were 31 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 that resulted in a serious adverse event was a 3-year old male who received a 30 mg dose of fexofenadine HCl for atopy once and experienced

anaphylaxis. The patient was hospitalized and recovered [clinstat\other\drugabuse.pdf, pages 6-9].

Reviewer comment:

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

7.1.14 Human Reproduction and Pregnancy Data

The applicant identified 14 postmarketing adverse events associated with drug exposure during pregnancy. These events included talipes, 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 96-97].

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 September 30, 2005, the applicant identified 24 spontaneous reports of overdose. Doses of fexofenadine HCl in these reports ranged from 30 mg to 1680 mg. Of these 24 reports, three were reported as being serious and 21 were non-serious. Fifteen of the 24 reports were not associated with an adverse event. The three serious cases included (1) a 8-year old male patient who experienced hallucination, increased lacrimation, 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 080]. The search was designed to capture all cases received through September 30, 2005 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

- 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 565 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 (91.9%, 519/565). The most frequent spontaneous adverse events in this group are summarized in Table 9 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 82].

Table 9 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 82].

Adverse event	Number of events
Drug ineffective	66
Headache	28
Back pain	18
Somnolence	14
Insomnia	11
Hypersensitivity	10
Overdose	10
Psychomotor hyperactivity	10

There were 46 serious adverse events (8.1%, 46/565) in patients less than 12 years of age, or 30 mg dose, or 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 [clinstat\iss\iss.pdf, pages 82-83].

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 June 2005 is estimated to be approximately 194 million patient treatment days or approximately 532,474 patient years [clinstat\iss\iss.pdf, page 82].

7.1.17.2 Patients less than 6 years of age

There were 85 postmarketing adverse events reported for patients less than 6 years of age. The majority of adverse events were non-serious (75.3%, 64/85). The most frequent spontaneous adverse events in this group are summarized in Table 10 below.

Table 10 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 84].

Adverse event	Number of events
Accidental exposure	6
Medication error	4
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 eight of the nine patients. Six 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. Other serious adverse events in this age group included muscle twitching in a 4-month old infant exposed to fexofenadine HCl through breast milk, overdose with no adverse reaction, and an anaphylactic reaction consisting of abdominal pain, vomiting, laryngospasm, and thoracic rigidity in a 3-year old [clinstat\iss\iss.pdf, pages 84-87; clinstat\iss\ae_tables.pdf, page 34].

Reviewer comment:

Postmarketing adverse events in this group were infrequent and the most common events reflect the fact that the product is not currently approved in this age group. Thirteen 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. The current Allegra label notes that anaphylaxis has been reported rarely. 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 242 postmarketing adverse events reported for patients 6 years to less than 12 years of age. The majority of adverse events were non-serious (93.0%, 225/242). The most frequent spontaneous adverse events in this group are summarized in Table 11 below.

Table 11 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 87].

Adverse event	Number of events
Drug ineffective	26
Headache	12
Psychomotor hyperactivity	7
Hypersensitivity	6
Overdose	6
Anxiety	5
Back pain	5
Depression	5
Somnolence	5

There were 17 serious adverse events occurred in eight patients (7.0 %, 17/242). There were two reports of hallucinations. Of note, 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 attention deficit disorder and concomitant treatment with methylphenidate. 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 87-90].

Reviewer comment:

As with younger children, 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 238 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 12 below. The majority of adverse events were non-serious (93.0%, 225/242).

Table 12 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 91].

Adverse event	Number of events
Drug ineffective	37
Headache	15
Back pain	13
Insomnia	8
Dizziness	7
Nausea	7
Somnolence	5
Rash	5

There were 8 serious adverse events occurred in eight 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, and generalized rash. 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; both were reported by a consumer and were not substantiated by a medical provider [clinstat\iss\iss.pdf, pages 90-93; clinstat\iss\isscioms.pdf, pages 32-37].

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 adult clinical pharmacology pivotal studies M016455I/1003 and M016455I/1004, and from pooled pediatric studies, including pivotal study M016455I/1005 and supportive studies M016455I/1005, M016455I/1114, M016455I/3112, M016455T/1123, M016455T/3001, and M016455T/3002. The safety information from these studies included adverse event data, laboratory data, vital signs data, and ECG data [clinstat\iss\iss.pdf, page 013].

7.2.1.1 Study type and design/patient enumeration

The applicant's program is based on a clinical pharmacology/bioequivalence approach. There were three pivotal studies in the applicant's drug development program for fexofenadine HCl suspension. These studies are described below and summarized in Table 13 [clinstat\clinsum.pdf, pages 26-27, 38-40]:

- Study M016455I/1003, a pivotal bioavailability study designed to compare the bioavailability of 30 mg of fexofenadine HCl suspension under fed and fasting conditions
- Study M016455I/1004, a pivotal bioequivalence study designed to compare the bioavailability of 30 mg of fexofenadine HCl suspension to the marketed 30 mg fexofenadine HCl tablet
- Study M016455I/1005, a pivotal bioavailability study designed to characterize the pharmacokinetics and safety of 30 mg of fexofenadine HCl suspension in pediatric patients 2 to 5 years of age

Table 13 Summary of pivotal clinical pharmacology studies providing safety information, NDA 21-963 [clinstatclinsum.pdf, pages 38-40].

