MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 20-625 NDA 20-872 NDA 20-786	**TRADE NAME:**	Allegra® Capsules Allegra® Tablets Allegra-D® Tablets
APPLICANT/SPONSOR:	Aventis Pharmaceuticals	**USAN NAME:**	Fexofenadine HCl
MEDICAL OFFICER:	Charles E. Lee, M.D.		Fexofenadine HCl/pseudoephedrine HCl
TEAM LEADER:	Badrul A. Chowdhury, M.D., Ph.D.	**CATEGORY:**	Antihistamine Antihistamine/decongestant
DATE:	12/23/02	**ROUTE:**	Oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
11/18/02	11/20/02	NDA 20-625 SE8-012 PM	Pediatric labeling supplement, Allegra Capsules
11/18/02	11/19/02	NDA 20-872 SE8-011 PM	Pediatric labeling supplement, Allegra Tablets
11/18/02	11/19/02	NDA 20-786 SE8-014 PM	Pediatric labeling supplement, Allegra-D Tablets

RELATED APPLICATIONS

Document Date	Application Type	Comments
7/12/00	NDA 20-872, SE8-003 PM	Pediatric labeling supplement
7/12/00	NDA 20-625, SE8-010 PM	Pediatric labeling supplement
[redacted]		(b) (4)
2/12/02	NDA 20-625, SE8-010	Pediatric labeling supplement
2/12/02	NDA 20-872, SE8-003	Pediatric labeling supplement

REVIEW SUMMARY: This is a 45-day clinical filing and planning review of a pediatric labeling supplement for Allegra® tablets (fexofenadine HCl) NDA 20-872. The sponsor is Aventis Pharmaceuticals. [redacted] (b) (4) There were three pivotal studies and two supportive studies submitted in support of this application. The pivotal studies were submitted in response to a Written Request for pediatric studies dated April 23, 2001, and amended on November 6, 2001. The three clinical studies include a pharmacokinetics study (M106455T/1123) and two safety studies (M106455T/3001 and M106455T/3002) in children ≥6 months to <2 years of age. The sponsor has also provided reports for two supportive pharmacology studies of the bioavailability of fexofenadine administered with applesauce (Study PJPR0076) and in other food delivery vehicles (Study M016455T/1001). The application does not include an Integrated Summary of Efficacy, subgroup analyses of safety by gender or race, review of worldwide spontaneous adverse event reports, review of the literature of publications related to the safety of fexofenadine in children, or a list of referenced INDs, NDAs, and DMFs. The sponsor will be asked to submit these items. The submission will be fileable when the required materials are submitted.

OUTSTANDING ISSUES: The sponsor will be asked to submit the requested items. The submission will be fileable when the required items are submitted.

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES:	___	**SAFE TO PROCEED**	___	**CLINICAL HOLD**		
NDA/SUPPLEMENTS:	X	**FILEABLE**	___	**NOT FILEABLE**		
	___	**APPROVAL**	___	**APPROVABLE**	___	**NOT APPROVABLE**
OTHER ACTION:						

1. GENERAL INFORMATION AND BACKGROUND

NDA 20-872, Allegra® (fexofenadine hydrochloride) tablets, was approved on February 25, 2000, for the following indications, dosing regimens, and age groups:

- Allegra 180-mg Tablets, 1 tablet po QD in SAR for adults and children >12 years of age
- Allegra 60-mg Tablets, 1 tablet po BID in adults and children >12 years of age for chronic idiopathic urticaria (CIU)
- Allegra 30-mg Tablets, 1 tablet po BID in SAR and CIU for children 6-11 years of age

The Division issued a Written Request for pediatric studies on March 27, 2000. The Written Request was for four studies. The four studies were: (1) a PK study in patients ages ≥2 to <6 years, (2) a safety study in patients ages ≥2 to <6 years, (3) a PK study in patients ages ≥6 months to <2 years, and (4) a safety study in patients ages ≥2 to <6 years. The sponsor submitted two studies in response to the Written Request on July 12, 2000. These studies were a PK study in patients ages ≥2 to <6 years and a safety study in patients ages ≥2 to <6 years. (b) (4) The studies in patients ≥2 to <6 years of age have been previously reviewed. [Medical Officer Review, NDA 20-872, SE8-003, 7/12/00, and NDA 20-872, SE8-003, 2/12/02]. The Division took an approvable action on May 14, 2001, and on August 12, 2002, and requested that the sponsor submit draft revised labeling. The sponsor has delayed the submission of the draft revised labeling pending completion of the studies submitted in this application.

This application is a pediatric labeling supplement for Allegra® Tablets (fexofenadine HCl), and is in response to a second Written Request, which was dated April 23, 2001, and amended on November 6, 2001. Two studies were requested in this second Written Request. These were a pharmacokinetics and safety study in pediatric patients ≥6 months to <2 years of age (Study 1) and a safety study in pediatric patients ≥6 months to <2 years of age (Study 2). This application includes reports of studies conducted to meet the specifications of the Written Request and reports for two additional supportive clinical pharmacology studies.

2. CONTENTS OF THIS SUBMISSION

This is a paper submission. The sponsor has provided an electronic copy of proposed labeling [N20-625\S-012\2002-11-18\labeling]. (b) (4) This submission includes the reports of three pivotal studies, Studies M106455T/1123, M106455T/3001 and M106455T/3002. Study M106455T/1123 was a Phase 1 study to characterize the pharmacokinetics of fexofenadine after a single oral dose of fexofenadine HCl 15-mg and 30-mg in children ≥6 months to <2 years of age [Volumes 2-7]. This study was designed to meet the specifications for the PK study (Study 1) in the second Written Request. The sponsor has also provided an analysis of PK data from multiple studies of fexofenadine administered in capsule and tablet forms in adults and children from 6 months to12 years of age [Volume 8].

The sponsor found it necessary to perform two safety and tolerability studies in children ≥6 months to <2 years of age, Studies M106455T/3001 and M106455T/3002, to meet the

specifications of the second study in the Written Request (Study 2) [Volumes 15-22 and Volumes 23-30, respectively]. The sponsor has provided reports for these studies, and has provided a report of the combined safety data from these studies as well [Volumes 9-14].

The sponsor has also provided reports for two supportive pharmacology studies of the bioavailability of fexofenadine administered with applesauce (Study PJPR0076) and in other food delivery vehicles (Study M016455T/1001) [Volume 31 and Volumes 32-33, respectively]. Other data supporting the CMC characteristics of formulations used in this application were also provided. These CMC data address the stability of fexofenadine 15-mg and 30-mg capsules, stability of fexofenadine in a variety of different pediatric dosing vehicles, accuracy of dose administration in a variety of different dosing vehicles [Volume 34].

(b) (4)

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

The following items were included in this submission:

- Form FDA 356h [Volume 1, page not numbered]
- Statements of Good Clinical Practice [Volume 2, page 132, Volume 15, page 286, Volume 23, page 321]
- Proposed labeling [Volume 34, pages 179-206; N20-625\S-012\2002-11-18\labeling]
- Debarment certification [Volume 34, page 257]
- Financial disclosure statement [Volume 34, page Volume 34, pages 241-256]
  - There were no investigators with disclosable financial interests in any of the studies in this application [Volume 34, pages 241-256].
- Integrated Summary of Safety (ISS) [Volume 34, pages 207-240]
- Case report forms for patients with SAEs or discontinuing studies [Volume 34, pages 258-328; Volume 35, pages 1-226]

The following items were not included in this submission:

- Integrated Summary of Efficacy (ISE)
- Although an Integrated Summary of Safety (ISS) was submitted, the following components of the ISS were not provided:
  - Subgroup analysis of safety by gender or race
  - Review of worldwide spontaneous reports
  - Review of the literature
- Environmental assessment
  - The sponsor has requested a categorical exclusion of the environmental impact statement, as per 21 CFR 25.31(a) because the approval of the supplement would not increase the use of the active moiety [Cover Letter, page 2]

- Safety update

4. CLINICAL STUDIES

This submission refers to three pivotal studies, Studies M106455T/1123, M106455T/3001 and M106455T/3002. Study M106455T/1123 was a Phase 1 study to characterize the pharmacokinetics of fexofenadine after a single oral dose of fexofenadine HCl 15-mg and 30-mg in children ≥6 months to <2 years of age. This study was designed to meet the specifications for the PK study (Study 1) in the second Written Request.

The sponsor found it necessary to perform two safety and tolerability studies in children ≥6 months to <2 years of age to meet the specifications of the second study in the Written Request (Study 2). Two studies were necessary because pharmacokinetics data indicated a smaller dose of fexofenadine would be appropriate for children less than or equal to 10.5 kg. These two studies were Study M106455T/3001 and M106455T/3002. Study M106455T/3001 was a Phase 3 multicenter safety and tolerability study designed to compare the safety and tolerability of fexofenadine HCl 15 mg BID to placebo in children with allergic rhinitis ≥6 months to <2 years of age and weighing ≤10.5 kg. Study M106455T/3002 was a Phase 3 multicenter safety and tolerability study designed to compare the safety and tolerability of fexofenadine HCl 30 mg BID to placebo in children with allergic rhinitis ≥6 months to <2 years of age and weighing >10.5 kg. The sponsor provided a combined study report for M106455T/3002 and M106455T/3002 and also provided individual study reports.

The sponsor has also provided reports for two supportive pharmacology studies of the bioavailability of fexofenadine administered with applesauce (Study PJPR0076) and in other food delivery vehicles (Study M016455T/1001).

The volumes containing the study report are appropriately indexed and organized to allow review. These studies are summarized in Table 1. More detailed descriptions of these studies follow below.

4.1. Pivotal studies

The sponsor's three pivotal studies are briefly summarized below.

4.1.1. Study M106455T/1123, Pharmacokinetics study

This was a multicenter, open-label, single-dose, Phase 1 study. Pharmacokinetic sampling was performed after a single dose of fexofenadine HCl 15 mg or 30 mg. The primary objective of this study was to characterize the pharmacokinetics of fexofenadine in children ≥6 months to <2 years of age after a single oral dose of 15 mg or 30 mg. A secondary objective was to assess the safety and tolerability of fexofenadine HCl 15 mg and 30 mg BID in children of this age group. Twenty centers participated in this study. There were 65 patients enrolled in this study, and 48 patients received study medication. Two panels of sequential, escalating dose groups were to receive a single dose of study medication. The first panel of patients was given a single oral dose of fexofenadine HCl 15-mg (b) (4) powder. Pharmacokinetic blood samples were collected prior to administration of the first dose and serially up to 24 hours postdose. Safety variables included adverse events (AEs), vital signs, physical examinations, hematology, blood chemistry,

and urinalysis. An interim safety assessment was performed based on AEs, clinical laboratory evaluations, vital signs, physical examinations, and ECGs collected from 18 patients in the first panel who consumed the entire 15-mg dose. A decision was made to proceed to the second panel of patients based on these safety data. The second panel of patients was given a single oral dose of fexofenadine HCl 30-mg (b) (4) powder. Pharmacokinetic blood samples were collected prior to administration of the first dose and serially up to 24 hours postdose. Safety variables for the second panel of patients were the same as for the first [Volume 2, pages 24, 25, 26].

4.1.2. Study M106455T/3001, Safety study

This was a double blind, randomized, and placebo-controlled Phase 3 study. The objective of this study was to compare the safety and tolerability of fexofenadine 15 mg BID to placebo in children ≥6 months to <2 years of age with allergic rhinitis and weighing ≤10.5 kg. A secondary objective was to assess efficacy at 1 week. There were 174 patients in the study and there were 43 study centers. Safety variables included AEs, vital signs, physical examinations, and ECGs. Investigators were to assess the overall severity of allergic rhinitis (AR) symptoms at baseline and at the final visit (1 week or early discontinuation) using a 0 to 4, complete relief to no relief, five-point AR severity scale. Investigators also made an overall assessment of study medication effectiveness taking into account the AR symptom assessments and changes in AR physical finding between the baseline and final visits. This overall assessment of study medication effectiveness also used the 0 to 4, complete relief to no relief, five point AR severity scale [Volume 15, pages 3, 19, 22, 22, 33, 39].

4.1.3. Study M106455T/3002, Safety study

This was a double blind, randomized, and placebo-controlled Phase 3 study. The objective of this study was to compare the safety and tolerability of fexofenadine 30 mg BID to placebo in children ≥6 months to <2 years of age with allergic rhinitis and weighing more than 10.5 kg. A secondary objective was to assess efficacy at 1 week. There were 218 patients in the study and there were 44 study centers. Safety variables included AEs, vital signs, physical examinations, and ECGs. Investigators were to assess the overall severity of AR symptoms at baseline and at the final visit (1 week or early discontinuation) using a 0 to 4, complete relief to no relief, five-point AR severity scale. Investigators also made an overall assessment of study medication effectiveness taking into account the AR symptom assessments and changes in AR physical findings between the baseline and final visits. This overall assessment of study medication effectiveness also used the 0 to 4, complete relief to no relief, five point AR severity scale [Volume 23, pages 3, 4, 20, 31, 38].

4.2. Supportive studies

The sponsor's two supportive pharmacology studies are described below, and are summarized in Table 1.

4.2.1. Study PJPR0076

This was a single center, open-label, single-dose, four period, randomized, complete crossover, Phase 1 study. There was a washout period of 6 days between study periods. The primary objective of this study was to determine the bioavailability of fexofenadine HCl (b) (4) formulation relative to the marketed immediate release capsule. A

secondary objective was to determine the bioavailability of the fexofenadine HCl marketed immediate release capsule when administered with applesauce. The four study treatments were: (1) 2 x [redacted] 60 mg [redacted], (2) 2 x [redacted] 60 mg [redacted], (3) 2 x marketed 60 mg capsule in applesauce, and (4) 2 x marketed 60 mg capsule. Twenty centers participated in this study. Subjects were healthy adult males. There were 22 subjects enrolled in this study, and 22 subjects received study medication. Pharmacokinetic blood samples were collected prior to administration of study treatment and serially up to 48 hours postdose. Safety variables included adverse events (AEs), vital signs, and clinical laboratory specimens. A case report form was not provided for the one SAE, a subject who had an episode of syncope [Volume 31, pages 9, 10, 17, 19, 20, 35, 308].

4.2.2. Study M016455T/1001

This was a single center, open-label, single-dose, four period, randomized, complete crossover, Phase 1 study. There was a washout period of 6 days between study periods. The objective of this study was to compare the bioavailability of 60-mg fexofenadine HCl administered in food delivery vehicles relative to a 60-mg fexofenadine HCl reference capsule. The four study treatments were: (1) 60 mg oral [redacted] powder in 10 mL of Karo syrup, (2) 60 mg oral [redacted] powder in 10 mL of Dannon vanilla yogurt, (3) 60 mg oral [redacted] powder in 10 mL of Gerber rice cereal prepared with Similac with Iron, and (4) marketed 60 mg capsule. Twenty centers participated in this study. Subjects were healthy adult males. There were 24 subjects enrolled in this study, and 24 subjects received study medication. Pharmacokinetic blood samples were collected prior to administration of study treatment and serially up to 48 hours postdose. Safety variables included adverse events (AEs), vital signs, physical examinations, and clinical laboratory specimens. [Volume 31, pages 4, 19, 20, 28, 39, 43, 50, 51].

Table 1. Summary of studies, NDA 20-872, SE8-011.

Study Number	Study Type	Treatment Groups	Duration of treatment	Design	Number of subjects	Population	Materials submitted in this efficacy supplement
M106455T/1123	Pivotal pharmacology study	Fexofenadine HCl (b) (4) powder, 15 mg and 30 mg Single dose, two panels of patients	Single dose	Open-label, 20 centers	48	AR or candidates for antihistamine therapy 6 to 24 months of age	Protocol Study report Line listings Case report forms
M106455T/3001	Pivotal safety study	Fexofenadine HCl (b) (4) powder, 15 mg BID Placebo (b) (4) powder	1 week	Double-blind, randomized, placebo-controlled, parallel group, 43 centers	174	AR or candidates for antihistamine therapy 6 to 24 months of age weight ≤10.5 kg	Protocol Study report Line listings Case report forms
M106455T/3002	Pivotal safety study	Fexofenadine HCl (b) (4) powder, 30 mg BID Placebo (b) (4) powder	1 week	Double-blind, randomized, placebo-controlled, parallel group, 44 centers	218	AR or candidates for antihistamine therapy 6 to 24 months of age weight >10.5 kg	Protocol Study report Line listings Case report forms
PJPR0076	Supportive pharmacology study	2 x (b) (4) 60 mg (b) (4) 2 x (b) (4) 60 mg (b) (4) 2 x marketed 60 mg capsule in applesauce 2 x marketed 60 mg capsule	Single dose	Open-label, four period, randomized, complete crossover Single center	22	Healthy adult males 19-39 years of age	Protocol Study report Line listings Case report form not provided for single SAE
M016455T/1001	Supportive pharmacology study	60 mg oral (b) (4) powder in 10 mL of Karo syrup 60 mg oral (b) (4) powder in 10 mL of Dannon vanilla yogurt 60 mg oral (b) (4) powder in 10 mL of Gerber rice cereal prepared with Similac with Iron 60 mg marketed capsule	Single dose	Open-label, four period, randomized, complete crossover Single center	24	Healthy adult males 19-44 years of age	Protocol Study report Line listings

(b) (4)

[redacted]

6. DSI REVIEW/AUDIT

DSI audit will not be requested, as assessment of efficacy was not a primary objective of these studies. The sponsor is not seeking changes to the INDICATIONS AND USAGE or DOSAGE AND ADMINISTRATION sections of the label. The following sites may be considered for inspection if a concern appears during the review cycle. These investigators had sites among those with the largest number of patients enrolled.

1. Bettina Hilman, M.D. (Study M106455T/1123, Center Number 109)
   Louisiana State University Health Science Center
   1501 Kings Highway
   P.O. Box 33932
   Shreveport, LA 71130
   Phone: Not provided
   Fax: Not provided
   [Volume 2, page 295; Volume 3, page 220; Volume 5, page 249]

2. Jerry Bernstein, M.D. (Study M106455T/3001)
   Raleigh Pediatric Associates, P.A.
   4905 Professional Court
   Raleigh, NC 27609
   Phone: Not provided
   Fax: Not provided
   [Volume 15, page 71; Volume 16, page 5; Volume 17, page 1]

3. Julius H. Van Bavel, M.D. (M106455T/3002)
   Allergy and Asthma Associates
   3410 Far West Boulevard, Suite 146
   Austin, TX 78731
   Phone: Not provided
   Fax: Not provided
   [Volume 23, page 70; Volume 24, page 70; Volume 27, page 200]

7. PEDIATRIC EXCLUSIVITY

This submission constitutes the full response to the second Written Request for pediatric studies. This submission will be discussed at the Division's Pediatric Exclusivity Working Group meeting on January 15, 2003. This application will be presented to the Pediatric Exclusivity Board on January 27, 2003. The Pediatric Exclusivity Board will make an exclusivity determination on this application at that time.

8. SUMMARY

This is a 45-day clinical filing and planning review of a pediatric labeling supplement for Allegra® Tablets (fexofenadine HCl) NDA 20-872. It is also filed to NDA 20-625 for Allegra® Capsules and NDA 20-786 for Allegra-D® Tablets. The sponsor is Aventis Pharmaceuticals. There were three pivotal studies and two supportive studies submitted in support of this application. The pivotal studies were submitted in response to a Written Request for pediatric studies dated 4/23/01 and amended on November 6, 2001. The three pivotal studies were Studies M106455T/1123, M106455T/3001 and M106455T/3002. Study M106455T/1123 was a Phase 1 study to characterize the pharmacokinetics of fexofenadine after a single oral dose of fexofenadine HCl 15 or 30 mg in children ≥6 months to <2 years of age. Study M106455T/3001 was a Phase 3 multicenter safety and tolerability study designed to compare the safety and tolerability of fexofenadine HCl 15 mg BID to placebo in children ≥6 months to <2 years of age with allergic rhinitis and weighing ≤10.5 kg. Study M106455T/3002 was a Phase 3 multicenter safety and tolerability study designed to compare the safety and tolerability of fexofenadine HCl 30 mg BID to placebo in children ≥6 months to <2 years of age with allergic rhinitis and weighing >10.5 kg. The sponsor provided a combined study report for M106455T/3002 and M106455T/3002 and also provided individual study reports. The sponsor has also provided reports for two supportive pharmacology studies of the bioavailability of fexofenadine administered with applesauce (Study PJPR0076) and in other food delivery vehicles (Study M016455T/1001).

The application did not include an Integrated Summary of Efficacy, subgroup analyses of safety by gender or race, review of worldwide spontaneous adverse event reports, or a review of the literature of publications related to the safety of fexofenadine in children. The sponsor will be asked to submit these items. The sponsor has submitted proposed labeling in electronic form, and in the paper copies of the application. (b) (4) [redacted]. The sponsor will be asked to submit the requested items. The submission will be fileable when the required materials are submitted.

9. TIME LINE FOR REVIEW

Write-up will be concomitant with the review process. The schedule for review is displayed in Table 2. Review to determine if the pivotal studies included in the application meet the specifications of the Written Request will be complete by January 15, 2003. The Pediatric Exclusivity Board will be meeting on January 27, 2003, to consider this application. Study M106455T/1123 will be reviewed first, followed by review of Studies M106455T/3001 and M106455T/3002. A combined safety review for studies M106455T/3001 and M106455T/3002 will be performed. Supporting studies will be reviewed by February 28, 2003. The review of the ISE and ISS will be complete by March 21, 2003. Label review will be complete by April 4, 2003. Draft review will be complete by April 18, 2003, one month before the action date.

Table 2. Proposed schedule for review of efficacy supplement, NDA 20-872, SE8-011 PM

Milestone	Target Date for Completion
Pediatric Exclusivity Working Group Meeting	1/15/03
Pediatric exclusivity determination	1/27/03
Study M106455T/1123	1/31/03
Study M106455T/3001, excluding safety review	2/7/03
Study M106455T/3002, excluding safety review	2/14/03
Studies M106455T/3001 and M106455T/3002, combined safety review	2/28/03
Supporting studies	3/7/03
ISE, ISS	3/21/03
Label Review	4/4/03
Draft Review	4/18/03
Action Date, 6 months	5/19/03

10. COMMENTS FOR THE SPONSOR

The following comments are to be communicated to the sponsor.

