CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20872

MEDICAL REVIEW

Application Number: 20-872 **Application Type:** NDA Response Review

Sponsor: Aventis Pharmaceuticals **Proprietary Name:** Allegra® tablets 30 mg , 60 mg, 180 mg

USAN Name: Fexofenadine HCl

Category of Drug: Histamine H_1-receptor antagonist **Route of Administration:** Oral

Medical Reviewer: Charles E. Lee, M.D. **Review Date:** 2/14/00

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date:	Submission Type	Comments:
4/9/99	Date pending	NDA 20-872	Response to IR regarding QTc prolongation
8/16/99	8/17/99	NDA 20-872	Correspondence addressing safety update requested in response to approval letter
8/26/99	8/27/99	NDA 20-872	Response to approval letter (10 volumes)
12/15/99	12/16/99	NDA 20-872	Response to IR, selected CRFs
1/7/00	1/10/00	NDA 20-872	Response to IR, selected CRFs
1/19/00	1/27/00	NDA 20-625	Follow-up AE report, prolonged QTc
1/28/00	Date pending	NDA 20-872	Telecon, response to IR, study design

RELATED APPLICATIONS (if applicable):

Document Date:	Application Type:	Comments:
7/31/95	NDA 20-625	NDA application for Allegra® 60 mg capsules
1/2/97	NDA 20-786	NDA application for Allegra-D® tablets

REVIEW SUMMARY:

This document is a review of a response to approvable letter for Allegra® tablets. The approvable letter included chemistry, marketing, and controls and clinical deficiencies. The sponsor was also asked to submit a safety update and revised product labeling for Allegra. The sponsor withdrew

to meet the clinical deficiencies.

The sponsor submitted a safety update covering 9 clinical trials in progress at the time of the original NDA submission, adverse event reports in other clinical and postmarketing studies, postmarketing and worldwide safety data, and proposed product labeling. The safety update and the product labeling are the focus of this review. Review of the AEs, SAEs, and early discontinuations from the 9 clinical trials reveals no new safety signal for fexofenadine. Likewise, review of postmarketing and worldwide safety data do not reveal any new safety signal. Preliminary comments on proposed product labeling are included in this review. The final product labeling will follow as a separate document. This update reveals no new safety concerns, and this application is recommended for approval.

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION: Approval: X

New Clinical Studies: **Clinical Hold:** **Study May Proceed:**

NDA, Efficacy/Label Supplement: **Fileable:** **Not Fileable:**

SIGNED:

Medical Reviewer: /S/ **Date:** 2/18/00

Medical Team Leader: /S/ **Date:** 2/18/00

1. Table of contents

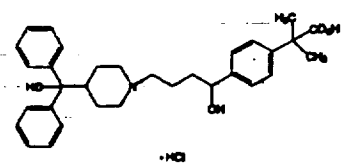
2. Drug name

2.1.1. Generic name: Fexofenadine HCl 30 mg, 60 mg, 180 mg

2.1.2. Trade name: ALLEGRA® Tablets

2.1.3. Chemical name: Fexofenadine HCl: (±)-4-[1-Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α-α-dimethylbenzenacetic acid HCl (MDL 16,455A)

2.2. Structural formula:



2.3. Molecular formula: $C_{32}H_{39}NO_4 \cdot HCl$

2.4. Molecular weight: 538.13

2.5. Sponsor: Aventis Pharmaceuticals

2.6. Pharmacologic category: Histamine H_1-receptor antagonist

2.7. Indications: Treatment of symptoms due to seasonal allergic rhinitis and chronic idiopathic urticaria in adults (≥ 12 years of age) and children (6-11 years of age).