Study Number	Study Type	Treatment Groups	Treatment duration	Design	Number of subjects /patients	Diagnosis, age of subjects
M016455I/1003	Pivotal food effect study	F 5 mL of 30 mg/5 mL suspension, single dose, fasting conditions F 5 mL of 30 mg/5 mL suspension, single dose, fed conditions	Single dose	Single center, randomized, open label, two period, two-way crossover	54	Healthy men and women, 18-42 years
M016455I/1004	Pivotal BA and BE study	F 5 mL of 30 mg/5 mL suspension, single dose, fasting conditions F 30 mg marketed tablet, single dose, fasting conditions	Single dose	Single center, randomized, open label, two period, two-way crossover	54	Healthy men and women, 18-45 years
M016455B/1005	Pivotal BA study	F 5 mL of 30 mg/5 mL suspension, single dose, fasting conditions	Single dose	Multiple center, open label, no control, single period	50	Pediatric patients, 2-5 years, candidates for or history of antihistamine therapy

F = fexofenadine HCl

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. Most of these studies have been previously submitted to IND 43,573, IND 51,709, NDA 20-625, or NDA 20-872 and have previously been reviewed. Among these are the following five studies in pediatric patients 6 months to 5 years of age: (1) M016455I/1114, (2) M016455T/1123, (3) M016455I/3112, (4) M016455T/3001, and (5) M016455T/3002. Safety data from pivotal study M016455I/1005 was pooled with safety data from these five studies to provide integrated analyses of adverse events, vital signs, laboratory evaluations, and ECGs for the Integrated Summary of Safety (ISS) [clinstat\iss\iss.pdf, page 013]. These five previously performed safety studies in pediatric patients 6 months to 5 years of age are described below:

- Study M016455I/1114, an open-label, multiple-dose, multicenter design in pediatric patients 2 to 5 years of age, designed to characterize the pharmacokinetics, safety, and

tolerance of fexofenadine HCl following a single oral dose of 30 mg, administered as granulation powder (capsule content) in applesauce and following BID dosing for 4 to 7 days [clinsum/clinsum.pdf, page 28].

- Study M016455T/1123 a phase 1, open-label, single escalating-dose, multicenter design in pediatric patients 6 months to less than 2 years of age designed to characterize the pharmacokinetics of fexofenadine HCl after a single oral dose of 15 mg and 30 mg administered as granulation powder (capsule content) in applesauce [clinsum/clinsum.pdf, page 28].
- Study M016455I/3112, a double-blind, randomized, placebo-controlled, parallel design, multicenter study designed to assess the safety and tolerability of oral fexofenadine HCl 30 mg administered BID for the treatment of allergic rhinitis in pediatric patients 2 to 5 years of age. Fexofenadine HCl and placebo were administered as granulation powder (capsule content) in applesauce [clinsum/clinsum.pdf, page 31].
- Study M016455T/3001, a phase 3, double-blind, randomized, placebo-controlled, parallel design, multicenter study designed to compare the safety and tolerability of fexofenadine HCl 15 mg BID to placebo in pediatric patients 6 months to less than 2 years of age and ≤10.5 kg in weight. Fexofenadine HCl and placebo were administered as granulation powder (capsule content) a dosing vehicle (applesauce, yogurt, or formula) [clinsum/clinsum.pdf, page 31].
- Study M016455T/3002, a phase 3, double-blind, randomized, placebo-controlled, parallel design, multicenter study designed to compare the safety and tolerability of fexofenadine HCl 30 mg BID to placebo in pediatric patients 6 months to less than 2 years of age and greater than 10.5 kg in weight. Fexofenadine HCl and placebo were administered as granulation powder (capsule content) in a dosing vehicle (applesauce, yogurt, or formula) [clinsum/clinsum.pdf, page 31].

7.2.1.2 Demographics

Demographics in pivotal clinical pharmacology studies in adult subjects are summarized in Table 14 below. The majority of subjects were of male gender and White race. The mean age of subjects was 24.3 years [clinstat\iss\iss.pdf, page 51].

Table 14 Demographics in pivotal clinical pharmacology studies in adult subjects [clinstat\iss\iss.pdf, page 51].

Demographic characteristic	Fexofenadine HCl 30 mg	
	N = 107 n	(%)
Gender		
Female	35	(35.5)
Male	69	(64.5)
Race		
White	96	(89.7)
Non-White	11	(10.3)

Clinical Review
 Charles E. Lee, M.D.
 NDA 21-963, N-000, 12/15/05
 Allegra (fexofenadine HCl) — Suspension 30/ mg/5 mL (6 mg/mL)

Demographic characteristic	Fexofenadine HCl 30 mg
	N = 107 n (%)
Age, years	
Mean ± SD	24.3 ± 6.50
Range	18.0-45.0

Demographics in supporting studies in pediatric patients 6 to 11 years of age are summarized in Table 15 below. The majority of patients were of male gender and of White race. The mean age was 8.9 years [clinstat\iss\iss.pdf, pages 51-52; clinstat\iss\isstable.pdf, pages 353, 355, 358].

Table 15 Demographics in pivotal clinical pharmacology studies in pediatric patients 6 to 11 years of age
 [clinstat\iss\iss.pdf, pages 51-52; clinstat\iss\isstable.pdf, pages 353, 355, 358].