1. *Please submit the following information*
   - (b) (4) [redacted]
   - *Subgroup analyses of safety by gender and race for data from the clinical studies submitted in the application*
   - *Review of worldwide spontaneous adverse event reports for fexofenadine in children less than 12 years of age*

- *Review of the literature of publications related to the safety of fexofenadine in children less than 12 years of age*

Reviewed by:

_____

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

_____

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

cc: Original NDA
HFD-570/Division File
HFD-570/Chowdhury/Acting Division Director
HFD-570/Lee/Medical Reviewer
HFD-870/S. Kim/Clinical Pharmacology Reviewer
HFD-715/Gebert/Biometrics Reviewer
HFD-570/RogersChemistry Reviewer
HFD-570/Sancilio/Pharmacology-Toxicology Reviewer
HFD-570/Yu/CSO

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/s/

Charles Lee
12/27/02 07:52:21 AM
MEDICAL OFFICER

Badrul Chowdhury
12/27/02 09:13:15 AM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 20-625 NDA 20-786 NDA 20-872	**TRADE NAME:**	Allegra® Capsules Allegra-D® Tablets Allegra® Tablets
APPLICANT/SPONSOR:	Aventis Pharmaceuticals	**USAN NAME:**	Fexofenadine HCl
MEDICAL OFFICER:	Charles E. Lee, M.D.		Fexofenadine HCl/pseudoephedrine HCl
TEAM LEADER:	Lydia Gilbert-McClain, M.D.	**CATEGORY:**	Antihistamine Antihistamine/decongestant
DATE:	1/24/03	**ROUTE:**	Oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
11/18/02	11/20/02	NDA 20-625, SE8-012	NDA supplement, Allegra Capsules
11/18/02	11/19/02	NDA 20-786, SE8-014	NDA supplement, Allegra-D Tablets
11/18/02	11/19/02	NDA 20-872, SE8-011	NDA supplement, Allegra Tablets
1/14/03	1/15/03	NDA 20-625, SE8-012 C	Response to IR, 2 submissions
1/14/03	1/15/03	NDA 20-786, SE8-014 C	Response to IR, 2 submissions
1/14/03	1/14/03	NDA 20-872, SE8-011 C	Response to IR, 2 submissions

RELATED APPLICATIONS

Document Date	Application Type	Comments
7/12/00	NDA 20-872, SE8-003	Previous response to Written Request
2/12/02	NDA 20-872, SE8-003	Previous response to Written Request

REVIEW SUMMARY:

Allegra® (fexofenadine hydrochloride) is an antihistamine with selective H_1 -receptor antagonist activity. Allegra is currently approved for the following indications and in the following age groups:

- Allegra 180 mg po QD in seasonal allergic rhinitis (SAR) for adults and children ≥12 years of age
- Allegra 60 mg po BID in SAR and chronic idiopathic urticaria (CIU) for adults and children ≥12 years of age
- Allegra 30 mg po BID in SAR and CIU for children 6-11 years of age

The sponsor has submitted complete study reports for studies of fexofenadine that were requested in a Written Request for Pediatric Studies (WR). The sponsor conducted studies and submitted complete study reports to meet the Agency's amended second WR. The sponsor has conducted a single dose, conventional PK study in patients ≥6 months to <2 years of age who were candidates for antihistamine therapy or who had tolerated any antihistamine in the last year. Safety included AEs, VS, PE, laboratory studies, and ECGs. The sponsor conducted two double-blind, randomized, placebo-controlled, parallel group safety studies of 1 week in duration in patients ≥6 months to <2 years of age who were candidates for antihistamine therapy or who had tolerated any antihistamine in the last year. Safety endpoints included AEs, VS, PE, and ECGs. The complete study reports indicate that the sponsor has fairly met all of the specifications of the amended second WR.

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES:	____ SAFE TO PROCEED	____ CLINICAL HOLD		
NDA/SUPPLEMENTS:	____ FILEABLE	____ NOT FILEABLE		
	____ APPROVAL	____ APPROVABLE	____ NOT APPROVABLE	
OTHER ACTION:	PEDIATRIC EXCLUSIVITY DETERMINATION--X			

1. BACKGROUND

Allegra® (fexofenadine hydrochloride) is an antihistamine with selective H_1 -receptor antagonist activity. Allegra is currently approved for the following indications and in the following age groups:

- Allegra 180 mg po QD in seasonal allergic rhinitis (SAR) for adults and children ≥12 years of age
- Allegra 60 mg po BID in SAR and chronic idiopathic urticaria (CIU) for adults and children ≥12 years of age
- Allegra 30 mg po BID in SAR and CIU for children 6-11 years of age

The sponsor has submitted complete study reports for studies that were requested in a Written Request for Pediatric Studies (WR) for fexofenadine HCl [NDA 20-625, SE8-012, 11/18/02; NDA 20-786, SE8-014, 11/18/02; NDA 20-872, SE8-011, 11/18/02].

The following describes the history of the Agency's WR for fexofenadine.

Sponsor's PPSR, 12/2/99 and Agency's first WR, 2/3/00

Aventis submitted an outline of two proposed pediatric studies in a Proposed Pediatric Study Request (PPSR), dated 12/2/99. The first study was a PK study in patients ≥2 to <6 years of age. The second was a safety study in patients ≥2 to <6 years of age.

The Division drafted a WR that outlined four studies. The Division's proposed Study 1 was similar to the PK study proposed by Aventis, with small differences. The Division's proposed Study 2, a safety study in patients ages ≥2 to <6 years of age, was similar to the study proposed by Aventis, with the additional requirement of equal age distribution among patients in this age group. The WR also requested a conventional or population PK study (Study 3) and a safety study (Study 4) in patients ≥6 months to <2 years of age.

Sponsor's Response to WR, 7/12/00

The sponsor submitted two study reports to meet the WR on 7/12/00 [NDA 20-872, SE8-003]. Deficiencies in this submission, and its deviations from WR are listed below:

(b) (4)

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3.
4.
5.
6.

(b) (4)

Even though the two study reports did not meet the specifications of the Written Request, they provided a sizeable amount of PK and safety information for patients ages ≥2 to <6 years. Information on use of the drug in patients ages ≥6 months to <2 years was still needed.

Sponsor's second PPSR, 12/8/00
Aventis submitted a second PPSR, dated 12/8/00. The PPSR included outlined for a PK study in patients ≥2 to <6 years of age, a safety study in patients ≥ 2 to < 6 years of age, a PK study in patients ≥6 months to <2 years of age, and a safety study in patients ≥6 months to <2 years of age.

Agency's second WR
The Division drafted a second WR that outlined two studies. The Division's proposed Study 1, a PK study in patients ages ≥6 months to <2 years, was similar to the PK study outlined in the sponsor's second PPSR. It was a single or multiple dose, conventional or population PK study in patients who were candidates for antihistamine therapy or who had tolerated any antihistamine in the last year. Eighteen patients were to complete the study if a conventional PK study was chosen. Fifty patients were to complete the study if a population PK study was chosen. Safety endpoints were to include AEs, VS, PE, laboratory studies, and ECGs. The Division's proposed Study 2, a safety study in patients ages ≥6 months to <2 years, was similar to the safety study outlined in the sponsor's second PPSR. It was a double-blind, randomized, placebo-controlled, parallel group study of 1 or 2 weeks in patients who were candidates for antihistamine therapy or who had tolerated any antihistamine in the last year. A total of at least 200 patients were to complete the study if a 1-week study was chosen. Alternatively, 100 patients were to complete the study if a 2-week study was chosen. Safety endpoints were to include AEs, VS, PE, and ECGs. There was no need to request studies in patients ages ≥2 to <6 years because of the data in the two previously completed clinical studies. After the second WR was issued, the DPADP Pediatric Exclusivity Working Group (PEWG) decided that it was not essential for AEs be recorded in a diary record for the single dose, Phase 1, PK study. The second WR was amended on November 6, 2001 to include language specifying that for the PK study, AEs should be recorded. This language does not require AEs to be recorded in a diary record.

2. CONTENTS OF THIS SUBMISSION

The sponsor has submitted complete study reports for studies of fexofenadine that were requested in a Written Request for Pediatric Studies (WR) [NDA 20-625, SE8-012, 11/18/02; NDA 20-786, SE8-014, 11/18/02; NDA 20-872, SE8-011, 11/18/02]. The sponsor has also submitted additional information regarding the age distribution of patients in the studies and the percentage of ECGs in patients completing the study in response to a request from the Agency [NDA 20-625, SE8-012 C, 1/14/03; NDA 20-786, SE8-014 C, 1/14/03; NDA 20-872, SE8-011 C, 1/14/03].

3. PEDIATRIC EXCLUSIVITY REVIEW

The contents of the reports for the two studies were reviewed and compared with the specifications of the amended second WR. A detailed table comparing the contents of the study reports with the specifications of the WR is found in the appendix to this document. A summary of the sponsor's studies follows.

The sponsor's study M016455T/1123 was performed to meet the Agency's request for Study 1. The sponsor performed a single dose, conventional PK study in patients who were candidates for antihistamine therapy or who had tolerated any antihistamine in the last year. The sponsor studied two doses of fexofenadine HCl, 15 mg and 30 mg. There were 41 patients who completed the study. Safety endpoints were to include AEs, VS, PE, laboratory studies, and ECGs.

The sponsor performed two studies to meet the Agency's request for Study 2. The sponsor performed two double-blind, randomized, placebo-controlled, parallel group studies of 1 week duration in patients who were candidates for antihistamine therapy or who had tolerated any antihistamine in the last year. Study M106455T/3001 was performed using 15 mg BID of fexofenadine HCl and study M016455T/3002 was performed using 30 mg BID of fexofenadine HCl. The sponsor provided a safety analysis that combined both studies. A total of 265 patients completed these studies. Safety endpoints included AEs, VS, PE, and ECGs.

Reviewer comment:
There were not sufficient data regarding the age distribution of patients in these studies in the initial submission. However, additional information submitted by the sponsor confirmed that children were acceptably distributed among the ages to be studied [NDA 20-625, SE8-012 C, 1/14/03; NDA 20-786, SE8-014 C, 1/14/03; NDA 20-872, SE8-011 C, 1/14/03].

The protocols for the safety studies M016455T/3001 and M016455T/3002 called for patients to have ECGs at 2.5±0.5 hours following the last dose of study treatment, however, the statistical plan allowed for patients to be considered completers if the ECG was performed within 8 hours following the dose. Initially it was unclear what proportion of completers had their ECGs outside of the 2.5±0.5 hour window. Additional information submitted by the sponsor revealed that 12% of patients had ECGs outside of the window. A total of 235 patients had ECGs within 2.5±0.5 hours of their dose, a greater number than the 200 patients specified in the second WR [NDA 20-625, SE8-012 C, 1/14/03; NDA 20-786, SE8-014 C, 1/14/03; NDA 20-872, SE8-011 C, 1/14/03].

4. SUMMARY AND CONCLUSION

The sponsor has conducted studies and submitted complete study reports to meet the specifications of the Agency's amended second WR. The sponsor has conducted a single dose, conventional PK study in patients ≥6 months to <2 years of age who were candidates for antihistamine therapy or who had tolerated any antihistamine in the last year. Safety included AEs, VS, PE, laboratory studies, and ECGs. To meet the

specifications for Study 2 of the WR, the sponsor has conducted two double-blind, randomized, placebo-controlled, parallel group safety studies of 1 week in duration in patients ≥6 months to <2 years of age. Patients were candidates for antihistamine therapy or had tolerated any antihistamine in the last year. Safety endpoints included AEs, VS, PE, and ECGs.

The complete study reports indicate that the sponsor has fairly met all of the specifications of the amended second WR.

Appears this way on original

5. APPENDIX

Written Request Items	Information Submitted/ Sponsor's response
Types of studies to be performed: Study 1: Pharmacokinetic and safety study in pediatric patients ≥6 months to <2 years of age Study 2: Safety study in pediatric patients ≥6 months to <2 years of age Perform Study 1 first to determine the appropriate dose(s) to be used in Study 2.	**Types of studies performed:** Study 1: Pharmacokinetics and safety study in pediatric patients ≥6 months to <2 years of age [Volume 2, page 26] Study 2: Safety study in pediatric patients ≥6 months to <2 years of age [Volume 9, page 11] Study 1 was performed before Study 2 and was used to determine the appropriate dose for Study 2.
Objective/Rationale: Study 1: To assess the pharmacokinetics of fexofenadine in order to determine the dose for patients ≥6 months to <2 years of age that results in comparable concentrations and exposures (i.e., Cmax and AUC) of fexofenadine to those seen in adolescents and adults given labeled doses of fexofenadine. You should use these data to determine the appropriate dosage by age and/or by weight for safety assessment in Study 2. Study 2: To assess the safety of fexofenadine in patients ≥6 months to <2 years of age when administered at an age- and/or weight-appropriate dose.	**Objective/Rationale:** Study 1: The pharmacokinetics of fexofenadine were assessed in order to determine the dose for patients ≥6 months to <2 years of age that results in comparable concentrations and exposures (i.e., Cmax and AUC) of fexofenadine to those seen in adolescents and adults given labeled doses of fexofenadine [Volume 1, page 24]. These data were used to determine the appropriate dosage by age and/or by weight for safety assessment in Study 2 [Volume 1, page 24]. Study 2: To compare the safety and tolerability of fexofenadine 15 mg and 30 mg BID in young children ≥6 months to <2 years of age with allergic rhinitis [Volume 15, page 22; Volume 23, page 21].

Indications to be studied:	**Indications studied:**
Study 1 and Study 2: Allergic rhinitis, or urticaria, or other conditions that are appropriately treated with antihistamines	Study 1: Candidate for antihistamine therapy or patient who had tolerated a therapeutic course of antihistamine therapy, [Volume 2, page 28] Study 2: Diagnosis of allergic rhinitis and candidate for antihistamine therapy or patient who had tolerated a therapeutic course of antihistamine therapy, [Volume 9, page 12]
Study Design: Study 1: Perform a single- or multiple-dose pharmacokinetic study with one or more dose levels of fexofenadine to evaluate an age- and/or weight appropriate dose. Either a conventional or population pharmacokinetic study is acceptable; however, for each patient, obtain a minimal amount and limited number of blood samples at adequate sampling times to evaluate pharmacokinetics appropriately. Sampling times may be selected based on an optimum sampling strategy for the best estimation of the pharmacokinetics of fexofenadine. Study 2: Perform a randomized, double-blind, placebo controlled, parallel-group safety study with a treatment duration of at least one week of a single age- and/or weight-appropriate dose utilizing an age appropriate dosage form of fexofenadine. Select the dose based on results of Study 1.	**Study Design:** Study 1: Single-dose pharmacokinetic study [Volume 2, page 27] Two dose levels of fexofenadine, 15 mg and 30 mg [Volume 2, page 27] Conventional PK study [Volume 2, pages 57-58] 7 sample times—predose, 1, 2.5, 5, 8, 12, 24 hours 0.5 mL x 7 plus 2 x 4 mL = 11.5 mL/patient [Volume 2, pages 27, 73, 117, 176] Study 2: Two identical, randomized, double-blind, placebo controlled, parallel group safety studies [Volume 9, page 11] Treated for a minimum of 7 days [Volume 9, page 11] Two age and or weight-appropriate doses [Volume 1, pages 20, 22] 15 mg BID age ≥6 months to <1 year 30 mg BID age ≥1 year to <2 years Age appropriate dosage form of fexofenadine [Volume 1, pages 72-78] Dose selected based on results of Study 1 [Volume 1, page 19]

Age group and population in which study will be performed:	**Age group and population in which study was performed:**
Study 1 : Children ≥6 months to <2 years of age distributed in a ratio of approximately 1:2 between the following age groups: ≥6 months to <1 year and ≥1 to <2 years. Appropriate representation of children of various ages across the age range of ≥6 months to <1 year should be achieved. Study 2: Children ≥6 months to <2 years of age distributed in a ratio of approximately 1:2 between the following age groups: ≥6 months to <1 year and ≥1 to <2 years. Appropriate representation of children of various ages across the age range of ≥6 months to <1 year should be achieved.	Study 1: Patients with complete PK data Children ≥6 months to <2 years of age 41 patients (100%) Children ≥6 months to <1 year of age 13 patients (32%) Children ≥6 months to <9 months 5 patients (12%) Children ≥9 months to <12 months 8 patients (20%) ≥6 months to <7 months 2 patients ≥7 months to <8 months 0 patients ≥8 months to <9 months 3 patients ≥9 months to <10 months 2 patients ≥10 months to <11 months 3 patients ≥11 months to <12 months 3 patients Children ≥1 year to <2 years of age 28 patients (68%) Ratio for ≥6 months to <1 year and ≥1 to <2 years is 1:2.2 [Volume 2, pages 53, 77; IR 1/14/03] Study 2: Patients who completed Children ≥6 months to <2 years of age Pbo 133 patients Fexofenadine 132 patients Total 265 patients Children ≥6 months to <1 year of age Pbo 49 patients 15 mg BID 45 patients Total 94 patients ≥6 months to <7 months Total 14 patients ≥7 months to <8 months 12 patients ≥8 months to <9 months 16 patients ≥9 months to <10 months 16 patients ≥10 months to <11 months 18 patients ≥11 months to <12 months 18 patients Children ≥1 year to <2 years of age Pbo 84 patients 30 mg BID 87 patients Total 171 patients Ratio for ≥6 months to <1 year and ≥1 to <2 years is 1:1.8 [Volume 9, pages 66-67; IR 1/14/03]

Number of patients to be studied or power of study to be achieved:	**Number of patients studied or power achieved:**
Study 1: For a conventional pharmacokinetic study, a minimum of 18 children per dose level must complete the study, with at least 6 patients in each of the two following age groups: ≥6 months to <1 year and ≥1 to <2 years. For a population pharmacokinetic study, a minimum of 50 children per dose level must complete the study, with at least 15 patients for each dose level studied in each of the two following age groups: ≤6 months to <1 year and ≥1 to <2 years. Study 2: A total of at least 100 children per treatment arm (i.e., a total of at least 200 patients for the study) must complete the study. As an alternative, a total of at least 50 children per treatment arm (i.e., a total of at least 100 patients for the study) must complete the study for a study duration of two weeks.	Study 1: Conventional pharmacokinetics study [Volume 2, pages 57-58] Patients with complete PK data [Volume 2, page 77] **15 mg cohort** **19 patients** **(100%)** ≥6 months to <1 year 6 patients (32%) ≥1 to <2 years 13 patients (68%) **30 mg cohort** **22 patients** **(100%)** ≥6 months to <1 year 7 patients (32%) ≥1 to <2 years 15 patients (68%) Study 2: Completed study (1 week duration) 265 Fexofenadine 132 Fexofenadine 15 mg 45 (34%) Fexofenadine 30 mg 87 (66%) Placebo 133 [Volume 9, page 18]
Entry criteria: Study 1: Children ≥6 months to <2 years of age who are either current candidates for antihistamine therapy or who have tolerated a therapeutic course of antihistamine in the past Study 2: Children ≥6 months to <2 years of age who are either current candidates for antihistamine therapy or who have tolerated a therapeutic course of antihistamine in the past	**Entry criteria used:** Study 1: Children ≥6 months to <2 years of age, a candidate for antihistamine therapy or has tolerated a therapeutic course of antihistamine therapy within the preceding 6 months without adverse effects [Volume 2, page 28] Study 2: Children ≥6 months to <2 years of age, candidate for antihistamine therapy or has tolerated a therapeutic course of antihistamine therapy within the preceding 6 months without adverse effects [Volume 9, pages 11, 12]

Clinical endpoints:	**Clinical endpoints used:**
Study 1: Determine the plasma concentration of fexofenadine using the same validated assay method employed previously or using an adequately cross-validated assay method. Safety endpoints must include adverse events, vital signs, physical examinations, and ECGs. Adverse events must be recorded ~~in a diary record~~. Vital signs and physical examinations must be performed at screening or baseline and at the end of the study. If a single-dose study is performed, a twelve-lead ECG should be performed at the estimated T_{max}. If a multiple-dose study is performed, clinical chemistries, and hematology profiles must be performed at screening or baseline, and at steady-state, and ECGs should be performed at baseline or screening, at the time of estimated Tmax after the initial dose, and at the time of estimated Tmax after steady-state is achieved. (Amendment #1, 11/06/01)	Study 1: Method previously used, modified and validated to LLQ from 2 ng/mL to 0.5 ng/mL LC/MS/MS validated by (b) (4) standard curve range 0.5 to 100 ng/mL, assay was cross-validated [Volume 2, page 36; Volume 6, pages 5, 9] Safety endpoints included (single-dose study): Adverse events—were recorded [Volume 1, page 46; Volume 2, page 83] Vital signs, physical examinations—were performed at screening and end of study [Volume 2, pages 39, 47] ECGs—were performed at 2.5 hours (approximate Tmax) and at screening and end of study [Volume 1, page 46; Volume 2, page 39]

Study 2: Safety endpoints must include adverse events, vital signs, physical examinations, and appropriately timed ECGs. Adverse events must be recorded in a diary record. Vital signs, physical examinations, and 12-lead ECGs must be performed at screening or baseline and toward the end of the study while participants are still on study drug.	Study 2: Safety endpoints included (single-dose study): Adverse events—were recorded in a diary record [Volume 15, pages 30, 266, 355; Volume 23, pages 29, 300] Safety evaluable patients with baseline and end-of-study evaluations Vital signs Systolic BP ≥6 months to <2 years Pbo 61 Fexo 58 ≥1 to <2 years Pbo 125 Fexo 125 Vital signs Diastolic BP ≥6 months to <2 years Pbo 61 Fexo 60 ≥1 to <2 years Pbo 124 Fexo 124 Vital signs HR ≥6 months to <2 years Pbo 65 Fexo 63 ≥1 to <2 years Pbo 128 Fexo 129 Vital signs RR ≥6 months to <2 years Pbo 65 Fexo 63 ≥1 to <2 years Pbo 129 Fexo 129 [Volume 9, pages 138-149] Physical examinations—were performed at screening and end of study [Volume 9, pages 174-187] ECGs—were performed at screening and end of study while on study drug ≥6 months to <1 years Pbo 67 Fexo 63 ≥1 to <2 years Pbo 128 Fexo 126 ≥6 months to <1 year Pbo 195 Fexo 189 [Volume 9, page 165]