2.8. Dosage form, frequency, and route of administration:

Fexofenadine HCL 30 mg, 1 tablet po twice daily
Fexofenadine HCl 60 mg, 1 tablet po twice daily
Fexofenadine HCl 180 mg, 1 tablet po once daily

2.9. Related drugs:

NDA 20-625: Allegra ® capsules (fexofenadine 60 mg capsules), approved 7/25/96
NDA 20-786: Allegra-D® tablets (fexofenadine 60 mg plus pseudoephedrine hydrochloride, 120 mg extended release tablet), approved 1/2/98

2.10. Related reviews:

Medical officer review, NDA 20-872 dated: 5/20/99, revised 7/1/99
Chemistry reviews, NDA 20-872 dated: 7/15/99, 10/7/99, 12/13/99
Statistical reviews, NDA 20-872 dated: 7/12/99
Biopharmaceutics review, NDA 20-872 dated: 7/13/99

3. Background

NDA 20-872, Allegra® (fexofenadine hydrochloride) tablets, dated 7/17/99, is for new indications, dosing regimens, and age groups for Allegra. Currently Allegra is indicated for the relief of symptoms associated with seasonal allergic rhinitis (SAR) in adults and children 12 years of age and older as a 60-mg capsule. The recommended dose is 60 mg po BID.

The original submission included the following proposed indications, regimens, and age groups:

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

The application was found to be approvable, but had clinical and chemistry marketing and controls (CMC) deficiencies. The sponsor was instructed to address the following four clinical deficiencies:

In addition, the sponsor was asked to provide an update of all safety and revised draft labeling information for fexofenadine HCl.

The sponsor responded to the clinical deficiencies in the application with the following actions:

In addition, Aventis Pharmaceuticals submitted an update of safety information for Allegra® tablets and revised draft labeling.

The following indications, regimens, and age groups are now proposed for Allegra:

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

4. Conduct of the review and content of the submission

This review focuses on the update of safety information and the revised draft labeling. The safety information and labeling include the following:

- AEs from 9 North American and Japanese clinical studies that were in progress at the time of the original submission
  - Review of AEs in the clinical studies update followed the format submitted by the sponsor. AEs were grouped by primary indication for review and compared with frequencies from the original NDA submission. AEs from one study, a pollen chamber study, were reviewed separately.
- SAEs from 9 North American and Japanese clinical studies that were in progress at the time of the original submission
  - SAEs were reviewed and compared with frequencies of SAEs seen in the original NDA submission.
- Dropouts from these 9 clinical studies
  - These were reviewed and compared with the original NDA submission. Case Report Forms (CRFs) of selected subjects with AEs leading to study withdrawal were reviewed.
- SAEs from 5 foreign clinical studies in progress at the time of the original submission
- Two semi-annual Periodic Safety Update Reports (PSURs) covering 3/11/98-9/10/98 and 9/11/98-3/10/99 and 2 supplemental listings of postmarketing spontaneous reports of AEs covering 3/1/98-3/10/98 and 3/11/99-7/16/99
- Foreign labeling that was not previously submitted under NDA 20-872
- Proposed product labeling

The sponsor's submission did not include reports of changes in vital signs, physical examination, laboratory values, or ECGs from the studies noted above. Study reports or study protocols were not submitted for any of the studies.

5. North American and Japanese clinical studies

AEs, SAEs, and dropouts from 2 clinical pharmacology studies, 1 CIU study, 3 perennial allergic rhinitis (PAR) studies, 2 SAR studies, and 1 pollen chamber study are reviewed in the sections that follow. These studies are displayed in Table 1.

5.1.1. Adverse events in clinical studies

Somnolence and dry mouth with dose response effects were noted in the CIU studies in this update. Somnolence and dry mouth were seen in the PAR studies in this update, but no dose response effect was seen. These AEs were not represented in the other studies in this update. The studies covered by this update do not consistently show the presence of somnolence and dry mouth or a dose response effect for these AEs. It is unlikely that they represent new safety signals.

Other AEs in the update of clinical studies were similar to those noted in the original NDA submission, and reveal no new safety concerns. Details of AEs in the clinical studies update are discussed in the following sections.

5.1.1.1. Adverse events in clinical pharmacology studies

Two clinical pharmacology studies were completed after the 120-day review. These studies are M106455/1104 and MM016455/1105.