Demographic characteristic	Fexofenadine HCl 30 mg
	N = 1825 n (%)
Gender	
Female	703 (38.5)
Male	1122 (61.5)
Race	
White	1516 (83.1)
Black	11 (10.3)
Asian	32 (1.8)
Other	129 (7.1)
Age, years	
Mean	8.9
Range	5.0-12.0

Demographics in supporting studies in pediatric patients 6 months to 5 years of age are summarized in Table 16 below. The majority of patients in the placebo and fexofenadine HCl total groups were of male gender and White race. The mean age in the placebo group and the fexofenadine HCl total group was 2.5 years [clinstat\iss\iss.pdf, page 52].

Table 16 Demographics in supporting studies in pediatric patients 6 months to 5 years of age
 [clinstat\iss\iss.pdf, page 52].

Demographic characteristic	Placebo	Fexofenadine HCl 15 mg	Fexofenadine HCl 30 mg	Fexofenadine HCl Total
	N = 430 n (%)	N = 108 n (%)	N = 426 n (%)	N = 534 n (%)
Gender				
Female	196 (45.6)	48 (44.4)	185 (43.4)	233 (43.6)
Male	234 (54.4)	60 (55.6)	241 (56.6)	301 (56.4)
Race				
White	334 (77.7)	71 (65.7)	323 (75.8)	394 (73.8)
Black	54 (12.6)	23 (21.3)	55 (12.9)	78 (14.6)
Other	42 (9.8)	14 (13.0)	48 (11.3)	62 (11.6)
Age, years				
Mean	2.5	1.0	2.9	2.5
Range	0.5-5.0	0.5-1.8	0.5-5.0	0.5-5.0

7.2.1.3 Extent of exposure (dose/duration)

A total of 107 subjects were exposed to fexofenadine HCl 30 mg in the pivotal clinical pharmacology studies in adult subjects. Patients were exposed from 1 to 16 days. The mean duration of exposure was 7.7 days [clinstat\iss\iss.pdf, pages 47-48].

Extent of exposure in pediatric patients 6 to 11 years of age is summarized in Table 17 below. Patients were exposed to two single doses of study treatment in clinical pharmacology studies PJPR0037 and M016455I/1119. Patients were exposed to twice daily study treatment for up to 14 days in studies PJPR0037 and M016455C/3212. The mean duration of exposure to fexofenadine HCl in study PJPR0037 was 15.5 days and the mean number of doses of fexofenadine HCl in study M016455C/3212 was 28.6 [clinstat\iss\iss.pdf, pages 48-49].

Table 17 Extent of exposure in pediatric patients 6 to 11 years of age [clinstat\iss\iss.pdf, pages 48-49].

Study	Placebo	Fexofenadine HCl 15 mg	Fexofenadine HCl 30 mg	Fexofenadine HCl 60 mg
	n	n	n	n
PJPR0037	--	--	14	14
M016455I/1119	18	17	18	18
PJPR0066/77	229	224	209	213
M016455C/3212	471	--	464	--

Extent of exposure in pediatric patients 6 months to 5 years of age is summarized in Table 18 below. Of 534 patients enrolled, 532 were exposed to fexofenadine HCl 15 mg or 30 mg. The overall mean duration of exposure to fexofenadine HCl was 9.4 days [clinstat\iss\iss.pdf, page 49].

Table 18 Extent of exposure in pediatric patients 6 months to 5 years of age [clinstat\iss\iss.pdf, page 49].

	Placebo	Fexofenadine HCl 15 mg	Fexofenadine HCl 30 mg	Fexofenadine HCl Total
	N = 430	N = 108	N = 426	N = 534
Exposure, patients	422	107	425	532
Mean duration of exposure, days	11.1	6.7	10.1	9.4
Range of duration of exposure, days	1.0-17.0	1.0-11.0	1.0-22.0	1.0-22.0

Reviewer comments:

The extent of exposure in the population proposed for this NDA supplement, pediatric patients 6 months to 5 years of age, is adequate to assess safety. Although the duration of exposure in this population is fairly 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.

7.2.2 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 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 080]. The search was designed to capture all cases received through September 30, 2005 where the age was reported to be less than 12 years. Where the age was unknown, the applicant included all cases where a dose of 30 mg appeared in any dosing field or where a dose of 60 mg appeared in the total daily dose field of their database. There were 207 reports identified based on age less than 12 years and 147 cases based on the dose [clinstat\iss\iss.pdf, pages 97-98].

The applicant estimates that post-marketing exposure to fexofenadine HCl 30 mg from June 2000 through June 2005 is estimated to be approximately 194 million patient treatment days or approximately 532,474 patient years [clinstat\iss\iss.pdf, page 82]. Safety information relevant to the applicant's review of postmarketing and spontaneous adverse event reports is addressed in Section 7.1.17 Postmarketing Experience.

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 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.