Study evaluations:	**Study evaluations used:**
Study 1: Report plasma concentrations and estimated apparent oral clearance of fexofenadine. Report pharmacokinetic parameters such as Cmax, Tmax, AUC, and T1/2 for fexofenadine. Effects of covariates, such as age, weight, height, and body surface area, should be studied. For study of these effects of covariates, utilize appropriate prior pharmacokinetic data available in children and adults. Reported safety data must include descriptive analyses of changes in vital signs, physical examinations, ECGs, and adverse reactions. Clinical chemistries and hematology profiles should be included if a multiple-dose study is performed. Study 2: Safety data must include changes in vital signs, physical examinations, ECGs, and adverse reactions.	Study 1: Pharmacokinetic parameters provided—C_{max}, T_{max}, AUC_{0-z}, $t_{1/2}$, AUC_{0-inf}, Cl_{po} [Volume 2, page 58] Covariates Age, weight, height, body surface area [Volume 2, pages 57-60] Use prior PK data in children and adults [Volume 1, pages 49-54] Safety data Descriptive analyses Changes in vital signs [Volume 7, pages 95-98] Changes in physical examinations [Volume 7, pages 2-6] Changes in ECGs [Volume 7, pages 99-102] Adverse Reactions [Volume 2, pages 83-84] Clinical chemistries and labs performed, but were not required [Volume 7, pages 25-93] Study 2: Changes in vital signs [Volume 9, pages 132-151] Changes in physical examinations [Volume 9, pages 167-187] Changes in ECGs [Volume 9, pages 152-166] Adverse Reactions [Volume 9, pages 22, 80, 81, 74-130]
Drug information: Study 1: • **Route of administration:** Oral • **Dosage form:** Age-appropriate dosage form (for which relative bioavailability has been established) • **Regimen:** Single- or multiple-dose administration of one or more dose levels at age- and/or weight-appropriate doses Study 2: • **Route of administration:** Oral • **Dosage form:** Age-appropriate dosage form (for which relative bioavailability has been established) • **Regimen:** Repeat-dose administration on multiple days of an age- and/or weight appropriate dose with dosing intervals as determined by pharmacokinetic and other related data	**Drug information:** Study 1: • **Route of administration:** Oral [Volume 2, page 32] • **Dosage form:** (b) (4) powder supplied in capsules (age-appropriate, relative bioavailability established) in applesauce [Volume 2, pages 72-78] • **Regimen:** Single dose administration of two dose levels, age and weight appropriate doses [Volume 1, pages 72-78] Study 2: • **Route of administration:** Oral [Volume 15, page 26; Volume 23, page 25] • **Dosage form:** (b) (4) powder supplied in capsules (age-appropriate, relative bioavailability established) in applesauce and rice cereal mixed with Similac [Volume 15, page 26; Volume 23, page 25] • **Regimen:** Repeat dose administration on multiple days of two dose levels, age and weight appropriate doses with dosing intervals determined by pharmacokinetic data [Volume 1, pages 72-78; Volume 15, page 26; Volume 23, page 25]

Drug specific safety concerns:	**Drug specific safety concerns evaluated:**
Study 1: Unanticipated adverse reactions, particularly paradoxical excitability, somnolence, fatigue, and/or hyperkinesia. Study 2: Unanticipated adverse reactions, particularly paradoxical excitability, somnolence, fatigue, and/or hyperkinesia.	Study 1: Evaluation was made for paradoxical excitability, somnolence, fatigue, and hyperkinesia One patient with somnolence, asthenia (fatigue), and nervousness (increased irritability), 0111/00001 One patient with somnolence, 0111/00003 [Volume 2, page 62] Study 2: Evaluation was made for paradoxical excitability, somnolence, fatigue, and hyperkinesia One patient with nervousness (irritable), 0158/00004, Pbo One patient with agitation (hyperactivity), 0160/00002, Pbo One patient with somnolence, 0207/00006, Pbo One patient with somnolence, 0123/00004, Fexo 15 mg One patient with somnolence, 0255/00001, Fexo 30 mg [Volume 9, pages 26-27]
Statistical information (statistical analyses of the data to be performed): Study 1: Provide pharmacokinetic parameters and descriptive analyses of vital signs, physical examinations, ECGs and adverse events. Include descriptive analyses of laboratory studies if a multiple-dose study is performed. Study 2: Provide descriptive analyses of adverse events, vital signs, physical examinations, and ECGs.	**Statistical information (statistical analyses of the data performed):** Study 1: Pharmacokinetic parameters provided—C_{max}, T_{max}, AUC_{0-z}, $t_{1/2}$, AUC_{0-inf}, Cl_{po} {Volume 2, page 58] Descriptive analyses provided: Vital signs [Volume 2, pages 66-67; Volume 7, pages 95-97] Physical examinations [Volume 2, page 66; Volume 7, pages 3-6] ECGs [Volume 2, page 67; Volume 7, pages 99-105] Adverse events [Volume 2, page 61, Volume 1, pages 81-82] Descriptive analyses of laboratory studies [Volume 2, pages 63-66, Volume 7, page 26-93] [Provided even though it was a single-dose study] Study 2: Provide descriptive analyses of adverse events, vital signs, physical examinations, and ECGs. Descriptive analyses provided Adverse events [Volume 9, pages 22, 80, 81, 74-130] Vital signs [Volume 9, pages 132-151] Physical examinations [Volume 9, pages 167-187] ECGs [Volume 9, pages 152-166]

Labeling that may result from the studies:	**Did the sponsor submit proposed labeling?**
Study 1 and 2: Appropriate sections of the label may be changed to incorporate the findings of these studies.	Study 1 and 2: Labeling provided. (b) (4) (b) (4) [Volume 34, pages 191-206]
Format of reports to be submitted: Study 1 and 2: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.	**Format of reports submitted:** Study 1 and 2: Full study reports not previously submitted were submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.
Timeframe for submitting reports of the studies: Study 1 and 2: Reports of the above studies must be submitted to the Agency on or before January 31, 2003.	**Date study reports were submitted:** Study 1 and 2: Reports of the above studies were submitted to the Agency on November 18, 2002.
Additional Information **Timing of assessments: if appropriate** You should use these data [from Study 1] to determine the appropriate dosage by age and/or by weight for safety assessment in Study 2.	**Additional Information** **Timing of assessments:** The data from Study 1 were used to determine the appropriate dosage by age and/or by weight for safety assessment in Study 2 [Volume 1, page 078]

Reviewed by:

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

_____

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

cc: Original NDA
HFD-570/Division File
HFD-570/Gilbert-McClain/Acting Team Leader
HFD-570/Lee/Medical Reviewer
HFD-870/Kim/Clinical Pharmacology Reviewer
HFD-870/Fadiran/Clinical Pharmacology Team Leader
HFD-715/Gebert/Statistics Reviewer
HFD-570/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
1/31/03 08:07:25 AM
MEDICAL OFFICER

Lydia McClain
1/31/03 11:12:29 AM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 20-625	**TRADE NAME:**	Allegra® Capsules
	NDA 20-786		Allegra® D Tablets
	NDA 20-872		Allegra® Tablets
APPLICANT/SPONSOR:	Aventis Pharmaceuticals	**USAN NAME:**	Fexofenadine hydrochloride
MEDICAL OFFICER:	Charles E. Lee, M.D.		
TEAM LEADER:	Lydia Gilbert-McClain, M.D.	**CATEGORY:**	Antihistamine
DATE:	4/22/03	**ROUTE:**	Oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	Stamp Date	Submission	Comments
11/18/02	11/20/02	NDA 20-625 SE8-012	Allegra® Capsules, labeling supplement
11/18/02	11/19/02	NDA 20-786 SE8-014	Allegra® D Tablets, labeling supplement
11/18/02	11/19/02	NDA 20-872 SE8-011	Allegra® Tablets, labeling supplement
12/17/02	12/18/02	NDA 20-625 SE8-010 BL	Response to approvable letter
12/17/02	12/18/02	NDA 20-872 SE8-003 BL	Response to approvable letter
1/14/03	1/15/03	NDA 20-625 SE8-012 C	Information requests, age, ECGs
1/14/03	1/15/03	NDA 20-786 SE8-014 C	Information requests, age, ECGs
1/14/03	1/15/03	NDA 20-872 SE8-011 C	Information requests, age, ECGs
2/27/03	2/28/03	NDA 20-625 SE8-012 C	Information requests, subgroup analyses
2/27/03	2/28/03	NDA 20-625 SE8-012 BZ	Information requests, subgroup analyses
2/27/03	2/28/03	NDA 20-625 SE8-012 BL	Information requests, subgroup analyses
4/16/03	4/17/03	NDA 20-625 SE8-012 C	Information requests, formulation

RELATED APPLICATIONS

Document Date	Application Type	Comments
2/12/02	NDA 20-625, SE8-010	Pediatric labeling supplement, Allegra® Capsules
2/12/02	NDA 20-872, SE8-003	Pediatric labeling supplement, Allegra® Tablets
7/12/00	NDA 20-625, SE8-010 PM	Pediatric labeling supplement, Allegra® Capsules
(b) (4)	(b) (4)	(b) (4)
7/12/00	NDA 20-872, SE8-003 PM	Pediatric labeling supplement, Allegra® Tablets
7/17/98	NDA 20-872	NDA application for Allegra® Tablets
1/2/97	NDA 20-786	NDA application for Allegra D® Tablets
7/31/95	NDA 20-625	NDA application for Allegra® capsules

REVIEW SUMMARY:

This application is a pediatric labeling supplement submitted for Allegra® Capsules (fexofenadine HCl), Allegra® Tablets (fexofenadine HCl), and Allegra® D Tablets (fexofenadine HCl/pseudoephedrine HCl). Studies were performed in response to a Written Request for pediatric studies from the Agency. There were three pivotal studies in this application, Studies M106455T/1123, M106455T/3001 and M106455T/3002. Study M106455T/1123 was a Phase 1 study to characterize the pharmacokinetics of fexofenadine after a single oral dose of 15-mg and 30-mg in children ≥6 months to <2 years of age. Studies M106455T/3001 and M106455T/3002 were Phase 3 multicenter safety and tolerability studies designed to compare the safety and tolerability of fexofenadine HCl 15 mg BID and 30 mg BID to placebo in children ≥6 months to <2 years of age with allergic rhinitis. (b) (4) (b) (4) Evaluation of efficacy was only a secondary objective of these studies, however. A total of 415 patients were exposed to fexofenadine in studies in this application and in earlier pediatric studies. Exposure was adequate to assess safety. Adverse events were fairly common and occurred at similar frequencies for placebo (49.3%, 212/430), fexofenadine 15 mg (40.0%, 34/85), and fexofenadine 30 mg (45.2%, 149/330). Adverse events occurring at rate ≥3.0% in any group and more commonly in fexofenadine

than placebo included vomiting, otitis media, increased cough, rhinitis, sore throat/pharyngitis, accidental injury, diarrhea, rash, and gastroenteritis. The differences between fexofenadine and placebo in frequencies of adverse events are likely to be due to chance. Withdrawals due to adverse events, vital signs, physical examinations, laboratory studies, and ECGs reveal no safety signal. The sponsor's review of the literature and of their postmarketing pharmacovigilance database reveal no new safety signal. The disease course and pathophysiology of seasonal allergic rhinitis and chronic idiopathic urticaria and the drug's effect are substantially similar in children to that of adult patients. The sponsor's pharmacokinetics studies provide for an appropriate dose of fexofenadine in children of these ages. (b) (4)

OUTSTANDING ISSUES: The sponsor must revise proposed draft labeling.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	___ **FILEABLE**	___ **NOT FILEABLE**		
	APPROVAL	**X** **APPROVABLE**		**NOT APPROVABLE**

EXECUTIVE SUMMARY

1. RECOMMENDATIONS

(b) (4)

2. SUMMARY OF CLINICAL FINDINGS

2.1. Brief overview of clinical program

This application is a pediatric labeling supplement for Allegra® Tablets (fexofenadine HCl, NDA 20-625), Allegra® Capsules (fexofenadine HCl, NDA 20-872), and Allegra® D Tablets (fexofenadine HCl/pseudoephedrine HCl, NDA 20-786). This application was also filed as a response to two previous approvable actions.

The pivotal studies in the application were performed in response a Written Request for pediatric studies, dated April 23, 2001, and amended on November 6, 2001. The sponsor fairly met all specifications of this Written Request, and was granted pediatric exclusivity on January 27, 2003. There were three pivotal studies in this application, Studies M106455T/1123, M106455T/3001 and M106455T/3002. Study M106455T/1123 was a Phase 1 study to characterize the pharmacokinetics of fexofenadine after a single oral dose of 15-mg and 30-mg in children ≥6 months to <2 years of age. The sponsor found it necessary to perform two safety and tolerability studies in children ≥6 months to <2 years of age to meet the specifications of the Written Request. Two studies were necessary

because pharmacokinetics data indicated a smaller dose of fexofenadine would be appropriate for children less than or equal to 10.5 kg. These two safety and tolerability studies were Study M106455T/3001 and M106455T/3002. Study M106455T/3001 was a Phase 3 multicenter safety and tolerability study designed to compare the safety and tolerability of fexofenadine HCl 15 mg BID to placebo in children with allergic rhinitis ≥6 months to <2 years of age and ≤10.5 kg in weight. Study M106455T/3002 was a Phase 3 multicenter safety and tolerability study designed to compare the safety and tolerability of fexofenadine HCl 30 mg BID to placebo in children with allergic rhinitis ≥6 months to <2 years of age and >10.5 kg in weight. There were two supportive clinical pharmacology studies in this application, Study PJPR0076, and Study M016455T/1001. PK data from these studies were to determine an acceptable vehicle for fexofenadine (b) (4) powder in the pivotal studies.

The sponsor also included information from the previously reviewed safety and tolerability study M106455I/3112 in their safety analysis. This study evaluated the safety and tolerability of fexofenadine in children ≥2 to <6 years of age. (b) (4)

(b) (4)

2.2. Efficacy

(b) (4)

(b) (4)

2.3. Safety

The sponsor supported the safety of the drug in children of this age group with integrated safety data from pediatric safety studies, an evaluation of worldwide spontaneous adverse event reports in children <12 years of age, and a review of published literature related to safety in the pediatric age group.

A total of 415 children with allergic rhinitis ≥6 months to <6 years of age were exposed to fexofenadine in the sponsor's pediatric studies. Adverse events were fairly common and occurred at similar frequencies for placebo (49.3%, 212/430), fexofenadine 15 mg (40.0%, 34/85), and fexofenadine 30 mg (45.2%, 149/330). Adverse events occurring at rate ≥3.0% in any group and more commonly in fexofenadine than placebo included vomiting, otitis media, increased cough, rhinitis, sore throat/pharyngitis, accidental injury, diarrhea, rash, and gastroenteritis. The differences between fexofenadine and placebo in frequencies of the adverse events are likely to be due to chance. There were no meaningful differences between treatment groups in adverse events leading to withdrawal from the studies. Vital signs, physical examinations, laboratory studies, and ECGs reveal no safety signal. The sponsor's review of the literature reveals no new safety signal. Their search of the their global pharmacovigilance database and their literature provide no evidence of new safety signal.

In summary, there is no evidence of a safety signal in this application. (b) (4)

2.4. Dosing and administration

The pivotal studies in this application in children ≥6 months to <2 years in age and those previously performed in children ≥2 years to <6 years of age used fexofenadine (b) (4) powder. The (b) (4) powder is identical to the contents of the approved and marketed 60-mg fexofenadine capsules. The (b) (4) powder was administered in either Musselman's® applesauce or in Gerber® rice cereal mixed with either Similac® or Isomil® infant formulas. (b) (4)

(b) (4)

(b) (4)

2.5. Special populations

This application is a pediatric labeling supplement with clinical data. Use in the elderly was not addressed and is not relevant to this application. The percentages of male and female patients who experienced adverse events in pediatric safety studies M106455T/3001, M106455T/3002, and M106455I/3112 were comparable between treatment groups. No particular adverse event was identified that occurred more frequently in female or male patients. The majority of patients in pediatric safety studies M106455T/3001, M106455T/3002, and M106455I/3112 were of Caucasian race. No particular adverse event was noted that appeared to be more frequent in patients of a particular race.

CLINICAL REVIEW

1. INTRODUCTION AND BACKGROUND

Allegra® (fexofenadine hydrochloride) is second generation antihistamine with selective H_1 receptor antagonist activity. NDA 20-872, Allegra® Tablets (fexofenadine hydrochloride), was approved on February 25, 2000, for the following indications, dosing regimens, and age groups:

- Allegra 180-mg Tablets, 1 tablet po QD in seasonal allergic rhinitis (SAR) for adults and children >12 years of age
- Allegra 60-mg Tablets, 1 tablet po BID in adults and children >12 years of age for SAR and chronic idiopathic urticaria (CIU)
- Allegra 30-mg Tablets, 1 tablet po BID in SAR and CIU for children 6-11 years of age

Antihistamines represent first line choices for pharmacologic intervention for patients with SAR or CIU. Both of these conditions may occur in children less than 6 years of age. Second generation antihistamines, such as fexofenadine, cetirizine, and loratadine, are less likely to cause sedation than older conventional antihistamines. Currently, there are two second generation antihistamines approved in the US for children under the age of 6 years. These are loratadine, which is approved for SAR and CIU in children down to 2 years of age, and cetirizine, which is approved for SAR, perennial allergic rhinitis (PAR), and CIU indications in children down to 6 months of age.

The Division determined that there was the potential for fexofenadine to be useful for children less than 6 years of age. The Division issued a Written Request for pediatric studies for fexofenadine on March 27, 2000 to obtain needed pediatric information. The Written Request was for four studies. The four studies were: (1) a pharmacokinetics (PK) study in patients ages ≥2 to <6 years, (2) a safety study in patients ages ≥2 to <6 years, (3) a PK study in patients ages ≥6 months to <2 years, and (4) a safety study in patients ages ≥2 to <6 years. The sponsor submitted two studies in response to the Written Request on July 12, 2000. These studies were a PK study in patients ages ≥2 to <6 years and a safety study in patients ages ≥2 to <6 years. (b) (4) The studies in patients ≥2 to <6 years of age have been previously reviewed. [Medical Officer Review, NDA 20-872, SE8-003, 7/12/00, and NDA 20-872, SE8-003, 2/12/02]. The Division took approvable actions on May 14, 2001 and on August 12, 2002 and requested that the sponsor submit draft revised labeling. The sponsor delayed the submission of the draft revised labeling pending completion of the studies submitted in this application.

This application is a pediatric labeling supplement for Allegra® Tablets (fexofenadine HCl, NDA 20-625), Allegra® Capsules (fexofenadine HCl, NDA 20-872), and Allegra® D Tablets (fexofenadine HCl/pseudoephedrine HCl, NDA 20-786). The application was also filed as a response to the two previous approvable actions.

The pivotal studies in the application were performed in response the Division's second Written Request, which was dated April 23, 2001 and amended on November 6, 2001. Two studies were requested in this second Written Request. These were a pharmacokinetics and safety study in pediatric patients ≥6 months to <2 years of age (Study 1) and a safety study in pediatric patients ≥6 months to <2 years of age (Study 2). This application includes reports of studies conducted to meet the specifications of the Written Request and reports for two additional supportive clinical pharmacology studies. The sponsor fairly met all specifications of the second written request, and was granted pediatric exclusivity on January 27, 2003. The details of the sponsor's satisfaction of the specifications of the second Written Request are described in a separate review, and are not described in this review [NDA 20-625, SE8-012, 11/18/02, Medical Officer Review dated 1/24/03, Charles E. Lee, M.D.].

(b) (4)

2. CLINICALLY RELEVANT FINDINGS FROM CHEMISTRY, TOXICOLOGY, MICROBIOLOGY, BIOPHARMACEUTICS, STATISTICS AND/OR OTHER CONSULTANT REVIEWS

2.1. Chemistry, Manufacturing, and Controls

The composition of the fexofenadine (b) (4) powder used in studies M106455T/1123, M106455T/3001, and M106455T/3002 was identical to that of the contents of the approved and marketed 60-mg fexofenadine capsules [NDA 20-625, SE8-012 C, 4/16/03, Cover Letter, Attachment 1, pages 1-12].

Batch numbers of fexofenadine used in the studies in this application are noted in Table 2.1. For PK study M106455T/1123, the sponsor used 15 mg and 30 mg of fexofenadine HCl (b) (4) powder supplied in capsules. Study treatment was administered in Musselman's® applesauce [Volume 1, page 73]

For safety study M106455T/3001, the sponsor used 15 mg fexofenadine HCl (b) (4) powder supplied in capsules. Study treatment was administered in Musselman's® applesauce or Gerber® rice cereal mixed with Similac® or Isomil® infant formula [Volume 15, page 26].

For safety study M106455T/3002, the sponsor used 30 mg fexofenadine HCl (b) (4) powder supplied in capsules. Study treatment was administered in Musselman's® applesauce or Gerber® rice cereal mixed with Similac® or Isomil® infant formula [Volume 23, page 25].

Table 2.1. Batch of active drug product, Studies M106455T/1123, M106544T/3001, and M106455T/3002 [Volume 1, page 73; Volume 2, pages 32-33; Volume 4, page 234; Volume 15, page 26; Volume 19, page 253; Volume 23, page 25; Volume 27, page 235].

Study	Dosage of fexofenadine HCl	Batch number
M106455T/1123	15 mg 30 mg	KN2000001 KN1999032
M106455T/3001	15 mg	KD2001027
M106455T/3002	30 mg	KD2001028

(b) (4)

2.2. Nonclinical pharmacology and toxicology

Fexofenadine is approved in the US as a prescription drug product. Nonclinical safety studies were not required for this application. The sponsor is not seeking an indication for this age group with this application. (b) (4)

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

There was one pivotal clinical pharmacology study included in this application, study M106455T/1123. This was a multicenter, open-label, single-dose, Phase 1 study. Pharmacokinetic sampling was performed after a single dose of fexofenadine HCl 15 mg or 30 mg. The primary objective of this study was to characterize the pharmacokinetics of fexofenadine in children ≥6 months to <2 years of age after a single oral dose of 15 mg or 30 mg. Following the single 15-mg and 30-mg doses of fexofenadine HCl (b) (4) powder administered in applesauce, the mean AUC_{0-z} values were 767.05 ng.h/mL and 1579.51 ng.h/mL, respectively. Mean AUC_{0-inf} values for 15 mg and 30 mg were 804.29 ng.h/mL and 1660.31 ng.h/mL, respectively. The mean oral clearance was 21.70 L/h for 15 mg and 21.94 for 30 mg. The maximal plasma concentration was 168.69 mg/mL for 15 mg and 328.95 for 30 mg. The mean time to maximum plasma concentration was 1.10 hours for both 15-mg and 30-mg doses [Volume 2, page 58]. Please see Dr. S. Kim's biopharmacology review for more detailed information on PK results from this study.

There were two supportive clinical pharmacology studies in this application, Study PJPR0076, and Study M016455T/1001. PK data from these studies indicate that applesauce was an acceptable vehicle for pivotal pediatric studies M106455T/1123, M106544T/3001, and M106455T/3002. The PK data from the supportive clinical pharmacology studies also indicate that Gerber® rice cereal prepared with Similac® with Iron was an acceptable vehicle for pediatric studies M106544T/3001 and M106455T/3002. These two supportive studies are described briefly below.