M106455/1104 was a double-blind, randomized, 3-way crossover study in healthy males. It was a three day single dose, single center Japanese study with fexofenadine 60 mg and 120 mg, and terfenadine 60 mg.

M016455/1105 was also a double-blind, randomized, 3-way crossover study in healthy males. It was a multiple dose study with fexofenadine 120 mg po BID, fexofenadine 120 mg po BID plus erythromycin 300 mg po QID, and erythromycin 300 mg po QID alone. It was a 7-day study, with a 14-day washout between treatments. AEs occurring at a frequency of ≥ 2.0% from both of these studies are displayed in Table 2. AEs occurring at a frequency of ≥ 2.0% in all clinical pharmacology studies in the original NDA are displayed in Table 3 for comparison.

Table 1. North American and Japanese clinical studies in progress at time of NDA submission

Study type and number	Design	Duration of treatment	Treatment Groups	Number of subjects	Population
Clinical pharmacology studies					
M016455/1104 Japan	Double-blind, randomized, Single dose, 3-way crossover, Single center	1 day each treatment period, 3 days	Fexo 60 mg, Fexo 120 mg, Terfenadine 60 mg	Healthy males	24
M016455/1105 Japan	Double-blind, randomized, Multiple dose, 3-way crossover, Single center	7 days each treatment period, 21 days	Fexo 120 mg BID, Fexo 120 mg BID+Erythromycin 300 mg QID, Erythromycin 30 mg QID	Healthy males	18
CIU study					
JTAM-CL-201 Japan	Double-blind, randomized, Parallel group, multiple dose, Multicenter	7 days	Fexo 10 mg BID, Fexo 60 mg BID, Fexo 120 mg BID	Patients with CIU	226
PAR studies					
JTAM-CL-202 Japan	Double-blind, randomized, Parallel group, multiple dose, Multicenter	2 weeks	Fexo 10 mg BID, Fexo 60 mg BID, Fexo 120 mg BID	Patients with PAR	314
M016455M/3097 U.S. and Canada	Double-blind, randomized, Placebo controlled, active controlled Parallel group, multiple dose, Multicenter	8 weeks	Placebo QD, Fexo 120 mg QD, Fexo 180 mg QD, Cetirizine 10 mg QD	Patients with PAR	1300
016455PR0057 Canada	Double-blind, randomized, Placebo controlled, Parallel group, multiple dose, Multicenter	4 weeks	Placebo BID, Fexo 60 mg BID, Fexo 120 mg QD	Patients with PAR	673
SAR studies, Multiple dose					
M016455/4049 U.S.	Double-blind, randomized, Placebo controlled, 4-way crossover, multiple dose, Single center	1 week each treatment period, 4 weeks	Placebo BID, Fexo 60 mg BID, Fexo 120 mg BID, Fexo 360 mg BID	Ragweed-allergic SAR patients, out of ragweed season	20
M016455/4092 U.S.	Double-blind, randomized, Placebo controlled, Parallel group, multiple dose, Multicenter	6 weeks	Placebo QD, Fexo 180 mg QD	SAR patients with mild asthma	350
SAR study, Single dose, Pollen chamber					
M016455F/3091	Double-blind, randomized, Placebo controlled, Parallel group, single dose, Multicenter	1 dose, followed for 72 hours	Placebo, Fexo 120 mg, Fexo 180 mg, Fexo 240 mg	Ragweed-allergic SAR patients, EEU	127

Table 2. Adverse events ≥ 2.0%, clinical pharmacology studies, update (Volume 26.2, page 285)