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 the population proposed for this NDA supplement, pediatric patients 6 months to 5 years of age, is adequate to assess safety. Although the duration of exposure in this population is fairly 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 April 13, 2006 [NDA 21-963, N-000 SU, 4/13/06]. 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/5 mL suspension 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 October 1, 2005 through March 15, 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 21-963, N-000 SU, 4/13/06, 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 fexofenadine HCl for treatment of symptoms of SAR in children from 2 years of age and uncomplicated skin manifestations of CIU in children from 6 months of age. Adverse events occurring at a frequency of greater than 2% and more commonly for fexofenadine HCl than placebo in pivotal and supportive studies in pediatric patients 6 months to less than 6 years of age included cough, otitis media, diarrhea, rhinorrhea, and somnolence. Frequencies of these adverse events were fairly similar and there was no dose ordering noted. The small differences in the frequencies of adverse events among treatment groups in these studies are not likely to be clinically meaningful. The data do not suggest a safety signal attributable to fexofenadine HCl for the proposed population. Data for less common adverse events also did not suggest a safety signal attributable to fexofenadine HCl for children from 6 months to 5 years of age. These data are discussed in greater detail in 7.1.5.4 Common adverse event tables.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The application is for a suspension formulation of fexofenadine HCl and proposes to expand the current indication for relief of symptoms associated with SAR to include children 2 years of age and treatment of uncomplicated skin manifestations of CIU to include children 6 months of age [labeling\proposed.pdf, page 6]. The current indication is relief of symptoms associated with SAR in adults and children 6 years of age and older and treatment of uncomplicated skin manifestations of CIU in adults and children 6 years of age and older [labeling\approved.pdf, page 6].

The proposed dose of Allegra Suspension for the treatment of symptoms of SAR in children 2 to 11 years of age is 30 mg twice daily. A dose of 30 mg (5 mL) once daily is recommended as the starting dose in pediatric patients with decreased renal function.

The proposed dose of Allegra Suspension for the treatment of symptoms of CIU is 30 mg (5 mL) twice daily. For pediatric patients with decreased renal function, the proposed starting doses are 30 mg (5 mL) once daily and 15 mg (2.5 mL). The bottle is to be shaken well, before each use [labeling\proposed.pdf, pages 14-15].

Dosing of fexofenadine HCl in the pediatric population was previously addressed in an earlier NDA supplement. In order to determine the optimal dose for children 6 months to 2 years of age, a population PK analysis was performed based on data from 269 treatment doses from 136 adult subjects, and 90 treatment doses from 77 pediatric patients. The modeling revealed that age and body weight are significant predictors of variability in fexofenadine pharmacokinetics in pediatrics. Although the model clearly indicated that age is the most significant factor (weight is the second most significant factor) for the PK of fexofenadine in this age group, it was determined that the appropriate dose for children 6 months to less than 2 years of age is 15 mg, and the appropriate dose in children 2 to 5 years of age (and up to less than 12 years old) is 30 mg. This decision was based on simplicity of dosing recommendation and the relative safety of fexofenadine [Clinical Pharmacology and Biopharmaceutics Review, Shinja Kim, Ph.D., NDA 20-872, SE08-011, 11/18/02].

The proposed dose should therefore be revised as follows:

The recommended dose of Allegra Suspension for the treatment of symptoms of SAR in children 2 to 11 years of age is 30 mg twice daily. A dose of 30 mg (5 mL) once daily is recommended as the starting dose in pediatric patients with decreased renal function.

The recommended dose of Allegra Suspension for the treatment of symptoms of CIU is 15 mg (2.5 mL) twice daily for patients 6 months to less than 2 years of age and 30 mg (5 mL) twice daily for patients 2 to 11 years of age. For pediatric patients 6 months to less than 2 years of age with decreased renal function, the proposed starting doses is 15 mg (2.5 mL) once daily and 30 mg (5 mL), once daily for 2 to 11 years of age.

Co-administration of fexofenadine HCl with food results in a decreased rate of absorption and a decreased extent of absorption of fexofenadine. Co-administration of the suspension formulation with a high-fat breakfast resulted in a 30% decrease in AUC, a 47% decrease in C_{max} , and a 1.5 hour increase in the median time to maximum plasma concentration (T_{max}) value [Section 5

11/18/02; Office of Clinical Pharmacology Review, Shinja Kim, Ph.D., NDA 21-963, N-000, 12/15/05].

8.4 Pediatrics

Allegra Suspension is proposed for use in children from 6 months 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) and 6 years to 11 years of age (NDA 20-872, N-000, 7/17/98). In this application, the applicant requested a waiver of pediatric studies in patients less than 6 months of age [other\pedwaiver.pdf, page 4].

The Agency has determined that the applicant has 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 and the applicant was notified after receipt of this application [NDA Acknowledgement Letter, dated 1/11/06, NDA 20-963, N-000, 12/15/05]. Studies were waived under the age of 6 months of age because the 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.

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.

9.4 Labeling Review

Detailed labeling review was performed. Recommended changes in the proposed labeling are noted below in ~~strikeout~~ and underlined text. A complete marked-up copy of proposed labeling with recommended changes will be sent to the applicant.

3 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

Clinical Review
Charles E. Lee, M.D.
NDA 21-963, N-000, 12/15/05
Allegra (fexofenadine HCl) — Suspension 30/ mg/5 mL (6 mg/mL)

Reviewed by:

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

Lydia Gilbert-McClain, M.D.
Medical Team Leader, Division of Pulmonary and Allergy Products

cc: Original NDA 21-963
HFD-570/Division File
HFD-570/Gilbert-McClain/Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-870/S. Kim/Clinical Pharmacology and Biopharmaceutics Reviewer
HFD-870/Fadiran/Clinical Pharmacology and Biopharmaceutics Team Leader
ONDQA/Haber/CMC Reviewer
HFD-570/L. Garcia/CSO

**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
8/7/2006 01:58:06 PM
MEDICAL OFFICER

Lydia McClain
8/7/2006 02:29:40 PM
MEDICAL OFFICER
I ocncur.