Study PJPR0076 was designed, in part, to determine the bioavailability of fexofenadine when administered in applesauce, the vehicle for study M106455T/1123 and the preferred vehicle for studies M106544T/3001 and M106455T/3002. This was a single center, open-label, single-dose, four period, randomized, complete crossover, Phase 1 study. The primary objective of this study was to determine the bioavailability of fexofenadine HCl (b) (4) formulation relative to the marketed immediate release capsule. A secondary objective was to determine the bioavailability of the fexofenadine HCl marketed immediate release capsule when administered with applesauce. The four study treatments were: (1) 2 x (b) (4) 60 mg (b) (4), (2) 2 x (b) (4) 60 mg (b) (4), (3) 2 x marketed 60 mg capsule in applesauce, and (4) 2 x marketed 60 mg capsule. The immediate release capsule administered with applesauce was bioequivalent to the marketed immediate release capsule with respect to AUC. The rate of exposure was higher for the immediate release capsule administered with applesauce than when administered without applesauce, slightly exceeding the upper 90% confidence interval for C_{max} (132.0%) and falling below the lower 90% confidence interval for t_{max} [Volume 31, page 13]. More details may be found in the Dr. Shinja Kim's Clinical Pharmacology and Biopharmaceutics review.

Study M016455T/1001 was designed, in part, to determine the bioavailability of fexofenadine when administered in various vehicles other than applesauce. This study was performed in adults, and does not provide safety data relevant to the proposed labeling. This was a single center, open-label, single-dose, four period, randomized, complete crossover, Phase 1 study. The objective of this study was to compare the bioavailability of 60-mg fexofenadine HCl administered in food delivery vehicles relative

to a 60-mg fexofenadine HCl reference capsule. The drug product studied was oral (b) (4) powder from the marketed immediate release 60-mg fexofenadine capsule. The four study treatments were: (1) 60 mg oral (b) (4) powder in 10 mL of Karo® syrup, (2) 60 mg oral (b) (4) powder in 10 mL of Dannon® vanilla yogurt, (3) 60 mg oral (b) (4) powder in 10 mL of Gerber® rice cereal prepared with Similac® with Iron, and (4) the marketed 60-mg capsule. [Volume 32, pages 4, 19, 20,21, 28]. The fexofenadine (b) (4) powder administered in Gerber® rice cereal prepared with Similac® with Iron applesauce was bioequivalent to the reference fexofenadine capsule administered alone with respect to AUC. C_{max} was slightly higher for the fexofenadine (b) (4) powder administered with Gerber® rice cereal prepared with Similac® with Iron than the fexofenadine capsule administered alone. The C_{max} slightly exceeded the upper 90% confidence interval (127.06) [Volume 32, page 42]. More details may be found in the Dr. Shinja Kim's Clinical Pharmacology and Biopharmaceutics review.

The sponsor performed a population PK analysis of combined data from the pivotal PK study in this application, M106455T/1123, and seven previously performed PK studies in adults and children. Based on this analysis, the sponsor concluded that the appropriate dosage of fexofenadine in children ≥6 months to <6 years of age and ≤10.5 kg in weight was 15 mg twice daily. The sponsor concluded that the appropriate dosage of fexofenadine in children ≥6 months to <6 years of age and >10.5 kg in weight was 30 mg twice daily [Volume 8, page 7].

(b) (4)

Reviewer comment:

(b) (4)

The clinical pharmacology data for fexofenadine 30-mg in children ≥2 to <6 years of age was also reviewed in an earlier submission by Dr. Young-Moon Choi. He concluded that the 30-mg dose of fexofenadine administered in applesauce provided exposures that were

less than that of the approved 30-mg fexofenadine tablets in children ≥6 to <12 years of age, but greater than those achieved in adults with the approved 60-mg capsules and 60-mg tablets [NDA 20-625, SE8-010, 7/12/00, Clinical Pharmacology and Biopharmaceutics Review, Y. Choi, Ph.D.]. (b) (4)

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

This submission refers to three pivotal studies, Studies M106455T/1123, M106455T/3001 and M106455T/3002. Study M106455T/1123 was a Phase 1 study to characterize the pharmacokinetics of fexofenadine after a single oral dose of 15-mg and 30-mg in children ≥6 months to <2 years of age. This study was designed to meet the specifications for the PK study (Study 1) in the second Written Request.

The sponsor found it necessary to perform two safety and tolerability studies in children ≥6 months to <2 years of age to meet the specifications of the second study in the Written Request (Study 2). Two studies were necessary because pharmacokinetics data indicated a smaller dose of fexofenadine would be appropriate for children less than or equal to 10.5 kg. These two studies were Study M106455T/3001 and M106455T/3002. Study M106455T/3001 was a Phase 3 multicenter safety and tolerability study designed to compare the safety and tolerability of fexofenadine HCl 15 mg BID to placebo in children with allergic rhinitis ≥6 months to <2 years of age and ≤10.5 kg in weight. Study M106455T/3002 was a Phase 3 multicenter safety and tolerability study designed to compare the safety and tolerability of fexofenadine HCl 30 mg BID to placebo in children with allergic rhinitis ≥6 months to <2 years of age and >10.5 kg in weight. The sponsor provided a combined study report for M106455T/3002 and M106455T/3002 and also provided individual study reports.

The sponsor also provided reports for two supportive pharmacology studies of the bioavailability of fexofenadine administered with applesauce (Study PJPR0076) and in other food delivery vehicles (Study M016455T/1001).

4.1. Pivotal studies

The sponsor's three pivotal studies are briefly summarized below.

4.1.1. Study M106455T/1123, Pharmacokinetics study

This was a multicenter, open-label, single-dose, Phase 1 study. Pharmacokinetic sampling was performed after a single dose of fexofenadine HCl 15 mg or 30 mg. The primary objective of this study was to characterize the pharmacokinetics of fexofenadine in children ≥6 months to <2 years of age after a single oral dose of 15 mg or 30 mg. A secondary objective was to assess the safety and tolerability of fexofenadine HCl 15 mg and 30 mg BID in children of this age group. Twenty centers participated in this study. There were 65 patients enrolled in this study, and 48 patients received study medication. Two panels of sequential, escalating dose groups were to receive a single dose of study medication. The first panel of patients was given a single oral dose of fexofenadine HCl 15-mg (b) (4) powder. Pharmacokinetic blood samples were collected prior to administration of the first dose and serially up to 24 hours postdose. Safety variables

included adverse events (AEs), vital signs, physical examinations, hematology, blood chemistry, and urinalyses. An interim safety assessment was performed based on AEs, clinical laboratory evaluations, vital signs, physical examinations, and ECGs collected from 18 patients in the first panel who consumed the entire 15-mg dose. A decision was made to proceed to the second panel of patients based on these safety data. The second panel of patients was given a single oral dose of fexofenadine HCl 30-mg (b) (4) powder. Pharmacokinetic blood samples were collected prior to administration of the first dose and serially up to 24 hours postdose. Safety variables for the second panel of patients were the same as for the first [Volume 2, pages 24, 25, 26].

4.1.2. Study M106455T/3001, Safety study

This was a double blind, randomized, and placebo-controlled Phase 3 study. The objective of this study was to compare the safety and tolerability of fexofenadine 15 mg BID to placebo in children ≥6 months to <2 years of age with allergic rhinitis and ≤10.5 kg in weight. A secondary objective was to assess efficacy at 1 week. There were 174 patients in the study and there were 43 study centers. Safety variables included AEs, vital signs, physical examinations, and ECGs. Investigators were to assess the overall severity of allergic rhinitis (AR) symptoms at baseline and at the final visit (1 week or early discontinuation) using a 0 to 4, complete relief to no relief, five-point AR severity scale. Investigators also made an overall assessment of study medication effectiveness taking into account the AR symptom assessments and changes in AR physical finding between the baseline and final visits. This overall assessment of study medication effectiveness also used the 0 to 4, complete relief to no relief, five point AR severity scale [Volume 15, pages 3, 19, 22, 22, 33, 39].

4.1.3. Study M106455T/3002, Safety study

This was a double blind, randomized, and placebo-controlled Phase 3 study. The objective of this study was to compare the safety and tolerability of fexofenadine 30 mg BID to placebo in children ≥6 months to <2 years of age with allergic rhinitis and more than 10.5 kg in weight. A secondary objective was to assess efficacy at 1 week. There were 218 patients in the study and there were 44 study centers. Safety variables included AEs, vital signs, physical examinations, and ECGs. Investigators were to assess the overall severity of AR symptoms at baseline and at the final visit (1 week or early discontinuation) using a 0 to 4, complete relief to no relief, five-point AR severity scale. Investigators also made an overall assessment of study medication effectiveness taking into account the AR symptom assessments and changes in AR physical findings between the baseline and final visits. This overall assessment of study medication effectiveness also used the 0 to 4, complete relief to no relief, five point AR severity scale [Volume 23, pages 3, 4, 20, 31, 38].

4.2. Supportive studies

The sponsor's two supportive pharmacology studies are described below, and are summarized in Table 4.1.

4.2.1. Study PJPR0076

This was a single center, open-label, single-dose, four period, randomized, complete crossover, Phase 1 study. There was a washout period of 6 days between study periods. The primary objective of this study was to determine the bioavailability of fexofenadine HCl (b) (4) formulation relative to the marketed immediate release capsule. A secondary objective was to determine the bioavailability of the fexofenadine HCl marketed immediate release capsule when administered with applesauce. The four study treatments were: (1) 2 x (b) (4) 60 mg (b) (4) (2) 2 x (b) (4) 60 mg (b) (4) (3) 2 x marketed 60 mg capsule in applesauce, and (4) 2 x marketed 60 mg capsule. Twenty centers participated in this study. Subjects were healthy adult males. There were 22 subjects enrolled in this study, and 22 subjects received study medication. Pharmacokinetic blood samples were collected prior to administration of study treatment and serially up to 48 hours postdose. Safety variables included adverse events (AEs), vital signs, and clinical laboratory specimens. A case report form was not provided for the one serious adverse event (SAE), a subject who had an episode of syncope [Volume 31, pages 9, 10, 17, 19, 20, 35, 308].

4.2.2. Study M016455T/1001

This was a single center, open-label, single-dose, four period, randomized, complete crossover, Phase 1 study. There was a washout period of 6 days between study periods. The objective of this study was to compare the bioavailability of 60-mg fexofenadine HCl administered in food delivery vehicles relative to a 60-mg fexofenadine HCl reference capsule. The four study treatments were: (1) 60 mg oral (b) (4) powder in 10 mL of Karo® syrup, (2) 60 mg oral (b) (4) powder in 10 mL of Dannon® vanilla yogurt, (3) 60 mg oral (b) (4) powder in 10 mL of Gerber® rice cereal prepared with Similac® with Iron, and (4) marketed 60 mg capsule. Twenty centers participated in this study. Subjects were healthy adult males. There were 24 subjects enrolled in this study, and 24 subjects received study medication. Pharmacokinetic blood samples were collected prior to administration of study treatment and serially up to 48 hours postdose. Safety variables included AEs, vital signs, physical examinations, and clinical laboratory specimens. [Volume 31, pages 4, 19, 20, 28, 39, 43, 50, 51].

Table 4.1. Summary of studies, NDA 20-625, SE8-012.

Study Number	Study Type	Treatment Groups	Duration of treatment	Design	Number of subjects	Population	Materials submitted in this efficacy supplement
M106455T/1123	Pivotal pharmacology study	Fexofenadine HCl (b) (4) powder, 15 mg and 30 mg Single dose, two panels of patients	Single dose	Open-label, 20 centers	48	AR or candidates for antihistamine therapy 6 to 24 months of age	Protocol Study report Line listings Case report forms
M106455T/3001	Pivotal safety study	Fexofenadine HCl (b) (4) powder, 15 mg BID Placebo (b) (4) powder	1 week	Double-blind, randomized, placebo-controlled, parallel group, 43 centers	174	AR or candidates for antihistamine therapy 6 to 24 months of age weight ≤10.5 kg	Protocol Study report Line listings Case report forms
M106455T/3002	Pivotal safety study	Fexofenadine HCl (b) (4) powder, 30 mg BID Placebo (b) (4) powder	1 week	Double-blind, randomized, placebo-controlled, parallel group, 44 centers	218	AR or candidates for antihistamine therapy 6 to 24 months of age weight >10.5 kg	Protocol Study report Line listings Case report forms
PJPR0076	Supportive pharmacology study	2 x (b) (4) 60 mg (b) (4) 2 x (b) (4) 60 mg (b) (4) 2 x marketed 60 mg capsule in applesauce 2 x marketed 60 mg capsule	Single dose	Open-label, four period, randomized, complete crossover Single center	22	Healthy adult males 19-39 years of age	Protocol Study report Line listings Case report form not provided for single SAE
M016455T/1001	Supportive pharmacology study	60 mg oral (b) (4) powder in 10 mL of Karo® syrup 60 mg oral (b) (4) powder in 10 mL of Dannon® vanilla yogurt 60 mg oral (b) (4) powder in 10 mL of Gerber® rice cereal prepared with Similac® with Iron 60 mg marketed capsule	Single dose	Open-label, four period, randomized, complete crossover Single center	24	Healthy adult males 19-44 years of age	Protocol Study report Line listings

5. CLINICAL REVIEW METHODS

A summary of review methods follows, and includes a description of the conduct of the review and an assessment of data quality.

5.1. Conduct of the review

This submission refers to three pivotal studies, Studies M106455T/1123, M106455T/3001 and M106455T/3002. Study M106455T/1123 was a Phase 1 study to characterize the pharmacokinetics of fexofenadine after a single oral dose of 15-mg and 30-mg in children ≥6 months to <2 years of age. This study was designed to meet the specifications for the PK study (Study 1) in the second Written Request. The sponsor was granted pediatric exclusivity on January 27, 2003.

The sponsor's pivotal studies were individually reviewed, with a focus on safety findings. The details of the sponsor's satisfaction of the specifications of the second Written Request are described in a separate review, and are not described in this review [NDA 20-625, SE8-012, 11/18/02, Medical Officer Review dated 1/24/03, Charles E. Lee, M.D.].

The sponsor also provided reports for two supportive pharmacology studies of the bioavailability of fexofenadine administered with applesauce (Study PJPR0076) and in other food delivery vehicles (Study M016455T/1001). These studies were briefly reviewed.

A brief Integrated Review of Efficacy is included in this review. In addition to the studies included in this submission, the sponsor refers to results from the previously completed and reviewed safety study M106455I/3112 and PK study M106455I/1114, both performed in children ≥2 to <6 years of age, in order to address use of fexofenadine in children over the entire age range from ≥6 months to <6 years of age.

Safety data supporting this application was reviewed in depth for this review's Integrated Review of Safety. These data included integrated safety data from pediatric safety studies, subpopulation analyses by gender and race of safety data from pediatric safety studies, the sponsor's evaluation of AE reports in children <12 years of age from worldwide spontaneous adverse event reports, and a review of published literature related to safety in the pediatric age group.

5.2. Data quality

DSI audit of the study center that performed both pivotal clinical pharmacology studies was not requested because assessment of efficacy was not the primary objective of this study and because the sponsor was not seeking an indication for the product.

5.2.1. Ethical standards and financial disclosure

The following items were included in this submission:

- Debarment certification [Volume 34, page 257]

- Financial disclosure statement [Volume 34, page Volume 34, pages 241-256]
  - There were no investigators with disclosable financial interests in any of the studies in this application [Volume 34, pages 241-256].

The sponsor certified that they did not use and would not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application. The sponsor 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 sponsor certified that the clinical investigators did not have a proprietary interest in the proposed product or a significant equity in the sponsor. The sponsor certified that no investigator was the recipient of significant payments.

Overall, the data in this application appear to be acceptable for review in this reviewer's opinion.

6. INTEGRATED REVIEW OF EFFICACY

In addition to the studies included in this submission, this Integrated Review of Efficacy also includes references to results from the previously completed and reviewed safety study M106455I/3112 and PK study M106455I/1114. Data from PK study M106455I/1114 was previously submitted in a pediatric supplement that received an approvable action on May 14, 2001 [NDA 20-625, SE8-010 PM, 7/12/00, Medical Officer Review, Charles E. Lee, M.D.]. Data from safety study M106455I/3112 was previously submitted in a pediatric labeling supplement that received an approvable action on August 12, 2002 [NDA 20-625, SE08-010, 2/12/02, Medical Officer Review, Charles E. Lee, M.D.]. This current NDA submission represents the sponsor's response to the Division's approvable actions for these submissions and addresses the efficacy of fexofenadine in children over the age range from 6 months to <6 years of age.

Allegra® is currently approved for SAR and CIU indications in adults and children 6 years of age and older in the United States. The approval of Allegra® for the treatment of SAR in patients 6 to 11 years of age was based on the results of one trial, the extrapolation of demonstrated efficacy in patients ages 12 years and above, and pharmacokinetic comparisons in adults and children. The approval of Allegra® for the treatment of CIU in patients 6 to 11 years of age was based on an extrapolation of the demonstrated efficacy of Allegra® in adults with this condition and the likelihood that the disease course, pathophysiology and the drug's effect are substantially similar in children to that of adult patients.

Studies M106455T/3001 and M106455T/3002 assessed the safety and tolerability of 15 mg and 30 mg of fexofenadine in children ≥6 months to <2 years of age. These studies were included in this submission. Study M106455I/3112 assessed the safety and tolerability of 30 mg of fexofenadine in children ≥2 years to <6 years of age. This study was previously reviewed [NDA 20-625 S010, 2/12/02, Medical Officer Review, Charles E. Lee, M.D.]. None of these three studies were designed to rigorously assess efficacy [NDA 20-625 SE8-012 BZ, 2/27/03. Cover Letter, page 2].

Studies M106455T/3001 and M106455T/3002 are reviewed in the Appendix to this review, Sections 11.2 and 11.3. Treatment groups in M106455T/3001 and M106455T/3002 had similar degrees of change from baseline in overall assessment of allergic rhinitis symptoms and similar degrees of relief in the overall assessment of study medication effectiveness. (b) (4) As noted above, however, assessment of efficacy was only a secondary objective of these studies.

Study M106455I/3112 has previously been reviewed [Medical Officer Review, NDA 20-625, SE8-010, 2/12/02, Charles E. Lee, M.D.]. Parent\guardian-assessed Total Symptom Scores showed little difference between fexofenadine and placebo in this study, as did most parent/guardian-assessed individual symptom scores. Investigator assessment of relief from AR signs and symptoms and change in detailed examination of individual AR signs provided some hint of efficacy in the fexofenadine group. This study, like M106455T/3001 and M106455T/3002, was designed to assess efficacy only as a secondary objective.

(b) (4)

(b) (4)

7. INTEGRATED REVIEW OF SAFETY

7.1. Summary and conclusions

A review of the pooled safety data from studies M106455T/3001, M106455T/3002, and M106455I/3112 follows. Collectively, these studies were designed to examine the safety and tolerability of fexofenadine in children with allergic rhinitis ≥6 months to <6 years of age. A total of 415 patients were exposed to fexofenadine in these studies. The majority of patients were of Caucasian race. Patients of Black race were represented in proportion to the general population. There were few patients of other races in these studies. Exposure was adequate to assess safety.

AEs were fairly common and occurred at similar frequencies for placebo (49.3%, 212/430), fexofenadine 15 mg (40.0%, 34/85), and fexofenadine 30 mg (45.2%, 149/330). AEs occurring at rate ≥3.0% in any group and more commonly in fexofenadine than placebo included vomiting, otitis media, increased cough, rhinitis, sore throat/pharyngitis, accidental injury, diarrhea, rash, and gastroenteritis. The differences

between fexofenadine and placebo in frequencies of AEs are likely to be due to chance. There were no meaningful differences between treatment groups in AEs leading to withdrawal from the studies. Vital signs, physical examinations, laboratory studies, and ECGs reveal no safety signal. The sponsor's review of the literature reveals no new safety signal. Their search of the their global pharmacovigilance database also provides no evidence of new safety signal.

7.2. Content

The following are reviewed in this Integrated Review of Safety:

- Integrated safety data from pediatric safety studies
  - The sponsor's analysis of integrated data from pediatric safety studies includes pooled data from the safety studies in this submission M106455T/3001 and M106455T/3002 and from a pediatric safety study previously submitted by the sponsor, M106455I/3112. Study M106455I/3112 was reviewed previously [NDA 20-625 S010, 2/12/02, Medical Officer Review, Charles E. Lee, M.D.]. The age groups in these studies were:
    - M106455T/3001: Ages ≥6 months to 2 years and ≤10.5 kg in weight, 15 mg fexofenadine BID
    - M106455T/3002: Ages ≥6 months to 2 years and >10.5 kg in weight, 30 mg fexofenadine BID
    - M106455I/3112: Ages ≥2 to <6 years of age, 30 mg fexofenadine BID
- Subpopulation analysis by gender and race of safety data from pediatric safety studies
- Sponsor's evaluation of AE reports in children <12 years of age from worldwide spontaneous adverse event reports
- Review of published literature related to safety in the pediatric age group

Reviewer comment:
The data from study M106455I/3112 was included in a pediatric labeling supplement that received an approvable action on August 12, 2002 [NDA 20-625, SE08-010, 2/12/02, Medical Officer Review, Charles E. Lee, M.D.]. It is acceptable to include data from the previously completed and reviewed study M106455I/3112 in this safety review because the current NDA submission represents the sponsor's response to the Division's approvable action. In addition, the sponsor's proposed labeling addresses the safety of fexofenadine in children over the age range from ≥6 months to <6 years of age.

7.3. Integrated safety data

A review of the pooled safety data from studies M106455T/3001, M106455T/3002, and M106455I/3112 follows.

7.3.1. Description of studies

Study M106455T/3001 was a multicenter, double blind, randomized placebo controlled, parallel group study to assess the safety and tolerability of fexofenadine in children with allergic rhinitis ages ≥6 months to <1 year and ≤10.5 kg in weight. Children ages ≥1 year to <2 years and ≤10.5 kg in weight could also be enrolled. The treatment period was 7

days [Volume 34, pages 209-210]. Study treatment was administered in applesauce or rice cereal prepared with infant formula [Volume 34, pages 209-210].

Study M106455T/3002 was a multicenter, double blind, randomized placebo controlled, parallel group study to assess the safety and tolerability of fexofenadine in children with allergic rhinitis ages ≥1 year to <2 years and ≥10.5 kg in weight. Children ages ≥6 months to <1 year and ≥10.5 kg in weight could also be enrolled. The treatment period was 7 days. Study treatment was administered in applesauce or rice cereal prepared with infant formula [Volume 34, pages 209-210].

Study M106455I/3112 was a multicenter, double blind, randomized placebo controlled, parallel group study to assess the safety and tolerability of fexofenadine in children with allergic rhinitis ages ≥2 years to <6 years. The treatment period was 2 weeks. Study treatment was administered in applesauce [Volume 34, pages 209-210].