Preferred Term	All fexo doses n = 42		Fexo 60 mg n = 23		Fexo 120 mg n = 42		Fexo 120 + erythro n = 18	
	n	(%)	n	(%)	n	(%)	n	(%)
Total occurrence rate	9	(21.4)	5	(21.7)	5	(11.9)	1	(5.6)
Vasodilation	3	(7.1)	3	(13)	1	(2.4)	0	(0)
Diarrhea	1	(2.4)	0	(0)	0	(0)	1	(5.6)
Chest pain	1	(2.4)	1	(4.3)	1	(2.4)	0	(0)
Throat constriction	1	(2.4)	0	(0)	1	(2.4)	0	(0)
Tooth disorder	1	(2.4)	1	(4.3)	0	(0)	0	(0)
Urine abnormal	1	(2.4)	0	(0)	1	(2.4)	0	(0)
ALT increased	1	(2.4)	0	(0)	1	(2.4)	0	(0)

Table 3. Adverse events ≥ 2.0%, clinical pharmacology studies, original NDA (Volume 26.2, page 286-288, data from Tables 7, 8, 9, and 10 pooled)

Preferred Term	Single dose fexo n = 192		Multiple dose fexo n = 46		All clinical pharmacology studies, n = 238	
	n	(%)	n	(%)	n	(%)
Total occurrence rate	58	(30.2)	13	(28.3)	67	(28.2)
Anemia	11	(5.7)	0	(0)	11	(4.6)
Headache	7	(3.6)	3	(6.5)	10	(4.2)
Monocytosis	6	(3.1)	0	(0)	6	(2.5)
Hyperchloremia	6	(3.1)	0	(0)	6	(2.5)
Hyperphosphatemia	1	(0.5)	4	(8.7)	5	(2.1)
Bradycardia	3	(1.6)	1	(2.2)	4	(1.7)
Nausea	3	(1.6)	1	(2.2)	4	(1.7)
Vasodilation*	1	(0.5)	0	(0)	1	(0.4)

*Event rate < 2.0%, but included for comparison with event in update studies

Small numbers of subjects were studied in the clinical pharmacology studies covered by this update. The total occurrence rates in the update for all fexofenadine doses combined and all doses individually were lower than those in the original NDA. Vasodilation was noted in the clinical pharmacology update at a higher rate than in clinical pharmacology studies in the original NDA. No other AEs occurred in the clinical pharmacology studies in more than one patient, making meaningful comparison with frequencies of AEs in the original NDA difficult.

5.1.1.2. Adverse events in CIU studies

The sponsor has submitted a compilation of non-serious AEs noted in a single CIU study, JTAM-CL-201, completed after the 120-Day safety update.

JTAM-CL-201 was a Japanese multicenter study. It was a double-blind, randomized, parallel group, and multiple dose study in 226 subjects with CIU. The treatment period was 7 days. Fexofenadine 10 mg po BID, fexofenadine 60 mg po BID, and fexofenadine 120 mg po BID were studied. There was no placebo control. AEs occurring in this study at a frequency ≥ 2.0% are displayed in Table 4. AEs occurring at a frequency of ≥ 2.0% in all CIU in the original NDA are displayed in Table 5 for comparison.

Table 4. Adverse events ≥ 2.0%, CIU study (Volume 26.2, page 294)

Preferred Term	All fexo n = 226		Fexo 10 mg bid n = 78		Fexo 60 mg bid n = 75		n = 73	
	n	(%)	n	(%)	n	(%)	n	(%)
Total occurrence rate	85	(37.6)	33	(42.3)	25	(33.3)	27	(37.0)
Somnolence	27	(11.9)	7	(9.0)	9	(12.0)	11	(15.1)
Malaise	12	(5.3)	5	(6.4)	5	(6.7)	2	(2.7)
Abdominal pain	10	(4.4)	2	(2.6)	3	(4.0)	5	(6.8)
Headache	9	(4.0)	2	(2.6)	3	(4.0)	4	(5.5)
Dry mouth	7	(3.1)	1	(1.3)	2	(2.7)	4	(5.5)
Urine abnormal	7	(3.1)	4	(5.1)	1	(1.3)	2	(2.7)
Diarrhea	6	(2.7)	3	(3.8)	2	(2.7)	1	(1.4)
Vasodilation	4	(1.8)	1	(1.3)	0	(0)	3	(4.1)
AST increased	3	(1.3)	1	(1.3)	0	(0)	2	(2.7)
Chest pain	3	(1.3)	1	(1.3)	0	(0)	2	(2.7)
Fever	3	(1.3)	0	(0)	2	(2.7)	1	(1.4)
Vomiting	3	(1.3)	0	(0)	2	(2.7)	1	(1.4)
Constipation	2	(0.9)	0	(0)	2	(2.7)	0	(0)
Leukocytosis	2	(0.9)	0	(0)	0	(0)	2	(2.7)
Proteinuria	2	(0.9)	2	(2.6)	0	(0)	0	(0)