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 6-11 years of age

The applicant has submitted an NDA for a suspension formulation of fexofenadine HCl 6 mg/mL. The proposed indication is for the relief of symptoms associated with SAR in children 2 to 11 years of age and treatment of uncomplicated skin manifestations of CIU in children 6 months to 11 years of age [labeling\proposed.pdf, page 006].

Detailed clinical review may be found in the medical officer review for the NDA [Charles E. Lee, M.D., Medical Officer Review, NDA 21-963, N-000, 12/15/05].

The Division of Medical Errors and Technical Support (DMETS) provided comments on labeling submitted with the NDA [Tselaine Jones Smith, Pharm.D., OSE Review #05-0179-1, NDA 21-963, N-000, 12/15/05]. Many of the comments related to CMC concerns and Prasad Peri, Ph.D., ONDQA PAL has provided his concurrence. Comments to the sponsor based on the DMETS review follow below.

2. COMMENTS FOR THE APPLICANT

The following comments should be communicated to the sponsor:

Regarding the package insert and bottle labels:

1. *Change the trade name to "Allegra Oral Suspension" rather than "Allegra  Suspension. Include "For Pediatric Use" as a separate phrase on the label under the phrase "Allegra Oral Suspension."*
2. *Enclose the established name in parenthesis to read as follows: (fexofenadine hydrochloride)*
3. *Revise the bottle labels and package insert to express the concentration of the products as "30 mg/5 mL (6 mg/mL)." Expression of the concentration as 30 mg/5 mL may decrease the probability of dosage calculation errors. Furthermore, the concentration of most oral liquid pharmaceutical preparations is expressed per 5 mL.*

Regarding the bottle labels:

4. *Relocate the net quantity away from the product strength so that they are not in close proximity of each other. Postmarketing experience has shown that medication errors have occurred due to confusion of the net quantity for the product strength when the net quantity is in close proximity or appears more prominent.*
5. *Relocate the "Rx Only" statement so that it appears on the principal display panel.*

6. *Increase the prominence of the statements "Shake Well Before Using" and "Avoid Freezing" to increase their visibility to the user.*

Reviewed by:

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

Lydia Gilbert-McClain, M.D.
Medical Team Leader, Division of Pulmonary and Allergy Products

cc: Original NDA
HFD-570/Division File
HFD-570/Gilbert-McClain/Medical Team Leader
HFD-570/Lee/Medical Reviewer
ONDQA/Peri/Chemist
HFD-570/L. Garcia/CSO

**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
8/1/2006 09:32:34 AM
MEDICAL OFFICER

Lydia McClain
8/1/2006 06:18:47 PM
MEDICAL OFFICER
I concur

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 6-11 years of age

The applicant has developed a suspension formulation of fexofenadine HCl 6 mg/mL. The proposed indication is for the relief of symptoms associated with SAR in children 2 to 11 years of age and treatment of uncomplicated skin manifestations of CIU in children 6 months to 11 years of age [labeling\proposed.pdf, page 006].

The excipients in the proposed formulation include  glycol, edentate disodium, propylparaben, butylparaben, xanthan gum, poloxamer 407, titanium dioxide, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, artificial raspberry cream flavor, sucrose, xylitol, and purified water [CMC\product\3.2.p-drug product.pdf, page 002].

The application is an electronic submission.

CLINICAL DEVELOPMENT PROGRAM

The applicant previously conducted three studies, Studies M016455T/1123, M016455T/3001 and M016455T/3002, in response to the Division's Written Request for pediatric studies. These studies were submitted in an NDA labeling supplement (NDA 20-872, SE8-011, 11/18/02). Study M016455T/1123 was a phase 1 study to characterize the pharmacokinetics of fexofenadine HCl in pediatric patients 6 months to less than 2 years of age after a single oral dose of 15 mg and 30 mg. Study M016455T/3001 was a phase 3 multicenter study designed to compare the safety and tolerability of fexofenadine HCl 15 mg BID to placebo in pediatric patients 6 months to less than 2 years of age and ≤ 10.5 kg in weight. Study M016455T/3002 was a phase 3 multicenter study designed to compare the safety and tolerability of fexofenadine HCl 30 mg BID to placebo in pediatric patients 6 months to less than 2 years of age and greater than 10.5 kg in weight. These studies were performed using 15 mg and 30 mg of fexofenadine granulation powder administered in applesauce or rice cereal. These studies, along with previously performed studies in children from 2 to 11 years of age, supported the use of their product in children 6 months to 5 years of age [Medical Officer Review, Charles E. Lee, M.D., NDA 20-872, SE8-011, 11/18/02]. PK data indicated that administration of 15 mg fexofenadine to children 6 months to less than 2 years of age and 30 mg of fexofenadine to children 2 to 11 years of age produced exposures comparable to those seen with a 60 mg dose administered to adults [Clinical Pharmacology and Biopharmaceutics Review, Shinja Kim, Ph.D., NDA 20-872, SE8-011, 11/18/02]. At the time of the application, the applicant did not have a marketable pediatric formulation, and an allergic rhinitis or chronic idiopathic urticaria indication for fexofenadine in children 6 months to 5 years of age could not be supported. The Division concluded that the applicant's pharmacokinetic studies provided an appropriate dose of fexofenadine for children from 6 months to 5 years of age, and that extrapolation of efficacy could be considered if the

applicant had a marketable pediatric formulation [BPCA Clinical Summary, Charles E. Lee, M.D., NDA 20-872, SE8-011, 11/18/02].