7.3.2. Demographics

Demographics of patients participating in safety studies M106455T/3001 and M106455T/3002, and M106455I/3112 are summarized in Table 7.3.1. As noted above, data from study M106455I/3112 for patients ≥2 to <6 years of age was included in a pediatric labeling supplement that received an approvable action on August 12, 2002 [NDA 20-625, SE08-010, 2/12/02, Medical Officer Review, Charles E. Lee, M.D.].

A total of 415 patients were exposed to fexofenadine in these studies. The majority of patients receiving fexofenadine were exposed to the 30-mg dose. The majority of patients were from ≥2 to<6 years of age (53.6%, 453/845), but patients <2 years of age were well represented (46.4%, 392/845). Patients in these studies were evenly distributed by gender. The majority of patients were of Caucasian race. Patients of Black race were represented in proportion to the general population. There were few patients of other races in these studies.

Table 7.3.1. Demographics, pooled data for safety studies M106455T/3001, M106455T/3002, and M106455I/3112 [Volume 34, page 211; NDA 20-625 SE08-012 BZ, Attachment S2, pages 5, 6].

	Placebo n	15 mg n	30 mg n	15 mg + 30 mg n	All patients n (%)
Studies					
All studies	430	85	330	415	845 (100)
M10455T/3001	89	85	0	85	174 (20.1)
M10455T/3002	110	0	108	108	218 (25.8)
M10455I/3112	231	0	222	222	453 (53.6)
					N = 845 n (%)
Age					
≥6 months to <1 year	69	58	5	63	132 (15.6)
≥1 year to <2 years	130	27	103	130	260 (30.8)
≥2 years to <6 years	231	0	222	222	453 (53.6)
Gender					
Female	196	38	142	180	376 (44.5)
Male	234	47	188	235	469 (55.5)

	Placebo n	15 mg n	30 mg n	15 mg + 30 mg n	All patients n (%)
Race					
Caucasian	334	59	268	327	661 (78.2)
Black	54	13	31	44	98 (11.6)
Asian/Oriental	1	1	1	2	3 (0.4)
Multiracial	23	7	13	20	43 (5.1)
Other	18	5	17	22	40 (4.7)

Note: Data in the sponsor's tables in Volume 34, page 211 and NDA 20-625 SE08-012 BZ, Attachment S2, page 4 includes a transposition error for patients in Study M106455T/3002. The above table includes the correct data.

7.3.3. Exposure

Exposure to study medication may be estimated by compliance data. Studies M106544T/3001 and M106455T/3002 were one week in duration. In study M10455T/3001, 84.7% (72/85) of fexofenadine-treated patients took ≥80% of all doses of study medication [Volume 15, page 92]. In study M10455T/3002, 87.0% (94/108) of fexofenadine-treated patients took ≥80% of all doses of study medication [Volume 23, page 89].

Study M106455I/3112 was two weeks in duration. In study M10455I/3112, 82.4%, (183/222) of fexofenadine-treated patients took ≥80% of the prescribed study medication [NDA 20-625 SE8-010, 2/12/02, clinstat\pediatricrhinitis\3112.pdf, pages 52, 107].

Reviewer comment:
Exposure was adequate to assess safety.

7.3.4. Adverse events

AEs are summarized below in Table 7.3.2. AEs were fairly common and occurred at similar frequencies for placebo (49.3%, 212/430), fexofenadine 15 mg (40.0%, 34/85), and fexofenadine 30 mg (45.2%, 149/330). AEs occurring at rate ≥3.0% in any group and more commonly in fexofenadine than placebo included vomiting, otitis media, increased cough, rhinitis, sore throat/pharyngitis, accidental injury, diarrhea, rash, and gastroenteritis. Vomiting was more frequent for the group receiving fexofenadine 15 mg (14.1%, 12/85) than for fexofenadine 30 mg (5.2%, 17/330) or placebo 8.8%, 38/430). The majority of subjects experienced AEs that were mild or moderate in intensity. Only two patients in the fexofenadine group (0.5%) but 8 subjects in the placebo group experienced AEs that were severe in intensity. The sponsor concluded that there were no meaningful differences in AEs for fexofenadine and placebo groups and that there were no AEs noted that were not part of the known safety profile for fexofenadine [Volume 34, pages 212-213, 217-220].

Table 7.3.2. Adverse events occurring more commonly in fexofenadine than placebo and at a frequency of ≥3.0% in any group, integrated data, safety studies M106455T/3001, M106455T/3002, and M106455I/3112 [Volume 34, pages 217-220].

Adverse event	Placebo N = 430		Fexofenadine 15 mg N = 85		Fexofenadine 30 mg N = 330		All fexofenadine N = 415	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients with AEs	212	(49.3)	34	(40.0)	149	(45.2)	183	(44.1)
Vomiting	38	(8.8)	12	(14.1)	17	(5.2)	39	(7.0)
Otitis media	14	(3.3)	3	(3.5)	15	(4.5)	18	(4.3)

Adverse event	Placebo N = 430		Fexofenadine 15 mg N = 85		Fexofenadine 30 mg N = 330		All fexofenadine N = 415	
	n	(%)	n	(%)	n	(%)	n	(%)
Cough increased	15	(3.5)	2	(2.4)	14	(4.2)	16	(3.9)
Rhinitis	14	(3.3)	2	(2.4)	12	(3.6)	14	(3.4)
Sore throat/pharyngitis*	6	(1.4)	0	(0)	11	(3.3)	11	(2.6)
Accidental injury	8	(1.9)	1	(1.2)	11	(3.3)	12	(2.9)
Diarrhea	11	(2.6)	4	(4.7)	11	(3.3)	15	(3.6)
Rash	9	(2.1)	5	(5.9)	5	(1.5)	10	(2.4)
Gastroenteritis	5	(1.2)	3	(3.5)	2	(0.6)	5	(1.2)

*AEs for sore throat and pharyngitis are combined.

The percentages of male and female patients who experienced AEs were comparable between treatment groups. No particular AE was identified that occurred more frequently in female or male patients. The majority of patients in the studies were of Caucasian race. No particular AE was noted that appeared to be more frequent in patients of a particular race [NDA 20-625, SE9-012 BZ, 2/27/03, Attachment 2, pages 9-10].

In the Written Requests for pediatric studies, the Agency asked the sponsor to evaluate AEs for paradoxical hyperexcitability, somnolence, fatigue, and/or hyperkinesia. These data are presented in Table 7.3.3. There was a suggestion of an association of somnolence with both fexofenadine dose, however there were small numbers of AEs noted, and this association could be due to chance.

Table 7.3.3. Adverse events of special interest, integrated data, safety studies M106455T/3001, M106455T/3002, and M106455I/3112 [Volume 34, pages 217-220].

			Fexofenadine					
Adverse event	Placebo N = 430		Fexofenadine 15 mg N = 85		Fexofenadine 30 mg N = 330		All fexofenadine N = 415	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients with AEs	212	(49.3)	34	(40.0)	149	(45.2)	183	(44.1)
Somnolence	1	(0.2)	1	(1.2)	5	(1.5)	6	(1.4)
Asthenia	0	(0)	0	(0)	1	(0.3)	1	(0.3)
Nervousness	1	(0.2)	0	(0)	1	(0.3)	1	(0.2)
Agitation	4	(0.9)	0	(0)	0	(0)	0	(0)

Reviewer comments:
Vomiting was noted in a higher proportion of patients taking 15 mg fexofenadine compared with placebo patients from all studies. However, the frequency of vomiting was similar in patients taking 15 mg fexofenadine (15.7, 14/89) and placebo (14.1%, 12/85) within study M106455T/3001 [Volume 15, page 103]. Otitis media, accidental injury, and coughing are noted in the current Allegra® label. The differences between fexofenadine and placebo in frequencies of AEs are likely to be due to chance. It is interesting that there was a suggestion of an association of somnolence with the 30-mg and 15-mg doses of fexofenadine, however there were small numbers of AEs noted.

7.3.5. SAEs and deaths

There were three SAEs in safety studies M106455T/3001, M106455T/3002, and M106455I/3112. There were no deaths. Two SAEs occurred in placebo-treated patients. These were a 9-month old male who developed bronchiolitis and required hospitalization, and a 3-year old male who experienced an allergic reaction with generalized itching,

sneezing, facial flushing, coughing, and wheezing after taking placebo treatment. The patient was treated with oral cetirizine. One SAE occurred in a fexofenadine treated patient. This patient was a 4-year old female who developed a worsening of asthma on day 8 of fexofenadine treatment. She required hospitalization, nebulizer treatments, and prednisone [Volume 34, pages 213-214].

Reviewer comment:
As noted in the previous review of study M106455I/3112, the severe allergic reaction experienced by the child with the first exposure to placebo treatment is interesting. The placebo product included denatonium benzoate (Bitrex®), gelatin, lactose, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, magnesium stearate, purified water, and was enclosed in a hard gelatin capsule [NDA 20-625, SE8-010 BZ, 6/1/02, page 12]. The child had allergies to milk, egg, peanut, cashew, and tomato, and reacted to exposure to these foods with worsening of atopic dermatitis. He had no history of anaphylaxis from exposure to these foods [NDA 20-625, SE8-010 BZ, 6/1/02, page 2]. The child must have been exquisitely sensitive if he reacted to milk proteins in the lactose excipient. It is also possible that he may have reacted to another excipient in the drug product, such as gelatin, or to the applesauce vehicle itself.

7.3.6. Withdrawals due to AEs

There was a slightly higher percentage of patients in the placebo group who withdrew from the study because of AEs (6.0%, 26/430) than patients treated with fexofenadine (4.1%, 17/415). AEs resulting in withdrawal from the study were fairly similar in character and frequency, and included asthma, increased cough, gastroenteritis, otitis media, among others. The sponsor noted that there was no clinically meaningful difference between treatment groups in AEs leading to withdrawal from the study [Volume 34, pages 214, 238-240].

Reviewer comment:
This reviewer concurs that there are no meaningful differences between treatment groups in AEs leading to withdrawal from the studies.

7.3.7. Vital signs

The sponsor did not pool data for analysis of vital signs [Volume 34, page 214]. Studies M106455T/3001 and M106455T/3002 are reviewed in the Appendix to this review, Sections 11.2 and 11.3. Study M106455I/3112 has previously been reviewed [Medical Officer Review, NDA 20-625, SE8-010, 2/12/02, Charles E. Lee, M.D.].

In studies M106455T/3001 and M106455T/3002, there were no clinically meaningful changes in vital signs and shift tables showed similar proportions of patients with increases and decreases in values for vital signs [Volume 15, pages 61, pages 129-147; Volume 23, pages 58, 128-133, 146]. In study M106455I/3112 there were no clinically meaningful differences between treatment groups in mean change from baseline in VS. In general, the distribution of patients that had abnormal VS meeting predefined criteria was similar between treatment groups [NDA 20-625, SE8-010,

clinstat\pediatricrhinitis\3112.pdf, pages 74, 364;
clinstat\pediatricrhinitis\3112\3112c.pdf, page 4035].

Reviewer comment:
Vital signs reveal no safety signal.

7.3.8. Physical examination

Physical examinations were performed as safety endpoints in all three safety studies [Volume 34, page 215]. The sponsor did not pool the data for analysis. Studies M106455T/3001 and M106455T/3002 are reviewed in the Appendix to this review, Sections 11.2 and 11.3. Study M106455I/3112 has previously been reviewed [Medical Officer Review, NDA 20-625, SE8-010, 2/12/02, Charles E. Lee, M.D.].

Summary tables for physical examinations were reviewed. There were no clinically significant changes noted in any of the three safety studies [Volume 15, page 62, 162-168; Volume 23, pages 60, 161-167l; NDA 20-625, SE8-010, 2/12/02, clinstat\pediatricrhinitis\3112.pdf, pages 371-376].

Reviewer comment:
Physical examinations reveal no safety signal.

7.3.9. Laboratory studies

Laboratory studies were not performed as part of studies M106455T/3001 or M106455T/3002. A subgroup of 130 patients in study M106455I/3112 had laboratory evaluations as safety endpoints [Volume 34, page 214]. Study M106455I/3112 has previously been reviewed [Medical Officer Review, NDA 20-625, SE8-010, 2/12/02, Charles E. Lee, M.D.]. There were no clinically significant changes from baseline in mean values for laboratory studies in either treatment group in this study [NDA 20-625, SE8-010, 2/12/02, clinstat\pediatricrhinitis\3112.pdf, pages 71-72, 321-354].

Reviewer comment:
Laboratory studies reveal no safety signal.

7.3.10. ECGs

The sponsor did not pool data for analysis of ECGs [Volume 34, page 214]. Studies M106455T/3001 and M106455T/3002 are reviewed in the Appendix to this review, Sections 11.2 and 11.3. Study M106455I/3112 has previously been reviewed [Medical Officer Review, NDA 20-625, SE8-010, 2/12/02, Charles E. Lee, M.D.].

No clinically significant differences were observed between treatment groups in PR interval, QRS interval, QTcB, QTcF, or heart rate. Shift tables showed similar proportions of patients in both treatment groups with increases and decreases in values for ECG parameters in the small number of patients whose values fell outside of the predefined change criteria [Volume 15, pages 61-62, 149-161; Volume 23, pages 58-59,

149-161; NDA 20-625, SE8-010, 2/12/02, clinstat\pediatricrhinitis\3112.pdf, pages 76-77].

Reviewer comment:
Review of data for ECGs reveals no evidence of clinically significant change or safety signal.

7.4. Subpopulation analysis by gender and race of safety data from pediatric safety studies

The percentages of male and female patients who experienced AEs in pediatric safety studies M106455T/3001, M106455T/3002, and M106455I/3112 were comparable between treatment groups. No particular AE was identified that occurred more frequently in female or male patients. The majority of patients in these studies were of Caucasian race. No particular AE was noted that appeared to be more frequent in patients of a particular race [NDA 20-625, SE9-012 BZ, 2/27/03, Attachment 2, pages 9-10].

7.5. Evaluation of safety information from the clinical literature

The sponsor performed a search of the medical literature of publications related to the safety of fexofenadine in children less than 12 years of age. The search was performed on Embase and Medline databases with the search keywords "pediatric," "paediatric," "Allegra," "fexofenadine," and "Telfast" [NDA 20-625, SE8-012 BZ, cover letter, page 3].

The search identified two articles describing clinical studies of fexofenadine in children. The first article describes results of two studies of the efficacy and safety of fexofenadine 15 mg, 30 mg, and 60 mg twice daily for two weeks in children with allergic rhinitis ages 6 through 11 years. These were double blind, randomized, placebo controlled studies. The author concluded that there was no relationship between incidence of AE and fexofenadine dose.[1]

The second article describes the results of a PK and skin test suppression study of 30 mg and 60 mg fexofenadine in 14 children, mean age 9.8 years. No safety signals were noted in this study.[2]

The sponsor's search also identified five abstracts describing studies of fexofenadine in children with seasonal allergic rhinitis [NDA 20-625, SE8-012 BZ, Attachment 4]. These abstracts provide little additional safety information.

Reviewer comment:
Although the author of the first paper concluded that there was no relationship between incidence of AE and fexofenadine dose, data presented in the article suggest a dose related association with accidental injury and fexofenadine. The frequency of this AE was higher for placebo (1.3%, 3/229) than with fexofenadine 15 mg (1.8%, 4/224), 30 mg

[1] Graft DF et. al. Ann Allergy Asthma Immunol 2001;87(2):22-26.
[2] Simons FE, et. al. J Allergy Clin Immunol 1996;98(6 part 1):106+2-1064.

(2.9%, 6/209), and 60 mg (4.2%, 9/213). These studies were those that provided support for the approval of fexofenadine 30 mg in children ages 6 through 11 years, and this AE is noted in the current Allegra® labeling. It is interesting to note that accidental injury was noted more frequently in the 30 mg fexofenadine group (3.3%, 11/330) than placebo (1.9%, 8/430) in the safety studies summarized in the Integrated Review of Safety of this application, Section 7.3.4. The sponsor's review of the literature reveals no new safety signal.

7.6. Sponsor's evaluation of safety information from worldwide spontaneous adverse event reports

The sponsor performed a search of the Aventis global pharmacovigilance database, ClinTrace™ using MedDRA to detect all cases of patients less than 12 years of age. The search covered the entire postmarketing period of fexofenadine since the first market approval of fexofenadine in children 6 to 12 years of age in New Zealand on October 14, 1999 [NDA 20-625, SE8-012 BZ, 2/27/03, Attachment 3, page 1].

The sponsor identified 245 spontaneous AE reports in 124 patients less than 12 years of age. Twenty-nine of these cases were assessed as serious. The five most common AEs in children less than 12 years of age overall were drug ineffective (17/245), no adverse drug effect (14/245), headache (10/245), psychomotor activity (8/245), and somnolence (7/245). There were four AEs with death with an outcome. These four AEs occurred in a baby boy with multiple congenital abnormalities who was born to a mother exposed to fexofenadine, loratadine, and beclomethasone for 13 days in early pregnancy. The infant died after an unsuccessful attempt to dilate a congenitally stenotic pulmonary artery [NDA 20-625, SE8-012 BZ, 2/27/03, Attachment 3, pages 1-2, and Children <12 years, Frequency Listing].

In children ages 6 to 12 years of age, the most common AEs were drug ineffective (15/183), headache (10/183), no adverse drug effect (7/183), psychomotor activity (7/183), and depression (4/183). In children less than 6 years of age, the most common AEs were no adverse drug effect (7/62), accidental exposure (3/62), somnolence (3/62), and vomiting (3/62) [NDA 20-625, SE8-012 BZ, 2/27/03, Attachment 3, Children 6-12 years and ≤6 years, Frequency Listings].

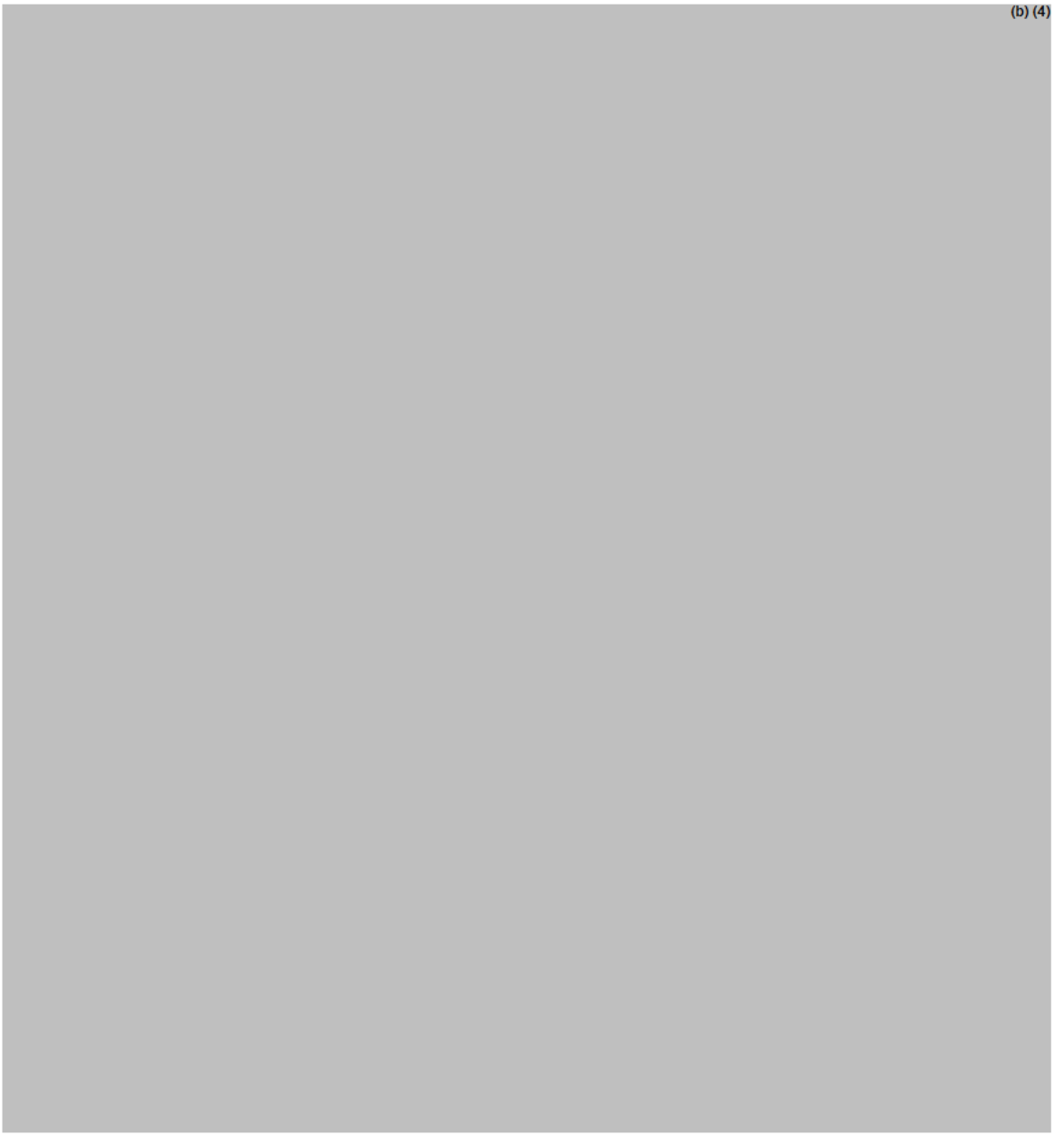
The sponsor concluded that the adverse events was comparable to the AE profile seen in adults and does not reveal evidence of a new safety signal [NDA 20-625, SE8-012 BZ, 2/27/03, Attachment 3, page 2].

Reviewer comment:
This reviewer agrees that these data provide no evidence of new safety signal.

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

The pivotal studies in this application in children ≥6 months to <2 years in age and those previously performed in children ≥2 years to <6 years of age used fexofenadine (b) (4) powder. The (b) (4) powder is identical to the contents of the approved

and marketed 60-mg fexofenadine capsules. The (b) (4) powder was administered in either Musselman's® applesauce or in Gerber® rice cereal mixed with either Similac® or Isomil® infant formulas.



9. USE IN SPECIAL POPULATIONS

Use in relevant special populations is discussed below.

9.1. Elderly

This application is a pediatric labeling supplement with clinical data. Use in the elderly was not addressed and is not relevant to this application.

9.2. Pediatric population

This application is a pediatric labeling supplement with clinical data. The pediatric population is the population addressed in this review. (b) (4)

9.3. Gender

There was no subgroup analysis of efficacy by gender in this application because evaluation of efficacy was not the primary objective of the studies in this application. The percentages of male and female patients who experienced AEs in pediatric safety studies M106455T/3001, M106455T/3002, and M106455I/3112 were comparable between treatment groups. No particular AE was identified that occurred more frequently in female or male patients [NDA 20-625, SE9-012 BZ, 2/27/03, Attachment 2, pages 9-10].