Table 5. Adverse events ≥ 2.0%, CIU studies in original NDA (26.2, page 296-305)

Preferred term	US, 4 weeks fexo bid n = 713		US, 4 weeks Placebo n = 178		Non-US, 6 weeks fexo qd n = 171		Non-US, 6 weeks Placebo n = 51	
	n	(%)	n	(%)	n	(%)	n	(%)
Total occurrence rate	441	(61.9)	105	(59.0)	120	(70.2)	37	(72.5)
Headache	157	(22.0)	34	(19.1)	69	(40.4)	16	(31.4)
URI	62	(8.7)	15	(8.4)	10	(5.8)	6	(11.8)
Pharyngitis	35	(4.9)	10	(5.6)	6	(3.5)	1	(2.0)
Nausea	35	(4.9)	7	(3.9)	13	(7.6)	3	(5.9)
Dyspepsia	31	(4.3)	9	(5.1)	5	(2.9)	0	(0)
Influenza	23	(3.6)	5	(2.8)	3	(1.8)	1	(2.0)
Pain	26	(3.6)	11	(6.2)	5	(2.9)	1	(2.0)
Rhinitis	23	(3.2)	9	(5.1)	3	(1.8)	1	(2.0)
Myalgia	22	(3.1)	5	(2.8)	2	(1.2)	0	(0)
Abdominal pain	19	(2.7)	6	(3.4)	8	(4.7)	1	(2.0)
Diarrhea	18	(2.5)	6	(3.4)	10	(5.8)	1	(2.0)
Sinusitis	18	(2.5)	2	(1.1)	0	(0)	0	(0)
Upper respiratory congestion	16	(2.2)	6	(3.4)	0	(0)	0	(0)
Dysmenorrhea	16	(2.2)	3	(1.7)	1	(0.6)	0	(0)
Arthralgia	15	(2.1)	3	(1.7)	5	(2.9)	0	(0)
Insomnia	15	(2.1)	2	(1.1)	5	(2.9)	1	(2.0)
Dizziness	14	(2.0)	1	(0.6)	9	(5.3)	3	(5.9)
Somnolence	13	(1.8)	0	(0)	0	(0)	1	(2.0)
Coughing	8	(1.1)	2	(1.1)	4	(2.3)	0	(0)
Tooth disorder	8	(1.1)	1	(0.6)	4	(2.3)	1	(2.0)
Vomiting	7	(1.0)	3	(1.7)	4	(2.3)	0	(0)
Fatigue	6	(0.8)	4	(2.2)	9	(5.3)	2	(3.9)
Urticaria	6	(0.8)	1	(0.6)	9	(5.3)	9	(17.6)
Leukopenia	0	(0)	0	(0)	4	(2.3)	1	(2.0)

The total occurrence rates in the update were less than those seen in the original NDA submission. Somnolence was noted in the update, with a rate of 11.9% in all fexofenadine doses and a dose response effect was seen. In comparison, somnolence was seen in 1.8% of the US CIU studies and not in the non-US CIU studies in the original NDA. Dry mouth was

seen in the CIU update studies at a rate of 3.1% with a dose response effect. Dry mouth was not noted in the CIU studies in the original NDA. Dose response effects were also noted in abdominal pain and in headache in the CIU update, but these adverse effects were noted in the original NDA.