The applicant's program is based on a clinical pharmacology/bioequivalence approach. There are three pivotal studies in the applicant's drug development program for the proposed suspension formulation. These studies are described below and summarized in greater depth later in this document [clinstat\clinsum.pdf, pages 26-27, 38-40]:

- Study M016455I/1003, a pivotal bioavailability study designed to compare the bioavailability of 30 mg of fexofenadine suspension under fed and fasting conditions
- Study M016455I/1004, a pivotal bioequivalence study designed to compare the bioavailability of 30 mg of fexofenadine suspension to the marketed 30 mg fexofenadine tablet
- Study M016455I/1005, a pivotal bioavailability study designed to characterize the pharmacokinetics and safety of 30 mg of fexofenadine suspension in pediatric patients 2 to 5 years of age.

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. Most of these studies have been previously submitted to IND 43,573, IND 51,709, NDA 20-625, or NDA 20-872 and have previously been reviewed. Among these are the five following studies in pediatric patients 6 months to 5 years of age: (1) M106455I/1114, (2) M106455T/1123, (3) M106455I/3112, (4) M106455T/3001, and (5) M106455T/3002. Safety data from pivotal study M016455I/1005 was pooled with safety data from these five studies to provide integrated analyses of adverse events, vital signs, laboratory evaluations, and ECGs for the Integrated Summary of Safety (ISS) [clinstat\iss\iss.pdf, page 013]. These five previously performed safety studies in pediatric patients 6 months to 5 years of age are described below:

- Study M106455I/1114, an open-label, multiple-dose, multicenter design in pediatric patients 2 to 5 years of age designed to characterize the pharmacokinetics, safety, and tolerance of fexofenadine HCl following a single oral dose of 30 mg, administered as granulation powder (capsule content) in applesauce and following BID dosing for 4 to 7 days [clinsum/clinsum.pdf, page 28].
- Study M106455T/1123 an open-label, single escalating-dose, multicenter design in pediatric patients 6 months to less than 2 years of age designed to phase 1 study to characterize the pharmacokinetics of fexofenadine HCl after a single oral dose of 15 mg and 30 mg administered as granulation powder (capsule content) in applesauce [clinsum/clinsum.pdf, page 28].
- Study M106455I/3112, a double-blind, randomized, placebo-controlled, parallel design, multicenter study designed to assess the safety and tolerability of oral fexofenadine HCl 30 mg administered BID for the treatment of allergic rhinitis in pediatric patients 2 to 5 years of age. Fexofenadine HCl and placebo were administered as granulation powder (capsule content) in applesauce [clinsum/clinsum.pdf, page 31].

- Study M106455T/3001, a phase 3, double-blind, randomized, placebo-controlled, parallel design, multicenter study designed to compare the safety and tolerability of fexofenadine HCl 15 mg BID to placebo in pediatric patients 6 months to less than 2 years of age and ≤ 10.5 kg in weight. Fexofenadine HCl and placebo were administered as granulation powder (capsule content) a dosing vehicle (applesauce, yogurt, or formula) [clinsum/clinsum.pdf, page 31].
- Study M106455T/3002, a phase 3, double-blind, randomized, placebo-controlled, parallel design, multicenter study designed to compare the safety and tolerability of fexofenadine HCl 30 mg BID to placebo in pediatric patients 6 months to less than 2 years of age and greater than 10.5 kg in weight. Fexofenadine HCl and placebo were administered as granulation powder (capsule content) in a dosing vehicle (applesauce, yogurt, or formula) [clinsum/clinsum.pdf, page 31].

Studies M106455I/1114, M106455T/1123, M106455I/3112, and M106455T/3001, and M106455T/3002 will be reviewed only in the context of the integrated analyses of adverse events, vital signs, laboratory evaluations, and ECGs in the ISS [clinsum/clinsum.pdf, pages 27-32, 41-53]. Supporting studies in this NDA submission will not otherwise be reviewed.

2. FOREIGN MARKETING AND REGULATORY HISTORY

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].

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 25 July 1996 and as Allegra® Tablets (NDA 20-872) on 25 February 2000, respectively. Fexofenadine HCl 180 mg QD was approved in the US for the CIU indication on 13 October 2005.

Comments on the applicant's End of Phase 2 meeting package were faxed to the applicant on March 29, 2005 and a teleconference was held with the applicant on March 30, 2005 [Meeting minutes and Medical Officer Review, IND 51,709, N-092 MP, 2/24/05]. 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.

Comments on the applicant's Pre-NDA meeting package were faxed to the applicant on August 2, 2005 and a teleconference was held with the applicant on August 3, 2005. The Division addressed the proposed INDICATIONS AND USAGE section. The Division concurred with the proposed content for the Integrated Summary of Efficacy and Integrated Summary of Safety. Although a separate package insert, as proposed by the applicant, was acceptable to the Division, the Division advised the applicant that a single package insert for all of the Allegra products would be preferable [Meeting minutes and Medical Officer Review, IND 51,709, N-099 MP, 7/1/05].