9.4. Race

There was no subgroup analysis of efficacy by race in this application because evaluation of efficacy was not the primary objective of the studies in this application. The majority of patients in pediatric safety studies M106455T/3001, M106455T/3002, and M106455I/3112 were of Caucasian race. No particular AE was noted that appeared to be more frequent in patients of a particular race [NDA 20-625, SE9-012 BZ, 2/27/03, Attachment 2, pages 9-10].

9.5. Pregnancy and lactation

This application is a pediatric labeling supplement with clinical data. Use in the pregnancy in lactation was not addressed and is not relevant to this application.

10. CONCLUSIONS AND RECOMMENDATIONS

This application is a pediatric labeling supplement for Allegra® Tablets (fexofenadine HCl, NDA 20-625), Allegra® Capsules (fexofenadine HCl, NDA 20-872), and Allegra® D Tablets (fexofenadine HCl, pseudoephedrine HCl, NDA 20-786). The application was also filed as a response to the two previous approvable actions. The pivotal studies in the application were performed in response the Division's second Written Request, which was dated April 23, 2001, and amended on November 6, 2001.

(b) (4)

Collectively, the clinical studies were designed to examine the safety and tolerability of fexofenadine in children with allergic rhinitis ≥6 months to <6 years of age. A total of 415 patients were exposed to fexofenadine in these studies. Exposure was adequate to assess safety. AEs were fairly common and occurred at similar frequencies for placebo (49.3%, 212/430), fexofenadine 15 mg (40.0%, 34/85), and fexofenadine 30 mg (45.2%, 149/330). AEs occurring at rate ≥3.0% in any group and more commonly in fexofenadine than placebo included vomiting, otitis media, increased cough, rhinitis, sore throat/pharyngitis, accidental injury, diarrhea, rash, and gastroenteritis. The differences between fexofenadine and placebo in frequencies of AEs are likely to be due to chance. There were no meaningful differences between treatment groups in AEs leading to withdrawal from the studies. Vital signs, physical examinations, laboratory studies, and ECGs reveal no safety signal. The sponsor's review of the literature and of their postmarketing pharmacovigilance database reveal no new safety signal. (b) (4)

The disease course and pathophysiology of SAR and CIU and the drug's effect are substantially similar in children to that of adult patients. Efficacy for SAR and CIU for antihistamines may be difficult to establish, even in studies of adults. (b) (4)

(b) (4)

(b) (4)

(b) (4)

11. APPENDIX, CLINICAL STUDIES

11.1. Study M106455T/1123: A multicenter study of single escalating dose safety and pharmacokinetics of oral fexofenadine hydrochloride in children from 6 months through 2 years of age

Date first patient enrolled: 6/6/01
Date last patient completed the study: 12/14/01
Date of study report: 8/2/02
[Volume 2, page 1]

11.1.1. Objectives

The primary objective of this study was to characterize the pharmacokinetics of fexofenadine following a single oral dose of fexofenadine HCl 15 mg or 30 mg in children from 6 months to 2 years of age. A secondary objective of this study was to characterize the safety and tolerability of 15 mg or 30 mg fexofenadine HCl in children of this age group [Volume 2, page 24].

11.1.2. Study design

This was a multicenter, open-label, single rising dose pharmacokinetic Phase 1 in children from 6 months to 2 years of age. The study recruited patients ages 6 months to 2 years who were candidates for antihistamine therapy or patients who had tolerated a therapeutic course of antihistamines in the preceding 6 months [Volume 2, pages 27-29]. Eighteen children per dose group in each of the two age groups (≥6 months to <1 year and ≥1 year to <2 years) were to complete the study, with at least 6 patients in each age group. The age distribution was to be in a ratio of approximately 1:2 between the younger and the older age group. To reach 18 completed patients per dose group, study sites were to enroll 24 patients for the 15 mg dose panel. Another 24 children were to receive a 30 mg dose after completion of the safety evaluation from the first dose panel. There were to be 30 study sites. Pharmacokinetic blood samples were to be collected prior to administration of study treatment and at 1, 2.5, 5, 8, 12, and 24 hours post-dose. Patients were either housed overnight at the clinic or released to go home overnight at the discretion of the investigator [Volume 2, pages 27, 50].

Study treatment was fexofenadine HCl (b) (4) powder, 15 mg and 30 mg, supplied in capsules. Study treatment was administered in Musselman's® applesauce. Patients were fasted approximately 1 hour prior to administration of study treatment and for 2 hours after administration of study treatment. The dose was administered by study staff under the supervision of the investigator or subinvestigator [Volume 2, pages 30, 33, 35, 51]. Safety variables included adverse events (AEs), vital signs, physical examinations, hematology, blood chemistry, and urinalyses [Volume 2, pages 7, 39].

11.1.3. Patient disposition

There were 65 patients enrolled at 20 study centers. Of these patients, 17 were not eligible or withdrew before dosing and did not receive study medication. There were 48 patients who received study treatment and were included in the safety analyses. Five patients withdrew because of adverse events (AEs). Four of these patients who withdrew before they were treated with study medication. One patient withdrew from the study because of an adverse event of respiratory disorder, after receiving study treatment. There were 47 patients who completed all study visits. There were 41 patients who completed all PK sampling and on whom the PK analyses were computed [Volume 2, pages 50, 76]. Patient disposition is summarized in Table 11.1.1.

Table 11.1.1. Patient disposition, Study M106455T/1123 [Volume 2, pages 50, 76]

	Treatment group					
	15 mg fexofenadine		30 mg fexofenadine		All groups	
	n	(%)	n	(%)	n	(%)
Patients enrolled					65	(135)
Patients treated	23	(100)	25	(100)	45	(100)
Patients with complete PK data	19	(82.6)	22	(88.0)	41	(85.4)
Discontinued after treatment received	0	(0)	1	(4.0)	1	(2.1)
Reason for discontinuation:						
Adverse event	0	(0)	1	(4.0)	1	(2.1)

Demographics are summarized in Table 11.1.2 below. Patients were distributed fairly even between genders and over the age groups studied [Volume 2, page 75; NDA 20-625 SE8-012 C, 1/14/03]. Patients of Caucasian and Black races represented the majority of patients. Patients of other races were not well represented in this study.

Table 11.1.2. Demographics, patients treated, Study M106455T/1123 [Volume 2, page 76; NDA 20-625 SE8-012 C, 1/14/03]

	Treatment group					
	15 mg fexofenadine		30 mg fexofenadine		All groups	
	n	(%)	n	(%)	n	(%)
Gender						
Female	10	(43.5)	9	(36.0)	19	(39.6)
Male	13	(56.5)	16	(64.0)	29	(60.4)
Age						
≥6 to <9 months	3	(13.0)	2	(8.0)	5	(10.4)
≥9 to <12 months	3	(13.0)	5	(20.0)	8	(16.7)
≥12 to <24 months	17	(73.9)	18	(72.0)	35	(72.9)
Mean age, months	14.4		15.8		15.1	
Range, months	6-22		6-21		6-22	
Race						
Caucasian	12	(52.2)	14	(56.0)	26	(54.2)
Black	10	(43.5)	10	(40.0)	20	(41.7)
Asian/Oriental	0	(0)	0	(0)	0	(0)
Other	1	(4.3)	1	(4.0)	2	(4.2)

There were minor protocol deviations that did not interfere with the interpretation of the efficacy or safety results of this study [Volume 2, page 50].

11.1.4. Pharmacokinetics

Selected PK results are displayed in Table 11.1.3. Following the single 15-mg and 30-mg doses of fexofenadine HCl [redacted] (b) (4) powder administered in applesauce, the mean AUC_{0-z} values were 767.05 ng.h/mL and 1579.51 ng.h/mL, respectively. Mean AUC_{0-inf}

values for 15 mg and 30 mg were 804.29 ng.h/mL and 1660.31 ng.h/mL, respectively. The mean oral clearance was 21.70 L/h for 15 mg and 21.94 for 30 mg. The maximal plasma concentration was 168.69 mg/mL for 15 mg and 328.95 for 30 mg. The mean time to maximum plasma concentration was 1.10 hours for both 15-mg and 30-mg doses [Volume 2, page 58]. Please see Dr. S. Kim's biopharmacology review for more detailed information on PK results from this study.

Table 11.1.3. PK results, single dose data, Study M106455T/1123[Volume 2, page 58]

PK parameter	Results
AUC_{0-z}	
15 mg	767.05 ng.h/mL
30 mg	1579.51 ng.h/mL
AUC_{0-inf}	
15 mg	804.29 ng.h/mL
30 mg	1660.31 ng.h/mL
Cl_{oral}	
15 mg	21.70 L/h
30 mg	21.94 L/h
C_{max}	
15 mg	168.69 ng/mL
30 mg	328.95 ng/mL
t_{max}	
15 mg	1.10 h
30 mg	1.10 h
Terminal $t_{½}$	
15 mg	6.19 h
30 mg	7.38 h

11.1.5. Safety outcomes

Safety endpoints in the study included adverse events (AEs), vital signs, physical examinations, hematology, blood chemistry, and urinalyses [Volume 2, pages 7, 39]. There were 48 patients exposed to a single oral dose of either 15 or 30 mg of fexofenadine HCl. There were 23 patients who received a 15-mg dose and 25 patients who received a 30-mg dose. The safety analysis was based on these patients [Volume 2, page 61].

There were no safety signals noted in this study. There was no control group in this study. AEs were fairly frequent in this single dose study (29.2%, 14/48). AEs are displayed in Table 11.1.4. AEs occurring more than once included rhinitis, asthenia, vomiting, URI, and somnolence. There were no other AEs reported more than once. There was no relationship between the dose and the frequency of AEs [Volume 2, page 83].

Table 11.1.4. AEs in fexofenadine-treated patients, Study M106455T/1123. There was no control group in this study [Volume 2, page 83].

Adverse event	15 mg fexofenadine N = 23		30 mg fexofenadine N = 25		All groups N = 48	
	n	(%)	n	(%)	n	(%)
All subjects with AEs	9	(39.1)	5	(20.0)	14	(29.2)
Rhinitis	2	(8.7)	2	(8.0)	4	(8.3)
Asthenia	3	(13.0)	0	(0)	3	(6.3)
Vomiting	1	(4.3)	1	(4.0)	2	(4.2)
URI	1	(4.3)	1	(4.0)	2	(4.2)

Adverse event	15 mg fexofenadine N = 23		30 mg fexofenadine N = 25		All groups N = 48	
	n	(%)	n	(%)	n	(%)
Somnolence	2	(8.7)	0	(0)	2	(4.2)
Respiratory disorder	0	(0)	1	(4.0)	1	(2.1)
Urticaria	0	(0)	1	(4.0)	1	(2.1)
Otitis media	0	(0)	1	(4.0)	1	(2.1)
Fever	1	(4.3)	0	(0)	1	(2.1)
Pain	1	(4.3)	0	(0)	1	(2.1)
Anorexia	1	(4.3)	0	(0)	1	(2.1)
Nervousness	1	(4.3)	0	(0)	1	(2.1)
Bronchiolitis	1	(4.3)	0	(0)	1	(2.1)
Sinusitis	1	(4.3)	0	(0)	1	(2.1)
Rash	1	(4.3)	0	(0)	1	(2.1)
Maculopapular rash	1	(4.3)	0	(0)	1	(2.1)

There was one SAE in this study. Patient 0109/00004, randomized to fexofenadine 30 mg, experienced reactive airways disease beginning 3 days before administration of study medication. His condition worsened with tachycardia, dyspnea, retractions, and wheezing the day after treatment administration. He received treatment with an antibiotic on the day of treatment and received albuterol and prednisone for the wheezing on the day after treatment administration. The patient discontinued from the study on the day after treatment administration and required hospitalization. The event resolved without sequelae on Day 4. The investigator considered the event to be not related to study medication [Volume 2, pages 62, 94].

A small decrease in mean absolute neutrophil count from 3.46 GG/L to 2.08 GG/L was noted in patients weighing ≤10.5 kg. This change was not noted in patients weighing >10.5 kg. The sponsor noted that there were no clinically significant changes observed in mean laboratory values from baseline to end of the study. There were no AEs reported for abnormal laboratory values [Volume 2, pages 63-66].

There were 11 subjects with abnormal physical examinations at the end of the study that had developed or worsened since the beginning of the study. Most of these abnormalities were related to respiratory system disorders such as otitis media, URI and were reported as AEs. Two of these abnormalities were considered to be related to study treatment—urticaria and maculopapular rash [Volume 2, page 66].

The sponsor reported that there were no trends or clinically meaningful changes observed in mean vital sign data from baseline to end-of-study. One patient had an increase in heart rate that met predefined change criteria for vital signs. Patient 0146/00001 was a 19-month old white male who was treated with 30 mg fexofenadine. He entered the study with a non-crying heart rate of 120/minute and had a non-crying heart rate of 160/minute at the end of the study. Other vital signs for this patient were within normal limits at baseline and at the end of the study [Volume 2, page 66; Volume 5, page 288; Volume 7, page 382].

The sponsor notes that there were no clinically significant changes in mean ECG results from baseline to 2.5 hours post-dose or from baseline to end of study. There was one

patient who met predefined change criteria for increase in heart rate on ECG. Patient 0103/00003 was an 11-month old black female treated 15 mg of fexofenadine. She had an increase in ECG heart rate from 125/minute at baseline to 168/minute 2.5 hours post-dose and to 135/minute at the end of the study. There were two patients who met the predefined change criteria for decrease in heart rate on ECG. Patient 0109/00007 had an ECG heart rate of 114/minute at baseline 84/minute at 2.5 hours postdose and 93/minute at the end of the study. Patient 0121/00005 had ECG heart rate of 135/minute at baseline 125/minute at 2.5 hours postdose, and 109/minute at the end of the study. There were no AEs reported for abnormal ECGs [Volume 2, page 67; Volume 5, pages 249, 287].

Reviewer comment:
The small number of AEs and the lack of a control group make it difficult to draw meaningful safety conclusions. The SAE for respiratory illness resulting was present prior to administration of study treatment, and is not likely to be related to treatment. The increases in heart rate on vital signs and ECG are interesting, however there were an equal number of patients who had decreases in heart rate. This reviewer concurs with the sponsor that these data provide no evidence for a safety signal.

11.1.6. Summary and conclusions

This was a multicenter, open-label, single rising dose pharmacokinetic Phase 1 study in children from 6 months to 2 years of age. The study was designed to characterize the pharmacokinetics of fexofenadine following a single oral dose of fexofenadine HCl 15 mg or 30 mg in children from 6 months to 2 years of age. A secondary objective of this study was to characterize the safety and tolerability of 15 mg or 30 mg fexofenadine HCl in children of this age group. The study recruited patients ages 6 months to 2 years who were candidates for antihistamine therapy or patients who had tolerated a therapeutic course of antihistamines in the preceding 6 months. There were 65 patients enrolled at 20 study centers. Following the single 15-mg and 30-mg doses of fexofenadine HCl (b) (4) powder administered in applesauce, the mean AUC_{0-z} values were 767.05 ng.h/mL and 1579.51 ng.h/mL, respectively. Mean AUC_{0-inf} values for 15 mg and 30 mg were 804.29 ng.h/mL and 1660.31 ng.h/mL, respectively. The mean oral clearance was 21.70 L/h for 15 mg and 21.94 for 30 mg. The maximal plasma concentration was 168.69 mg/mL for 15 mg and 328.95 for 30 mg. The mean time to maximum plasma concentration was 1.10 hours for both 15-mg and 30-mg doses. The small number of AEs and the lack of a control group make it difficult to draw meaningful safety conclusions. Physical examinations, vital signs, laboratory studies, and ECGs provide no evidence for a safety signal.

11.2. Study M106455T/3001: A multicenter, double-blind, randomized, placebo controlled, parallel study to assess the safety and tolerability of fexofenadine HCl 15 mg in children with allergic rhinitis

Date first subject enrolled: 12/13/01
Date last subject completed the study: 5/24/02
Date of study report: 11/5/02
[Volume 15, page 2]

11.2.1. Objective

The objective of this study was to compare the safety and tolerability of fexofenadine 15 mg BID to placebo in young children (≥6 months to <1 year of age and ≤10.5 kg in weight) with allergic rhinitis. A secondary objective was to characterize short-term (1 week) efficacy [Volume 15, page 22].

11.2.2. Study design

This was a double-blind, randomized, and placebo-controlled, parallel group, two-arm study, Phase 3 study. Patients had allergic rhinitis as diagnosed by previous medical history, pattern, and suggestive physical findings. There were to be approximately 70 centers participating in this study. Approximately 100 patients ages ≥6 months to <1 year and ≤10.5 kg in weight were to be enrolled. Patients ages ≥1 year to <2 years of age could also be enrolled, although their number was limited to approximately 50.

Patients were to be randomized to treatment with 15 mg fexofenadine HCl (b) (4) powder administered or matching placebo twice daily for a minimum of 7 days (14 doses). Study treatment was administered in the morning at about 8 AM and in the evening at about 8 PM. Study treatment was administered with either applesauce or rice cereal mixed with Similac or Isomil infant formula [Volume 15, pages 2, 22-23, 25-26]. Compliance was assessed by determining the amount of unopened capsules remaining at the time of the study visit [Volume 15, page 28].

There were two scheduled visits, Entry and Randomization, Visit 1, and Final or Discontinuation, Visit 2. The investigator performed an overall assessment of the patient's AR symptoms at the Entry and Randomization visit (Visit 1) and at the Final or Early Discontinuation visit (Visit 2). At Visit 2, the investigator made an overall assessment of the effectiveness of the study medication based on changes in the AR symptom assessments as well as changes in AR physical findings between baseline and the end of the study. The investigator used a five-point, 0-4 scale to rate the degree of medication effectiveness [Volume 15, pages 23-24, 33]. The five-point, 0-4 scale is found below in Table 11.2.1.

Table 11.2.1. Scale for investigator assessment of study medication effectiveness [Volume 15, page 33].

Score	Degree if relief	Definition
0	Complete relief	Symptoms not present
1	Marked relief	Symptoms are vastly improved and although still present, are scarcely troublesome

Score	Degree if relief	Definition
2	Moderate relief	Symptoms are noticeably improved but are still present and may be troublesome
3	Slight relief	Symptoms are present and only minimal improvement has been obtained
4	No relief/worse	Symptoms are unchanged or worse
N/A	Not applicable	No signs/symptoms present at baseline

Patients had a medical and medication history and physical examination performed at the entry and randomization visit, Visit 1. Patients meeting inclusion and exclusion criteria had an investigator baseline assessment of AR symptoms. Patients were randomized to treatment with either 15-mg fexofenadine HCl (b) (4) powder or placebo administered in applesauce. Parents were given a diary record in which adverse events, concomitant medication, and administration of study medication were to be recorded during the one-week treatment period. Parents/caregivers were contacted by telephone for follow-up on Day 4 or 5 to determine if any adverse events occurred or if concomitant medication had been taken and to assess compliance with study medication. The patient's diary and unused study medication were collected at Visit 2, on Day 8-9. Review of AEs, VS, physical examination, and investigator assessment of overall effectiveness were also performed at Visit 2, on Day 8-9 [Volume 15, page 30]. Safety variables included AEs, vital signs, physical examination, and ECGs [Volume 15, pages 30, 33]

11.2.3. Patient disposition

Patient disposition is presented in Table 11.2.2. A total of 174 patients were randomized at 43 study centers. There were 58 randomized and treated patients ages ≥6 months to < 1 year in the fexofenadine group and 64 randomized and treated patients ages ≥6 months to < 1 year in the placebo group. There were 27 randomized and treated patients ages ≥1 year to <2 years in the fexofenadine group and 25 randomized and treated patients ages ≥1 year to <2 years in the placebo group [Volume 15, pages 47, 49].

Among children ages ≥6 months to <1 year, there were more placebo-treated patients that withdrew from the study (7/64, 10.9%) than fexofenadine-treated patients (3/58, 5.2%). The number of patients ages ≥6 months to <1 year withdrawing because of AEs was the same for fexofenadine (2/58, 3.4%) and placebo (2/64, 3.1%) [Volume 15, page 49].

Among children ages ≥1 year to <2 years, there were more fexofenadine-treated patients that withdrew from the study (2/27, 7.4%) than placebo-treated patients (1/25, 4.0%). The number of patients ages ≥1 year to <2 years withdrawing because of AEs was greater for fexofenadine (2/27, 7.4%) than for placebo (1/25, 4.0%) [Volume 15, page 49].

Table 11.2.2. Patient disposition, Safety study M106455T/3001 [Volume 15, page 49]

	Ages ≥6 months to <1 year				Ages ≥1 year to <2 years			
	Fexofenadine, 15 mg BID		Pbo		Fexofenadine, 15 mg BID		Pbo	
Randomized patients	58	(100.0)	64	(100.0)	27	(100)	25	(100)
Randomized and treated patients	58	(98.0)	64	(100.0)	27	(100)	25	(100)
Withdrawals	3	(5.2)	7	(10.9)	2	(7.4)	1	(4.0)
Adverse event	2	(3.4)	2	(3.1)	2	(7.4)	1	(4.0)
Lost to follow-up	0	(0)	3	(4.7)	1	(3.7)	0	(0)
Lack of efficacy	0	(0)	1	(1.6)	0	(0)	0	(0)
Withdrew consent	0	(0)	1	(1.6)	0	(0)	0	(0)
Other	1	(1.7)	0	(0)	0	(0)	0	(0)

11.2.4. Demographics

Patient demographics of randomized patients are displayed in Table 11.2.3. The percentage of males and females was fairly similar in both treatment groups. Most patients were of Caucasian race. Patients of Black race were fairly well represented. There were small numbers of patients that were Asian/Oriental, multiracial, or of other race [Volume 15, page 52].

Table 11.2.3. Demographics of randomized patients, safety study M106455T/3001 [Volume 15, page 52].

	Ages ≥6 months to <1 year				Ages ≥1 year to <2 years			
	Fexofenadine, 15 mg BID		Pbo		Fexofenadine, 15 mg BID		Pbo	
	n	(%)	n	(%)	n	(%)	n	(%)
All patients	58	(100)	64	(100)	27	(100)	25	(100)
Gender								
Female	25	(43.1)	29	(45.3)	13	(48.1)	14	(56.0)
Male	33	(56.9)	35	(54.7)	14	(51.9)	11	(44.0)
Race								
Caucasian	41	(70.7)	44	(68.8)	18	(66.7)	20	(80.0)
Black	9	(15.5)	11	(17.2)	4	(14.8)	3	(12.0)
Asian/Oriental	0	(0)	0	(0)	1	(3.7)	0	(0)
Multiracial	4	(6.9)	5	(7.8)	3	(11.1)	0	(0)
Other	4	(6.9)	4	(6.3)	1	(3.7)	2	(8.0)

The age distribution of randomized patients in this study is presented below in Table 11.2.4. Patients were well represented in each of the age groups studied. There were proportionately fewer patients ≥1 year to <2 years of age because patients were to be ≤10.5 kg in weight [Volume 15, page 51].