5.1.1.3. Adverse events in PAR studies

There were three studies in subjects with PAR in this safety update. The studies were JTAM-CI-202, M016455M/3097, and 01655PR0057.

JTAM-CI-202 was a Japanese, multicenter study. It was a double-blind, randomized, parallel group study. The doses studied were 60 mg po BID,
There was no placebo control arm. The duration of treatment was 2 weeks.

M016455M/3097 was a US/Canadian multicenter study. It was a double-blind, randomized, placebo-controlled and active-controlled, parallel group study.
fexofenadine 180 mg po QD, and cetirizine 10 mg po QD were studied after a 6-7 day placebo lead-in. The duration of treatment was 8 weeks.

016455PR0057 was a Canadian multicenter study. It was a double-blind, randomized, placebo-controlled, parallel group study of 4 weeks treatment duration. Fexofenadine 60 mg po BID and fexofenadine 120 mg po QD were studied after a 7 day placebo lead-in. The duration of treatment was 4 weeks.

There were no PAR studies in the original NDA. Frequencies of AEs ≥ 2.0 % in all PAR studies in this update are displayed in Table 6.

Table 6. Adverse events ≥ 2.0%, PAR studies, update (Volume 26.2, page 332-337)

Preferred term	All fexo n = 1422		n = 100		Fexo 60 mg n = 333		n = 664		Fexo 180 mg n = 325		Placebo n = 539	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total occurrence rate	663	(46.6)	40	(40.0)	122	(36.6)	314	(47.3)	187	(57.5)	247	(45.8)
URI	179	(12.6)	11	(11)	31	(9.3)	82	(12.3)	55	(16.9)	61	(11.3)
Headache	133	(9.4)	9	(9)	30	(9.0)	64	(9.6)	30	(9.2)	48	(8.9)
Pharyngitis	58	(4.1)	3	(3)	8	(2.4)	25	(3.8)	22	(6.8)	15	(2.8)
Somnolence	49	(3.4)	11	(11)	17	(5.1)	18	(2.7)	3	(0.9)	2	(0.4)
Influenza	48	(3.4)	0	(0)	6	(1.8)	24	(3.6)	18	(5.5)	23	(4.3)
Sinusitis	31	(2.2)	0	(0)	2	(0.6)	11	(1.7)	18	(5.5)	23	(4.3)
Back pain	29	(2.0)	0	(0)	2	(0.6)	11	(1.7)	16	(4.9)	8	(1.5)
Pain	23	(1.6)	0	(0)	1	(0.3)	10	(1.5)	12	(3.7)	13	(2.4)
Dry mouth	23	(1.6)	4	(4)	5	(1.5)	13	(2.0)	1	(0.3)	4	(0.7)
Myalgia	22	(1.5)	0	(0)	0	(0)	10	(1.5)	12	(3.7)	10	(1.9)
Tooth disorder	16	(1.1)	0	(0)	1	(0.3)	4	(0.6)	11	(3.4)	4	(0.7)

The total occurrence rate in the PAR studies included in this update was similar in drug and placebo groups. URI and pharyngitis were more common in fexofenadine-treated groups, and a dose response effect was seen in these AEs. Somnolence and dry mouth were seen more frequently in fexofenadine-treated groups, but no dose response effect was seen in these AEs.

5.1.1.4. Adverse events in multiple dose SAR studies

There were two multidose studies in subjects with SAR covered by this update. They were M016455/4049 and M106455/4092.

M016455/4049 was a US single center study. It was a double-blind, randomized, placebo-controlled, 4-way crossover study in ragweed-sensitive patients. The doses studied were fexofenadine 60 mg po BID,

There was a 7-day washout between treatments. Each treatment phase of the study lasted 7 days.

M016455/4092 was a US multicenter study. It was a double-blind, randomized, parallel-group study in SAR patients with mild asthma. The dose studied was fexofenadine 180 mg po QD after a 1 week placebo lead-in. Treatment duration was 6 weeks.