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\1003.pdf, pages 001, 018; hpbio\hupharm\1004.pdf, pages 001, 019; hpbio\hupharm\1005.pdf, pages 001, 020]
- 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
- Integrated Summary of Safety (ISS) [clinstat\iss\iss.pdf] included the following:
 - Summary of safety information, including subgroup analyses, from adult clinical pharmacology studies in this application, M106455I/1003, M106455I/1004, and from pooled pediatric studies including pivotal study M106455I/1005 and supportive studies in pediatric patients six months to five years of age [clinstat\iss\iss.pdf, page 013]
 - Postmarketing and spontaneous adverse event reports for fexofenadine HCl entered into the applicant's ClinTrace safety database on or before September 30, 2005 [clinstat\iss\iss.pdf, page 078]
 - These events include cases from clinical trials, postmarketing surveillance studies, spontaneous notifications, cases from regulatory authorities, and the published literature [clinstat\iss\iss.pdf, page 080]
 - Drug-drug, drug-demographic, and drug-disease interactions [clinstat\iss\iss.pdf, pages 190-195].
 - Withdrawal information [clinstat\iss\iss.pdf, page 196]
 - Drug abuse and overdose information [clinstat\other\drugabuse.pdf, pages 006-012]
- Proposed labeling and annotated labeling [labeling\proposed.pdf; labeling\contain\contain.pdf; summary\summary.pdf, pages 009-038].
- Case report forms for patients with serious adverse events or discontinuing studies [crf\1003\0001\subject1053.pdf]
- List of referenced DMFs [356h.pdf]
- Environmental assessment [cmc\3.2.r-environ.pdf, pages 002-003].
- Request for waiver of pediatric studies [other\pedwaiver.pdf, page 004]

- The applicant is requesting a waiver of pediatric studies in patients less than six months of age

Reviewer comments:

No formal review of the literature for safety information relevant to fexofenadine HCl was performed. However, the sponsor's postmarketing safety database includes reports from the published medical literature. No additional formal literature review will be requested.

The applicant's request for a pediatric waiver is reasonable. SAR does not occur in children less than 2 years of age and CIU is rare in children less than 6 months of age. The Division historically has granted waivers for pediatric studies in children less than 6 months of age for oral antihistamines. The waiver should be granted.

4. CLINICAL STUDIES

There are three pivotal bioavailability and bioequivalence studies in this application, Study M016455I/1003, Study M016455I/1004, and Study M016455I/1005.

The clinical review of this application will focus on the safety data from the three pivotal bioavailability and bioequivalence studies, M016455I/1003, M016455I/1004, and M016455I/1005, and safety data from supportive studies in pediatric patients, M106455I/1114, M106455T/1123, M106455I/3112, M106455T/3001, and M106455T/3002.

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 M106455I/1003

Study M106455I/1003 was a pivotal clinical pharmacology study that compared the bioavailability of the to-be-marketed fexofenadine suspension under fed and fasted conditions. It was an open-label, randomized, single-dose, two-way, two-period, complete crossover study conducted in 54 healthy male and female adult subjects between 18 and 45 years of age [hpbio\hupharm\1003.pdf, pages 001-005, 027]. Study treatments were 5 mL of the 6 mg/mL fexofenadine HCl suspension administered under fasting conditions and 5 mL of the 6 mg/mL fexofenadine HCl suspension administered after a high fat breakfast [hpbio\hupharm\1003.pdf, pages 027-028]. 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\1003.pdf, page 023]. Safety endpoints included adverse events, vital signs, physical examinations, clinical laboratory studies, and ECGs [hpbio\hupharm\1003.pdf, page 034]. There were five withdrawals from the study. There were four subjects who withdrew consent and one patient who withdrew due to adverse event of abdominal pain, headache, dysgeusia, and nausea [hpbio\hupharm\1003.pdf, page 004]. There were no serious adverse events [hpbio\hupharm\1003.pdf, page 055].

4.2. Study M016455I/1004

M016455I/1004 was an open label, randomized, single dose, two-period, two-way crossover study designed to establish the bioequivalence of 30 mg fexofenadine when administered as the to-be-marketed suspension relative to the marketed 30 mg fexofenadine tablet under fasting conditions. There were 54 healthy adult male and female subjects, 18 to 45 years of age, enrolled in the study. Study treatments were 5 mL of the 6 mg/mL fexofenadine HCl suspension and one 30 mg marketed fexofenadine HCl tablet [hpbio\hupharm\1004.pdf, pages 27-28]. 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. Subjects were housed at the study site from check-in on Day -1 until Day 3 [hpbio\hupharm\1004.pdf, page 031]. Safety endpoints included adverse events, vital signs, physical examinations, laboratory studies, and ECGs [hpbio\hupharm\1004.pdf, pages 033-034]. There was one subject who was lost to follow-up. There were no withdrawals from the study due to adverse events and no serious adverse events [hpbio\hupharm\1004.pdf, pages 004-005].