Table 11.2.4. Age distribution of randomized patients, safety study M106455T/3001 [Volume 15, page 51.]

Age, years	Fexofenadine, 15 mg BID N = 85		Pbo N = 89	
	n	(%)	n	(%)
Ages ≥6 months to <1 year	58	(68.2)	64	(71.9)
Ages ≥1 year to <2 years	27	(46.6)	25	(28.1)

11.2.5. Protocol violations

Major protocol violations were fairly frequent, but occurred at similar frequencies in both treatment groups. There were protocol violations in 43.5% (37/85) of fexofenadine-treated patients and in 38.2% (34/89) of placebo treated patients. Noncompliance with study medication was the most common protocol violation and was present in 15.3%

(13/85) of fexofenadine-treated patients and in 19.1% (17/89) of placebo-treated patients. Noncompliance was defined as failing to ingest at least 80% of all of the doses of study medication. Other common protocol violations involved the physician assessment of allergic rhinitis and end-of-study ECGs. A different physician performed the assessment of overall condition of allergic rhinitis at the end of the study in 24.7% (21/85) of fexofenadine-treated patients and in 16.9% (15/89) of placebo-treated patients. The end-of-study ECG was performed >8 hours after dose of medication or after less than half of dose of medication was taken in 12.9% (11/85) of fexofenadine-treated patients and in 12.4% (11/89) of placebo-treated patients [Volume 15, page 80].

Reviewer comment:
The high rate of protocol violations is less than ideal and would have had some effect on the interpretation of efficacy data. However, the assessment of efficacy was a secondary objective of this study, and the reviewer does not consider this deficiency to be a major problem. Although protocol violations involving collection of ECG data were present in both treatment groups, they were similar in frequency in both groups and occurred in a small minority of patients. Although protocol violations involving safety data are not ideal, they occurred in a small minority of patients, and there is sufficient safety data remaining patients to allow interpretation.

11.2.6. Compliance

As noted above, noncompliance was defined as failing to ingest at least 80% of all of the doses of study medication. There were 84.7% (72/85) of fexofenadine-treated patients and 80.9% (72/89) of placebo-treated patients who took ≥80% of all doses of study medication. Mean compliance was 92.9% in the fexofenadine group and 90.0% in the placebo group [Volume 15, page 92].

Reviewer comment:
Compliance was adequate in both treatment groups.

11.2.7. Efficacy outcomes

Efficacy was examined as a secondary objective of the study. The investigator performed an overall assessment of the patient's AR symptoms at the Entry and Randomization visit (Visit 1) and at the Final or Early Discontinuation visit (Visit 2).

The mean change from baseline in investigator overall assessment of allergic rhinitis symptoms at the end of study for all patients was the same for fexofenadine and placebo (-0.5 points) [Volume 15, page 64]. The mean change from baseline in investigator overall assessment of allergic rhinitis symptoms at the end of study for patients ≥1 year to <2 years of age was similar for fexofenadine (-0.5) and placebo (-0.6 points). The mean change from baseline in investigator overall assessment of allergic rhinitis symptoms at the end of study for patients ≥6 months to <1 year of age was greater for fexofenadine (-0.4) than for placebo (-0.2 points). These data are presented in Table 11.2.5.

Table 11.2.5. Change from baseline in investigator overall assessment of allergic rhinitis symptoms, Study M106455T/3001 [Volume 15, page 64]

Age group	Fexofenadine			Placebo		
	N	Mean	(SD)	N	Mean	(SD)
All patients						
Baseline	84	1.4	(0.75)	85	1.5	(0.70)
Change from baseline at study end	84	-0.5	(0.86)	85	-0.5	(0.75)
≥6 months to <1 year						
Baseline	58	1.4	(0.79)	61	1.5	(0.72)
Change from baseline at study end	58	-0.5	(0.84)	61	-0.6	(0.69)
≥1 year to <2 years						
Baseline	26	1.3	(0.68)	24	1.4	(0.65)
Change from baseline at study end	26	-0.4	(0.90)	24	-0.2	(0.83)

Assessment of effectiveness of study treatment is summarized in Table 11.2.6. Only data for patients with both baseline and end-of-study assessments of allergic rhinitis symptoms performed by the same physician are displayed. For all patients, 61.0% (36/59) of fexofenadine-treated patients and 52.3% (34/65) of placebo-treated patients had moderate to complete relief from allergic rhinitis symptoms at the end of the study. In patients ≥6 months to <1 year of age, 57.9% (22/38) of fexofenadine-treated patients and 60% (27/45) of placebo-treated patients had moderate to complete relief from allergic rhinitis symptoms at the end of the study. In patients ≥1 year to <2 years of age, 66.7% (14/21) of fexofenadine-treated patients and 35.0% (7/20) of placebo-treated patients had moderate to complete relief from allergic rhinitis symptoms at the end of the study.

Table 11.2.6. Assessment of effectiveness of study treatment, patients with baseline and end-of-study assessments by the same physician, Study M106455T/3001 [Volume 15, page 64]

	Ages ≥6 months to <1 year				Ages ≥1 year to <2 years			
Assessment of relief	Fexofenadine, 15 mg BID N = 38		Pbo N = 45		Fexofenadine, 15 mg BID N = 21		Pbo N = 20	
Complete relief	11	(28.9)	4	(8.9)	6	(28.6)	5	(25.0)
Marked relief	8	(21.1)	15	(33.3)	5	(23.8)	1	(5.0)
Moderate relief	3	(7.9)	8	(17.8)	3	(14.3)	1	(5.0)
Slight relief	9	(23.7)	10	(22.2)	3	(14.3)	1	(5.0)
No relief/worse	7	(18.4)	8	(17.8)	4	(19.0)	12	(60.0)

Reviewer comment:
Treatment groups had similar degrees of change from baseline in overall assessment of allergic rhinitis symptoms and similar degrees of relief in the overall assessment of study medication effectiveness. (b) (4) *It should be noted however, that assessment of efficacy was only a secondary objective of this study.*

11.2.8. Safety outcomes

The degree of exposure to study treatment may be evaluated by compliance data. As noted above, there were 84.7% (72/85) of fexofenadine-treated patients and 80.9% (72/89) of placebo-treated patients who took ≥80% of all doses of study medication. Mean compliance was 92.9% in the fexofenadine group and 90.0% in the placebo group. Among patients treated with fexofenadine, 94.1% (80/85) had treatment for eight or more days. Among patients treated with placebo, 92.9% (78/84) had treatment for eight or more days [Volume 15, pages 89, 92].

Reviewer comment:
Exposure was adequate for assessment of safety.

AEs occurring at a frequency ≥ 2.0% and more commonly in fexofenadine than in placebo are displayed in Table 11.2.7. AEs were frequent and occurred in similar proportions of fexofenadine-treated (40.0%, 34/85) and placebo-treated (42.7%, 38/89) patients. [Volume 15, pages 103-104]. The most common AEs occurring more commonly in fexofenadine than placebo were rash, diarrhea, gastroenteritis, and rhinitis. Most AEs were mild in intensity in both treatment groups [Volume 15, page 57].

Table 11.2.7. AEs occurring at a rate ≥2.0% and more commonly in fexofenadine than in placebo, Study M106455T/3001 [Volume 15, pages 103-104]

AE	Fexofenadine, 15 mg BID N = 85		Placebo N = 89	
	n	(%)	n	(%)
Patients with AEs	34	(40.0)	38	(42.7)
Rash	5	(5.9)	2	(2.2)
Diarrhea	4	(4.7)	1	(1.1)
Gastroenteritis	3	(3.5)	0	(0)
Rhinitis	2	(2.4)	2	(2.2)

AEs for paradoxical excitability, somnolence, fatigue, and hyperkinesia were of special interest. There was one patient in the placebo group who had nervousness (1.1%, 1/89) and one who had agitation (1.1%, 1/89). There was one patient in the fexofenadine group who had somnolence (1.2%, 1/108) [Volume 15, page 59].

There were no deaths in the study. There was one SAE. Patient 0158/00001 was a 9-month old male who was treated with placebo. He developed a severe RSV infection and otitis media that resulted in hospitalization. Onset of symptoms was on Day 10, 2 days following the last dose of study medication. The patient received albuterol nebulizer treatment, ceftriaxone, and amoxicillin/clavulanate. The patient was discharged from the hospital after 4 days. The event was assessed by the investigator as not being related to study treatment [Volume 15, page 59].

Withdrawals from the study due to AEs occurred at similar frequencies in the fexofenadine group (3/85, 53.6%) and in the placebo group (3/89, 3.4%). Withdrawals due to AEs in both groups were also similar in character and included otitis media, sinusitis, increased cough, and gastroenteritis [Volume 15, page 60].

There were no clinically meaningful changes in vital signs [Volume 15, pages 61, Volume 15, pages 129-146]. Shift tables showed similar proportions of patients with increases and decreases in values for vital signs [Volume 15, page 147].

Both treatment groups had a similar increase from baseline in percentage of patients with normal allergic rhinitis examinations at the end of the study. In the fexofenadine group, 17.6% of patients had normal allergic examinations at baseline and 36.5% were normal at the end of the study, an increase of 18.9%. In the placebo group, 11.2% of patients had normal allergic rhinitis examinations at baseline and 29.2% were normal at the end of the

study, a difference of 18.0%. For other physical exam findings, 90% or more of patients in both treatment groups were rated as normal at both baseline and at the end of the study [Volume 15, page 62, 162-168].

ECGs were performed at baseline and at the end of the study. The end-of-study ECG was to be obtained at approximately 2.5 hours after administration of the last dose of study medication, or if this was not possible, was to be scheduled 1-2 days prior to the final visit at approximately 2.5 hours after the morning dose of study treatment.

No clinically significant differences were observed between treatment groups in PR interval, QRS interval, QTcB, QTcF, or heart rate. Shift tables showed similar proportions of patients in both treatment groups with increases and decreases in values for ECG parameters in the small number of patients whose values fell outside of the predefined change criteria [Volume 15, pages 61-62, 149-161].

Reviewer comment:
Rash, diarrhea, gastroenteritis, and rhinitis occurred more commonly in fexofenadine-treated patients, however it is difficult to draw conclusions about this observation given the small number of AEs noted. It should be noted that the study was performed during winter and spring, and the appearance of concomitant viral infections would be expected in the population studied. This reviewer concurs that the one SAE was not likely to be related to study treatment. Withdrawals due to AEs do not reveal a safety signal. Vital signs, physical examination, allergic rhinitis examinations, and ECGs reveal no safety signal.

11.2.9. Summary and conclusions

This was a double-blind, randomized, and placebo-controlled, parallel group, two-arm, Phase 3 study designed to compare the safety and tolerability of fexofenadine 15 mg BID to placebo in young children (≥1 year to <2 years of age and >10.5 kg in weight) with allergic rhinitis. A secondary objective was to characterize short-term (1-week) efficacy. Patients had allergic rhinitis as diagnosed by previous medical history, pattern, and suggestive physical findings. Patients were randomized to 15 mg fexofenadine or placebo twice daily for the one week treatment period. Study medication was administered in applesauce. A total of 174 patients were randomized at 43 study centers. Treatment groups had similar degrees of change from baseline in overall assessment of allergic rhinitis symptoms and similar degrees of relief in the overall assessment of study medication effectiveness. (b) (4) Rash, diarrhea, gastroenteritis, and rhinitis occurred more commonly in fexofenadine-treated patients, however it is difficult to draw conclusions about this observation given the small number of AEs noted. Withdrawals due to AEs, vital signs, physical examination, and ECGs reveal no safety signal.

11.3. Study M106455T/3002: A multicenter, double-blind, randomized, placebo controlled, parallel study to assess the safety and tolerability of fexofenadine HCl 30 mg in children with allergic rhinitis

Date first subject enrolled: 12/13/01
Date last subject completed the study: 5/9/02
Date of study report: 11/5/02
[Volume 23, page 2]

11.3.1. Objective

The objective of this study was to compare the safety and tolerability of fexofenadine 30 mg BID to placebo in young children (≥1 year to <2 years of age and >10.5 kg in weight) with allergic rhinitis. A secondary objective was to characterize short-term (1 week) efficacy [Volume 23, page 21].

11.3.2. Study design

This was a double-blind, randomized, and placebo-controlled, parallel group, two-arm study, Phase 3 study. Patients had allergic rhinitis as diagnosed by previous medical history, pattern, and suggestive physical findings. There were to be approximately 70 centers participating in this study. Approximately 200 patients ages ≥1 month to <2 years and >10.5 kg in weight were to be enrolled. Patients ages ≥6 months to <1 year of age could also be enrolled, although their number was anticipated to be limited.

Patients were to be randomized to treatment with 30 mg fexofenadine HCl (b) (4) powder administered with applesauce or matching placebo twice daily for a minimum of 7 days (14 doses). Study treatment was administered in the morning at about 8 AM and in the evening at about 8 PM. Study treatment was administered with either applesauce or rice cereal mixed with Similac® or Isomil® infant formula. [Volume 23, pages 2, 21-22, 25-26]. Compliance was assessed by determining the amount of unopened capsules remaining at the time of the study visit [Volume 23, page 27].

There were two scheduled visits, Entry and Randomization, Visit 1, and Final or Discontinuation, Visit 2. The investigator performed an overall assessment of the patient's AR symptoms at the Entry and Randomization visit (Visit 1) and at the Final or Early Discontinuation visit (Visit 2). At Visit 2, the investigator made an overall assessment of the effectiveness of the study medication based on changes in the AR symptom assessments as well as changes in AR physical findings between baseline and the end of the study. The investigator used a five-point, 0-4 scale to rate the degree of medication effectiveness [Volume 23, pages 22-23, 32]. The five-point, 0-4 scale is found below in Table 11.3.1.

Table 11.3.1. Scale for investigator assessment of study medication effectiveness [Volume 23, page 32].

Score	Degree if relief	Definition
0	Complete relief	Symptoms not present
1	Marked relief	Symptoms are vastly improved and although still present, are scarcely troublesome

Score	Degree if relief	Definition
2	Moderate relief	Symptoms are noticeably improved but are still present and may be troublesome
3	Slight relief	Symptoms are present and only minimal improvement has been obtained
4	No relief/worse	Symptoms are unchanged or worse
N/A	Not applicable	No signs/symptoms present at baseline

Patients had a medical and medication history and physical examination performed at the entry and randomization visit, Visit 1. Patients meeting inclusion and exclusion criteria had an investigator baseline assessment of AR symptoms. Patients were randomized to treatment with either 30-mg fexofenadine HCl (b) (4) powder or placebo administered in applesauce. Parents were given a diary record in which adverse events, concomitant medication, and administration of study medication were to be recorded during the one-week treatment period. Parents/caregivers were contacted by telephone for follow-up on Day 4 or 5 to determine if any adverse events occurred or if concomitant medication had been taken and to assess compliance with study medication. The patient's diary and unused study medication were collected at Visit 2, on Day 8-9. Review of AEs, VS, physical examination, and investigator assessment of overall effectiveness were also performed at Visit 2, on Day 8-9 [Volume 23, pages 29, 32-33]. Safety variables included AEs, vital signs, physical examination, and ECGs [Volume 23, page 32]

11.3.3. Patient disposition

Patient disposition is presented in Table 11.3.2. A total of 219 patients were randomized at 44 study centers. There were 5 randomized and treated patients ages ≥6 months to < 1 year in the fexofenadine group and 5 randomized and treated patients ages ≥6 months to < 1 year in the placebo group. There were 103 randomized and treated patients ages ≥1 year to <2 years in the fexofenadine group and 106 randomized and treated patients ages ≥1 year to <2 years in the placebo group [Volume 23, pages 45-47].

Among the few children in this study ages ≥6 months to <1 year, there were was one patient in the placebo group (1/5, 20%) who withdrew from the study. This patient withdrew because of an AE [Volume 15, page 49].

Among children ages ≥1 year to <2 years, there were more placebo-treated patients that withdrew from the study (10/106, 9.4%) than fexofenadine-treated patients (6/103, 5.8%). The number of patients ages ≥1 year to <2 years withdrawing because of AEs was greater for placebo (6/106, 5.7%) than fexofenadine (6/103, 5.8%) [Volume 23, page 47].

Table 11.3.2. Patient disposition, safety study M106455T/3002 [Volume 23, page 47]

	Ages ≥6 months to <1 year		Ages ≥1 year to <2 years	
	Fexofenadine, 30 mg BID	Pbo	Fexofenadine, 30 mg BID	Pbo
Randomized patients	5 (100.0)	5 (100.0)	103 (100)	106 (100)
Randomized and treated patients	5 (100.0)	5 (100.0)	103 (100)	105 (99.1)
Withdrawals	0 (0)	1 (20.0)	6 (5.8)	10 (9.4)
Adverse event	0 (0)	1 (20.0)	4 (3.9)	6 (5.7)
Lack of efficacy	0 (0)	0 (0)	1 (1.0)	0 (0)
Protocol violation	0 (0)	0 (0)	0 (0)	1 (0.9)
Withdrew consent	0 (0)	0 (0)	0 (0)	2 (1.9)
Other	0 (0)	0 (0)	1 (1.0)	1 (0.9)

11.3.4. Demographics

Patient demographics of randomized and treated patients are displayed in Table 11.3.3. The percentage of males and females was fairly similar in both treatment groups. Most patients were of Caucasian race. Patients of Black race were fairly well represented. There were small numbers of patients that were multiracial or of other race. There were no patients of Asian/Oriental race [Volume 23, page 50].

Table 11.3.3. Demographics of randomized and treated patients, safety study M106455T/3002 [Volume 23, page 50].

	Ages ≥6 months to <1 year				Ages ≥1 year to <2 years			
	Fexofenadine, 30 mg BID		Pbo		Fexofenadine, 30 mg BID		Pbo	
	n	(%)	n	(%)	n	(%)	n	(%)
All patients	5	(100)	5	(100)	103	(100)	105	(100)
Gender								
Female	2	(40.0)	3	(60.0)	41	(39.8)	36	(34.3)
Male	3	(60.0)	2	(40.0)	62	(60.2)	69	(65.7)
Race								
Caucasian	5	(100.0)	3	(60.0)	84	(81.6)	77	(73.3)
Black	0	(0)	1	(20.0)	9	(8.7)	16	(15.2)
Multiracial	0	(0)	0	(0)	3	(2.9)	3	(2.9)
Other	0	(0)	1	(20.0)	7	(6.8)	9	(8.6)
Asian/Oriental	0	(0)	0	(0)	0	(0)	0	(0)

The age distribution of randomized and treated patients in this study is presented below in Table 11.3.4. The great majority of patients in this study were from ≥1 year to <2 years of age because patients must also have been >10.5 kg in weight. As expected, there were very few patients ≥6 months to <1 year of age [Volume 23, page 50].

Table 11.3.4. Age distribution of randomized and treated patients, safety study M106455T/3002 [Volume 23, page 50.]

Age, years	Fexofenadine, 15 mg BID N = 108		Pbo N = 110	
	n	(%)	n	(%)
Ages ≥6 months to <1 year	5	(4.6)	5	(4.5)
Ages ≥1 year to <2 years	103	(95.4)	105	(95.5)

11.3.5. Protocol violations

Major protocol violations were frequent, but occurred at similar frequencies in both treatment groups. There were protocol violations in 40.7% (344/108) of patients randomized to fexofenadine and in 42.3% (47/111) of patients randomized to placebo. The most common protocol violation involved physician assessment of allergic rhinitis symptoms. A different physician performed the assessment of overall condition of allergic rhinitis at the end of the study in 21.3% (23/108) patients randomized to fexofenadine and in 25.2% (28/111) of patients randomized to placebo. Other common protocol violations involved the noncompliance with study medications and end-of-study vital signs, physical examinations, and ECGs. Noncompliance was defined as failing to ingest at least 80% of all of the doses of study medication. Noncompliance with study medication was present in 13.0% (14/108) of patients randomized to fexofenadine and in 20.7% (23/111) of patients randomized to placebo.

End-of-study vital signs were not obtained on the same day after the AM dose of medication or after less than half of dose of medication was taken in 11.1% (12/108) of fexofenadine-treated patients and in 15.3% (17/111) of placebo-treated patients. The end-of-study physical examinations were not obtained on the same day after the AM dose of medication or after less than half of dose of medication was taken in 10.2% (11/108) of fexofenadine-treated patients and in 15.3% (17/111) of placebo-treated patients. End-of-study ECGs were performed >8 hours after dose of medication or after less than half of dose of medication was taken in 10.2% (11/108) of fexofenadine-treated patients and in 14.4% (16/111) of placebo-treated patients [Volume 23, page 47, 78-80].

Reviewer comment:
The high rate of protocol violations is less than ideal and would have had some effect on the interpretation of efficacy data. However, the assessment of efficacy was a secondary objective of this study, and the reviewer does not consider this deficiency to be a major problem. Protocol violations involving collection of vital signs, physical examination, and ECG data were present in both treatment groups. However, they were similar in frequency in both groups and occurred in a minority of patients. Although the protocol violations involving safety data are not ideal, there is sufficient safety data remaining patients to allow interpretation.

11.3.6. Compliance

As noted above, noncompliance was defined as failing to ingest at least 80% of all of the doses of study medication. There were 87.0% (94/108) of fexofenadine-treated patients and 80.0% (88/110) of placebo-treated patients who took ≥80% of all doses of study medication. Mean compliance was 91.9% in the fexofenadine group and 87.5% in the placebo group [Volume 23, page 89].

Reviewer comment:
Compliance was adequate in both treatment groups.

11.3.7. Efficacy outcomes

Efficacy was examined as a secondary objective of the study. The investigator performed an overall assessment of the patient's AR symptoms at the Entry and Randomization visit (Visit 1) and at the Final or Early Discontinuation visit (Visit 2).

The mean change from baseline in investigator overall assessment of allergic rhinitis symptoms at the end of study for all patients was the same for fexofenadine and placebo (-0.4 points) [Volume 23, page 62]. The mean change from baseline in investigator overall assessment of allergic rhinitis symptoms at the end of study for the small number of patients who were ≥6 months to <1 year of age was greater for fexofenadine (-1.0) than for placebo (-0.4 points). The mean change from baseline in investigator overall assessment of allergic rhinitis symptoms at the end of study for patients ≥1 year to <2 years of age was the same for fexofenadine and placebo (-0.4 points). These data are presented in Table 11.3.5.