4.3. Study M016455I/1005

Study M016455I/1005 was a phase 1, open label, single period, single dose, multicenter study designed to characterize the pharmacokinetics of 30 mg fexofenadine when administered as a to-be-marketed suspension under fasted conditions in pediatric patients 2 to 5 years of age. The secondary objective of the study was to evaluate the safety and tolerability of fexofenadine suspension in these patients. There were 50 male and female patients, 2 to 5 years of age, enrolled in the study. There were six study sites, all in the United States. Patients had been determined by their physician to be a candidate for antihistamine therapy for the treatment of allergic rhinitis or to have tolerated a therapeutic course of antihistamine therapy for allergic rhinitis without adverse effects. Study treatment was 5 mL of the 6 mg/mL fexofenadine HCl suspension [hpbio\hupharm\1005.pdf, page 028]. Serial blood samples were collected at pre-dose, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose [hpbio\hupharm\1005.pdf, pages 036-037]. Safety endpoints included adverse events, vital signs, physical examinations, laboratory studies, and ECGs [hpbio\hupharm\1005.pdf, pages 001-004]. There were no withdrawals from the study and no serious adverse events [hpbio\hupharm\1005.pdf, page 004].

5. BRIEF REVIEW OF PROPOSED LABELING

Proposed package labeling has been included in this submission [labeling\proposed.pdf, pages 1-16; labeling\contain\contain.pdf, pages 1-2; summary\summary.pdf, pages 9-38]. A brief review of proposed labeling was performed. Proposed labeling is similar to current labeling for Allegra Tablets. A single package insert for both Allegra Tablets and Allegra Suspension is proposed. Labeling comments are noted below.

The proposed dosing regimen for pediatric patients with CIU is based on both age and weight. The Division previously noted that this may be unnecessarily complicated [Medical Officer Review, Charles E. Lee, M.D., IND 51,709, N-099 MP, 7/1/05]. PK data indicated that administration of 15 mg fexofenadine to children ≥ 6 months to 2 years of age and 30 mg of fexofenadine to children ≥ 2 to 12 years of age produced exposures comparable to those seen

Table 1. Summary of studies to receive clinical review, NDA 21-963 [clinstat/clinsum.pdf, pages 038-040].

Study Number	Study Type	Treatment Groups	Treatment duration	Design	Number of subjects/patients	Diagnosis, age of subjects	Materials submitted in this application
M106455I/1003	Pivotal food effect study	F 5 mL of 6 mg/mL suspension, single dose, fasting conditions F 5 mL of 6 mg/mL suspension, single dose, fed conditions	Single dose	Single center, randomized, open label, two period, two-way crossover	54	Healthy men and women, 18-42 years	Protocol Study report Tabulations Case report form
M106455I/1004	Pivotal bioavailability and bioequivalence study	F 5 mL of 6 mg/mL suspension, single dose, fasting conditions F 30 mg marketed tablet	Single dose	Single center, randomized, open label, two period, two-way crossover	54	Healthy men and women, 18-45 years	Protocol Study report Tabulations No case report forms necessary
M106455B/1005	Pivotal bioavailability study	F 5 mL of 6 mg/mL suspension, single dose, fasting conditions	Single dose	Multiple center, open label, no control, single period	50	Pediatric patients, 2-5 years, candidates for or history of antihistamine therapy	Protocol Study report Tabulations No case report forms necessary

F = fexofenadine HCl

with a 60 mg dose administered to adults [Clinical Pharmacology and Biopharmaceutics Review, Shinja Kim, Ph.D., NDA 20-872, SE8-011, 11/18/02]. The applicant's proposed dosing for CIU in children 6 months to 11 years of age will be discussed with the Office of Clinical Pharmacology and Biopharmaceutics review team.

Detailed label review will be performed later in the course of review of this 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 a suspension formulation of fexofenadine HCl. The applicant is Sanofi Aventis. The product contains fexofenadine HCl, 6 mg/mL. The proposed indication is for the relief of symptoms associated with seasonal allergic rhinitis in children 2 to 11 years of age and symptoms of CIU in children from 6 months to 11 years of age [summary\summary.pdf, page 019]. This application is an electronic submission. There are three pivotal clinical pharmacology studies submitted in support of this application. The study and 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.

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

The sponsor will be asked to provide information on whether fexofenadine HCl suspension is marketed in any country.

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 May 26, 2006. The review of the ISS will take place next and will be complete by June 16, 2006. Label review will be complete by June 30, 2006. Draft review will be complete by July 14, 2006, approximately two weeks before the GRMP date for the completed and signed primary and secondary review.

Table 2. Proposed schedule for review of NDA 21-963.

Milestone	Target Date for Completion
Clinical pharmacology study M1064551/1004	4/28/06
Clinical pharmacology study M1064551/1003	5/12/06
Clinical pharmacology study M1064551/1005	5/26/06
ISS	6/16/06
Label Review	6/30/06
Draft Review Complete	7/14/06
Primary review complete and signed, GRMP date	8/15/06
Action Date, 10 months	10/16/06

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

Lydia Gilbert-McClain, M.D.
Medical Team Leader, Division of Pulmonary and Allergy Products

cc: Original NDA
HFD-570/Division File
HFD-570/Gilbert-McClain/Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-870/S. Kim/Clinical Pharmacology and Biopharmaceutics Reviewer
HFD-570/Haber/Chemist
HFD-570/Peri/Chemist
HFD-570/Sancilio/Pharmacology Reviewer
HFD-570/C. Yu/CSO

**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
2/3/2006 02:47:37 PM
MEDICAL OFFICER

Lydia McClain
2/7/2006 02:37:39 PM
MEDICAL OFFICER
I concur