Table 11.3.5. Change from baseline in investigator overall assessment of allergic rhinitis symptoms, Study M106455T/3002 [Volume 23, page 62]

Age group	Fexofenadine			Placebo		
	N	Mean	(SD)	N	Mean	(SD)
All patients						
Baseline	108	1.4	(0.62)	108	1.5	(0.74)
Change from baseline at study end	108	-0.4	(0.78)	108	-0.4	(0.80)
≥6 months to <1 year						
Baseline	5	2.0	(0.0)	5	1.6	(0.55)
Change from baseline at study end	5	-1.0	(0.71)	5	-0.4	(0.55)
≥1 year to <2 years						
Baseline	103	1.4	(0.62)	103	1.5	(0.75)
Change from baseline at study end	103	-0.4	(0.78)	103	-0.4	(0.81)

Assessment of effectiveness of study treatment is summarized in Table 11.3.6. Only data for patients with both baseline and end-of-study assessments of allergic rhinitis symptoms performed by the same physician are displayed. For all patients, 50.6% (42/83) of fexofenadine-treated patients and 42.7% (32/75) of placebo-treated patients had moderate to complete relief from allergic rhinitis symptoms at the end of the study. In the small number of patients ≥6 months to <1 year of age, 100% (4/4) of fexofenadine-treated patients and 33.3% (1/3) of placebo-treated patients had moderate to complete relief from allergic rhinitis symptoms at the end of the study. In patients ≥1 year to <2 years of age, 48.1% (38/79) of fexofenadine-treated patients and 43.1% (31/72) of placebo-treated patients had moderate to complete relief from allergic rhinitis symptoms at the end of the study.

Table 11.3.6. Assessment of effectiveness of study treatment, patients with baseline and end-of-study assessments by the same physician, Study M106455T/3002 [Volume 23, page 63]

	Ages ≥6 months to <1 year				Ages ≥1 year to <2 years			
Assessment of relief	Pbo		Fexofenadine, 30 mg BID		Pbo		Fexofenadine, 30 mg BID	
	N = 3		N = 4		N = 72		N = 79	
Complete relief	11	(28.9)	4	(8.9)	6	(28.6)	5	(25.0)
Marked relief	8	(21.1)	15	(33.3)	5	(23.8)	1	(5.0)
Moderate relief	3	(7.9)	8	(17.8)	3	(14.3)	1	(5.0)
Slight relief	9	(23.7)	10	(22.2)	3	(14.3)	1	(5.0)
No relief/worse	7	(18.4)	8	(17.8)	4	(19.0)	12	(60.0)

Reviewer comment:
Treatment groups had similar degrees of change from baseline in overall assessment of allergic rhinitis symptoms and similar degrees of relief in the overall assessment of study medication effectiveness. (b) (4)

11.3.8. Safety outcomes

The degree of exposure to study treatment may be evaluated by compliance data. There were 87.0% (94/108) of fexofenadine-treated patients and 80.0% (88/110) of placebo-treated patients who took ≥80% of all doses of study medication. Mean compliance was 91.9% in the fexofenadine group and 87.5% in the placebo group. Among patients treated with fexofenadine, 92.6% (100/108) had treatment for eight or more days. Among patients treated with placebo, 90.0% (99/110) had treatment for eight or more days [Volume 23, pages 85, 89].

Reviewer comment:
Exposure was adequate for assessment of safety.

AEs occurring at a frequency ≥ 2.0% and more commonly in fexofenadine than in placebo are displayed in Table 11.3.7. AEs were fairly frequent and occurred in a greater proportion of placebo-treated patients (52.7%, 58/110) than fexofenadine-treated patients (35.2%, 38/108). [Volume 23, pages 100-101]. Most AEs were mild or moderate intensity in both treatment groups [Volume 23, page 55].

Table 11.3.7. AEs occurring at a rate ≥2.0% and more commonly in fexofenadine than in placebo, Study M106455T/3002 [Volume 23, pages 100-101].

AE	Fexofenadine, 30 mg BID N = 108		Placebo N = 110	
	n	(%)	n	(%)
Patients with AEs	38	(35.2)	58	(52.7)
Diarrhea	6	(5.6)	3	(2.7)
Otitis media	7	(6.5)	6	(5.5)

AEs for paradoxical excitability, somnolence, fatigue, and hyperkinesia were of special interest. There was one patient each in the fexofenadine group (0.9%, 1/108) and the placebo groups (0.9%, 1/110) with an AE for somnolence [Volume 23, page 57].

There were no deaths in the study. There were no SAEs in this study [Volume 23, page 56].

Withdrawals from the study due to AEs occurred were more frequent in the placebo group (6.4%, 7/110) than in the fexofenadine group (2.8%, 3/108). Withdrawals due to AEs in both groups were also similar in character and included diarrhea, gastroenteritis, infection (viral syndrome) [Volume 23, page 57].

There was a mean decrease from baseline of 13/minute was noted for the non-crying heart rate in the small group of fexofenadine-treated patients ≥6 months to <1 year of age. There was a mean decrease from baseline of 5.2 beats/minute in the crying heart rate patients of all ages. Changes in vital signs were otherwise similar in both treatment groups. Shift tables showed similar proportions of patients with increases and decreases in values for vital signs. The sponsor concluded that there were no clinically meaningful changes in vital signs [Volume 23, pages 58, 128-133, 146].

For physical exam findings, 95% or more of patients in both treatment groups were rated as normal at both baseline and at the end of the study. The percentage of patients with normal to abnormal changes from baseline to end of the study for "chest/lungs" was slightly higher for fexofenadine (5.6%, 6/108) than for placebo (2.7%, 3/110). The abnormalities consisted of wheezing, rhonchi, and cough. The incidence of subjects with any abnormal changes for other body areas were comparable between treatment groups [Volume 23, pages 60, 161-167].

ECGs were performed at baseline and at the end of the study. The end-of-study ECG was to be obtained at approximately 2.5 hours after administration of the last dose of study medication, or if this was not possible, was to be scheduled 1-2 days prior to the final visit at approximately 2.5 hours after the morning dose of study treatment. No clinically significant differences were observed between treatment groups in PR interval, QRS interval, QTcB, QTcF, or heart rate. Shift tables showed similar proportions of patients in both treatment groups with increases and decreases in values for ECG parameters in the small number of patients whose values fell outside of the predefined change criteria [Volume 23, pages 58-59, 149-161].

Reviewer comment:
Diarrhea and otitis media occurred more commonly in fexofenadine-treated patients, however it is difficult to draw conclusions about this observation given the small number of AEs noted. It should be noted that the study was performed during winter and spring, and the appearance of concomitant viral infections would be expected in the population studied. Withdrawals due to AEs do not reveal a safety signal. The significance of the changes in heart rate and the chest/lungs part of the physical examination are not clear. It is not likely that these represent safety signals. ECGs reveal no safety signal.

11.3.9. Summary and conclusions

This was a double-blind, randomized, and placebo-controlled, parallel group, two-arm, Phase 3 study designed to compare the safety and tolerability of fexofenadine 30 mg BID to placebo in young children (≥1 year to <2 years of age and >10.5 kg) with allergic rhinitis. A secondary objective was to characterize short-term (1 week) efficacy. Patients had allergic rhinitis as diagnosed by previous medical history, pattern, and suggestive physical findings. Patients were randomized to 30 mg fexofenadine or placebo twice daily for the one week treatment period. Study medication was administered in applesauce. A total of 219 patients were randomized at 44 study centers. Compliance was adequate in both treatment groups. Treatment groups had similar degrees of change from baseline in overall assessment of allergic rhinitis symptoms and similar degrees of relief in the overall assessment of study medication effectiveness. (b) (4) Diarrhea and otitis media occurred more commonly in fexofenadine-treated patients, however it is difficult to draw conclusions about this observation given the small number of AEs noted. Withdrawals due to AEs, vital signs, physical examination, and ECGs reveal no safety signal.

11.4. Study PJPR0076

This supportive clinical pharmacology study was designed, in part, to determine the bioavailability of fexofenadine when administered in applesauce, the vehicle for study M106455T/1123 and the preferred vehicle for studies M106544T/3001 and M106455T/3002. This study was performed in adults, and does not provide safety data relevant to the proposed labeling. A brief review of this supportive clinical pharmacology study follows.

This was a single center, open-label, single-dose, four period, randomized, complete crossover, Phase 1 study. There was a washout period of 6 days between study periods. The primary objective of this study was to determine the bioavailability of fexofenadine HCl (b) (4) formulation relative to the marketed immediate release capsule. A secondary objective was to determine the bioavailability of the fexofenadine HCl marketed immediate release capsule when administered with applesauce. The four study treatments were: (1) 2 x (b) (4) 60 mg t (b) (4) (2) 2 x (b) (4) 60 mg (b) (4), (3) 2 x marketed 60 mg capsule in applesauce, and (4) 2 x marketed 60 mg capsule. Subjects were healthy adult males. There were 22 subjects enrolled in this study, and 22 subjects received study medication. Pharmacokinetic blood samples were collected prior to administration of study treatment and serially up to 48 hours post-dose [Volume 31, pages 9, 10, 13, 17, 19].

Treatment comparisons relevant to the administration of study treatment in the pediatric studies M106455T/1123, M106544T/3001, and M106455T/3002 are displayed in Table 11.4.1 below. The immediate release capsule administered with applesauce was bioequivalent to the marketed immediate release capsule with respect to AUC. The rate of exposure was higher for the immediate release capsule administered with applesauce than when administered without applesauce, slightly exceeding the upper 90% confidence interval for C_{max} (132.0%) and falling below the lower 90% confidence interval for t_{max}. More details may be found in the Dr. Shinja Kim's Clinical Pharmacology and Biopharmaceutics review [Volume 31, page 13].

Table 11.4.1. Treatment comparisons, Study PJPR0076 [Volume 31, page 13]

PK parameter	Treatment	Adjusted Mean*	Ratio C/D (%)	90% CI for ratio
$AUC_{0\text{-}inf}$ ng.h/mL				
	C**	2195.65	104.95	92.3, 119.4
	D***	2092.17	--	--
C_{max} ng/mL				
	C	313.15	111.36	94.0, 132.0
	D	281.20	--	--
t_{max} h				
	C	1.50	67.64	53.8, 85.1
	D	2.22	--	--

*Least squares mean, log transformed data
**Fexofenadine HCl (2 x 60 mg) marketed immediate release capsules in 10 mL applesauce given as a single dose to fasted subjects, N = 20
***Fexofenadine HCl (2 x 60 mg) marketed immediate release capsules given as a single dose to fasted subjects, N = 21

Safety variables included adverse events (AEs), vital signs, urinalyses, and hematology and blood chemistry studies. Five of 22 patients (22.7%) experienced one or more AEs. The only AE reported more than once was headache. Headache was reported twice among the 22 patients (9.1%). There were no deaths. There was one SAE, a patient who had syncope with blood drawing. The patient sustained a laceration to the forehead that required suturing.

Review of urinalyses, hematology and blood chemistry studies revealed no safety signals. There were no abnormalities in vital signs reported as an AE. ECGs revealed no safety signal [Volume 31, pages 20, 35-37].

Reviewer comments:
The PK data indicate that applesauce was an acceptable vehicle for pediatric studies M106455T/1123, M106544T/3001, and M106455T/3002. Safety summaries and line listings for this study were reviewed and reveal no safety signal [Volume 31, pages 35-37, 273-287].

11.5. Study M016455T/1001

This supportive clinical pharmacology study was designed, in part, to determine the bioavailability of fexofenadine when administered in various vehicles other than applesauce. This study was performed in adults, and does not provide safety data relevant to the proposed labeling. A brief review of this supportive clinical pharmacology study follows.

This was a single center, open-label, single-dose, four period, randomized, complete crossover, Phase 1 study. There was a washout period of 6 days between study periods. The objective of this study was to compare the bioavailability of 60-mg fexofenadine HCl administered in food delivery vehicles relative to a 60-mg fexofenadine HCl reference capsule. The drug product studied was oral (b) (4) powder from the marketed immediate release 60-mg fexofenadine capsule. The four study treatments were: (1) 60 mg oral (b) (4) powder in 10 mL of Karo® syrup, (2) 60 mg oral (b) (4) powder in 10 mL of Dannon® vanilla yogurt, (3) 60 mg oral (b) (4) powder in 10 mL of Gerber® rice cereal prepared with Similac® with Iron, and (4) the marketed 60-mg capsule. Subjects were healthy adult males. There were 24 subjects enrolled in this study, and 24 subjects received study medication. Pharmacokinetic blood samples were collected prior to administration of study treatment and serially up to 48 hours postdose [Volume 32, pages 4, 19, 20,21, 28].

Treatment comparisons are displayed in Table 11.5.1 below. Rice cereal prepared with Similac with Iron was an alternate vehicle for administration of fexofenadine in pediatric studies M106544T/3001 and M106455T/3002.

The fexofenadine (b) (4) powder administered in Gerber® rice cereal prepared with Similac® with Iron was bioequivalent to the reference fexofenadine capsule administered alone with respect to AUC. C_{max} was slightly higher for the fexofenadine (b) (4) powder administered with Gerber rice cereal prepared with Similac with Iron than the fexofenadine capsule administered alone. The C_{max} slightly exceeded the upper 90% confidence interval (127.06). More details may be found in the Dr. Shinja Kim's Clinical Pharmacology and Biopharmaceutics review [Volume 32, page 42].

Table 11.5.1. Treatment comparisons, Study M106455T/1001 [Volume 32, page 42]

PK parameter	Treatment	Adjusted Mean*	Comparison	Ratio, (%)	90% CI for ratio
AUC_{0-inf} ng.h/mL					
	A	1045.25	A/D	115.29	103.6, 128.3
	B	948.95	B/D	104.67	93.95, 116.61
	C	867.19	C/D	95.65	85.83, 106.59
	D	906.63	--	--	--
C_{max} ng/mL					
	A	155.25	A/D	132.92	114.83, 153.85
	B	142.24	B/D	121.78	105.12, 141.08
	C	127.82	C/D	109.43	94.25, 127.06
	D	116.80	--	--	--

*Least squares mean, log transformed data
A: 60-mg fexofenadine (b) (4) powder in 10 ml of Karo® light syrup

B: 60-mg fexofenadine (b) (4) powder in 10 ml of Dannon® low fat yogurt
C: 60-mg fexofenadine (b) (4) powder in 10 ml of Gerber® rice cereal prepared with Similac® with Iron
D: 60-mg fexofenadine reference capsule

Safety variables included adverse events (AEs), vital signs, physical examinations, and clinical laboratory specimens. Two of 23 patients (8.3%) experienced one or more AEs. There were 4 AEs reported among the 23 patients (17.4%). There were no AEs reported more than once. There were no deaths or SAEs. Review of urinalyses, hematology and blood chemistry studies revealed no clinically meaningful changes from baseline. There were no abnormalities in vital signs reported as an AE. ECGs revealed no safety signal [Volume 32, pages 33, 43-45, 50, 51, 55].

Reviewer comments:
The PK data indicate that Gerber® rice cereal prepared with Similac® with Iron was an acceptable vehicle for pediatric studies M106544T/3001 and M106455T/3002. Safety summaries and line listings for this study were reviewed and reveal no safety signal [Volume 32, pages 43-46, Volume 34, pages 20-82].

2 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Reviewed by:

_____

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

_____

Lydia Gilbert McClain, M.D.
Acting Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original NDA
HFD-570/Division File
HFD-570/Gilbert-McClain/Acting Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-570/Rogers/Chemistry, Manufacturing, and Controls Reviewer
HFD-870/S. Kim/Clinical Pharmacology and Biopharmaceutics Reviewer
HFD-570/Yu/CSO

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/s/

Charles Lee
4/22/03 01:19:47 PM
MEDICAL OFFICER

Lydia McClain
4/22/03 03:16:26 PM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 20-625 NDA 20-786 NDA 20-872	**TRADE NAME:**	Allegra® Capsules Allegra® D Tablets Allegra® Tablets
APPLICANT/SPONSOR:	Aventis Pharmaceuticals	**USAN NAME:**	Fexofenadine hydrochloride
MEDICAL OFFICER:	Charles E. Lee, M.D.		
TEAM LEADER:	Lydia Gilbert-McClain, M.D.	**CATEGORY:**	Antihistamine
DATE:	4/30/03	**ROUTE:**	Oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	Stamp Date	Submission	Comments
11/18/02	11/20/02	NDA 20-625 SE8-012	Allegra® Capsules, labeling supplement
11/18/02	11/19/02	NDA 20-786 SE8-014	Allegra® D Tablets, labeling supplement
11/18/02	11/19/02	NDA 20-872 SE8-011	Allegra® Tablets, labeling supplement
12/17/02	12/18/02	NDA 20-625 SE8-010 BL	Response to approvable letter
12/17/02	12/18/02	NDA 20-872 SE8-003 BL	Response to approvable letter
1/14/03	1/15/03	NDA 20-625 SE8-012 C	Information requests, age, ECGs
1/14/03	1/15/03	NDA 20-786 SE8-014 C	Information requests, age, ECGs
1/14/03	1/15/03	NDA 20-872 SE8-011 C	Information requests, age, ECGs
2/27/03	2/28/03	NDA 20-625 SE8-012 C	Information requests, subgroup analyses
2/27/03	2/28/03	NDA 20-625 SE8-012 BZ	Information requests, subgroup analyses
2/27/03	2/28/03	NDA 20-625 SE8-012 BL	Information requests, subgroup analyses
4/16/03	4/17/03	NDA 20-625 SE8-012 C	Information requests, formulation

RELATED APPLICATIONS

Document Date	Application Type	Comments
2/12/02	NDA 20-625, SE8-010	Pediatric labeling supplement, Allegra® Capsules
2/12/02	NDA 20-872, SE8-003	Pediatric labeling supplement, Allegra® Tablets
7/12/00	NDA 20-625, SE8-010 PM	Pediatric labeling supplement, Allegra® Capsules
(b) (4)	(b) (4)	(b) (4)
7/12/00	NDA 20-872, SE8-003 PM	Pediatric labeling supplement, Allegra® Tablets
7/17/98	NDA 20-872	NDA application for Allegra® Tablets
1/2/97	NDA 20-786	NDA application for Allegra D® Tablets
7/31/95	NDA 20-625	NDA application for Allegra® capsules

REVIEW SUMMARY:

This application is a pediatric labeling supplement submitted for Allegra® Capsules (fexofenadine HCl), Allegra® Tablets (fexofenadine HCl), and Allegra® D Tablets (fexofenadine HCl/pseudoephedrine HCl). The supplement was also submitted as a response to previous approvable letters. This addendum to the medical officer review for this application corrects an error in the review regarding requirements for pharmacology-toxicology data. (b) (4)

OUTSTANDING ISSUES: The sponsor must revise proposed draft labeling.

RECOMMENDED REGULATORY ACTION					
NDA/SUPPLEMENTS:	___	FILEABLE	___	NOT FILEABLE	
	___	APPROVAL	X	APPROVABLE	NOT APPROVABLE

Reviewed by:

_____

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

_____

Lydia Gilbert McClain, M.D.
Acting Team Leader, Division of Pulmonary and Allergy Drug Products

cc: Original NDA
HFD-570/Division File
HFD-570/Gilbert-McClain/Acting Medical Team Leader
HFD-570/Lee/Medical Reviewer
HFD-570/Rogers/Chemistry, Manufacturing, and Controls Reviewer
HFD-870/S. Kim/Clinical Pharmacology and Biopharmaceutics Reviewer
HFD-870/Fadiran/ Clinical Pharmacology and Biopharmaceutics Team Leader
HFD-570/Sancilio/Pharmacology-Toxicology Reviewer
HFD-570/Sun/Pharmacology-Toxicology Team Leader
HFD-570/Yu/CSO

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/s/

Charles Lee
5/5/03 09:51:13 AM
MEDICAL OFFICER

Lydia McClain
5/5/03 11:14:12 AM
MEDICAL OFFICER

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 20-625 NDA 20-786 NDA 20-872	**TRADE NAME:**	Allegra® Capsules Allegra D® Tablets Allegra® Tablets
APPLICANT/SPONSOR:	Aventis Pharmaceuticals	**USAN NAME:**	Fexofenadine hydrochloride
MEDICAL OFFICER:	Charles E. Lee, M.D.		
SECONDARY REVIEWER:	Marianne Mann, M.D.	**CATEGORY:**	Antihistamine
DATE:	5/7/03	**ROUTE:**	Oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	Stamp Date	Submission	Comments
4/28/03	4/29/03	NDA 20-625 SE8-012 BL	Allegra® Capsules, labeling
4/28/03	4/29/03	NDA 20-786 SE8-014 BL	Allegra D® Tablets, labeling
4/28/03	4/29/03	NDA 20-872 SE8-011 BL	Allegra® Tablets, labeling
4/28/03	4/29/03	NDA 20-625 SE8-010 BL	Response to approvable letter, labeling
4/28/03	4/29/03	NDA 20-872 SE8-003 BL	Response to approvable letter, labeling

RELATED APPLICATIONS

Document Date	Application Type	Comments
7/17/98	NDA 20-872	NDA application for Allegra® Tablets
1/2/97	NDA 20-786	NDA application for Allegra D® Tablets
7/31/95	NDA 20-625	NDA application for Allegra® capsules

REVIEW SUMMARY:

This submission includes revised draft labeling for a pediatric labeling supplement submitted to NDAs for Allegra® Capsules (fexofenadine HCl), Allegra® Tablets (fexofenadine HCl), and Allegra D® Tablets (fexofenadine HCl/pseudoephedrine HCl). The supplement was also submitted as a response to previous approvable letters. The sponsor's data supported the addition of safety data to the CLINICAL PHARMACOLOGY Clinical Studies, PRECAUTIONS Pediatric Use, and ADVERSE REACTIONS sections of the Allegra® Capsules and Allegra® Tablets labels. The sponsor was asked to revise their proposed draft labeling. Review of the sponsor's revised proposed labeling reveals that the fifth paragraph in PRECAUTIONS Pediatric Use includes a sentence that is not acceptable. The sentence states: " (b) (4) This sentence should be changed to: "The safety and effectiveness of fexofenadine hydrochloride in pediatric patients under the age of 6 years have not been established." The remainder of the revised proposed labeling is acceptable. The application may be approved if the sponsor changes the sentence

OUTSTANDING ISSUES: The application may be approved if the sponsor changes the sentence noted above.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	___ **FILEABLE**	___ **NOT FILEABLE**		
	X **APPROVAL**	**APPROVABLE**	**NOT APPROVABLE**	

Reviewed by:

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

Marianne Mann, M.D.
Deputy Director, Division of Pulmonary and Allergy Drug Products

cc: Original NDA
HFD-570/Division File
HFD-570/Mann/Deputy Director
HFD-570/Gilbert-McClain/Acting 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
HFD-570/Yu/CSO

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/s/

Charles Lee
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Marianne Mann
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