AEs in multiple dose SAR studies in the update are listed in Table 7 and AEs from controlled SAR studies in the original NDA are presented in Table 8 for comparison.

Table 7. Adverse events ≥ 2.0%, multiple dose SAR studies, update (Volume 26.2, page 349-351)

Preferred term	Fexo, all (n = 192)		Fexo, 60 (n = 20)		(n = 20)		Fexo, 180 (n = 172)		(n = 20)		Placebo (n = 198)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total occurrence rate	97	(50.5)	3	(15)	2	(10)	92	(53.5)	1	(5)	90	(45.5)
Headache	33	(17.2)	1	(5)	0	(0)	32	(18.6)	0	(0)	30	(15.2)
URI	22	(11.5)	1	(5)	1	(5)	20	(11.6)	9	(0)	9	(4.5)
Pain	11	(5.7)	0	(0)	0	(0)	11	(6.4)	0	(0)	8	(4.0)
Pharyngitis	11	(5.7)	0	(0)	0	(0)	11	(6.4)	0	(0)	7	(3.5)
Sinusitis	11	(5.7)	0	(0)	0	(0)	11	(6.4)	0	(0)	12	(6.1)
Back pain	6	(3.1)	0	(0)	0	(0)	6	(3.5)	0	(0)	1	(0.5)
Myalgia	6	(3.1)	0	(0)	0	(0)	6	(3.5)	0	(0)	7	(3.5)
Asthma	5	(2.6)	0	(0)	0	(0)	5	(2.9)	0	(0)	8	(4.0)
Dysmenorrhea	5	(2.6)	0	(0)	0	(0)	5	(2.9)	0	(0)	6	(3.0)
Artharalgia	4	(2.1)	0	(0)	0	(0)	4	(2.3)	0	(0)	1	(0.5)
Bronchitis	4	(2.1)	0	(0)	0	(0)	4	(2.3)	0	(0)	1	(0.5)

Table 8. Adverse events ≥ 2.0%, controlled SAR Studies, original NDA (Volume 26.2, pages 352-360)

Preferred term	Fexo QD n = 1886		Placebo n = 944	
	n	(%)	n	(%)
Total occurrence rate	613	(32.5)	318	(33.7)
Headache	207	(11.0)	106	(11.2)
Somnolence	41	(2.2)	20	(2.1)
Pharyngitis	45	(2.4)	26	(2.8)

Total occurrence rate of AEs was higher in fexofenadine-treated patients in the SAR studies in the update, and was higher than the rate observed in the SAR studies in the original NDA. Somnolence was not seen in multiple dose SAR studies covered by this update, but was seen in SAR studies in the original NDA at similar rates in both fexofenadine- and placebo-treated patients. URI, pharyngitis, and back pain were more frequent in fexofenadine-treated subjects in the update studies than in the original NDA, but no dose response effect was seen. Interestingly, asthma was seen somewhat less frequently in fexofenadine-treated patients in the update studies.

5.1.1.5. Adverse events in the pollen chamber study

There was a single pollen chamber study that is included in the update, M016455/3091.

M016455F/3091 was a Canadian study. It was a double-blind, randomized, placebo-controlled, parallel group, single dose pollen chamber study in ragweed-sensitive patients. Fexofenadine 180 mg po, were studied as single doses. AEs occurring ≥ 2.0 % are listed in Table 9. There were no pollen chamber studies in the original NDA.

Table 9. Adverse events ≥ 2.0%, single dose pollen chamber study, update (Volume 26.2, page 362)

Preferred term	All fexo n = 95		n = 32		Fexo 180 n = 31		n = 32		Placebo n = 32	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total occurrence rate	6	(6.3)	3	(9.4)	2	(6.5)	1	(3.1)	1	(3.1)
Headache	3	(3.2)	0	(0)	2	(6.5)	1	(3.1)	1	(3.1)
Nausea	2	(2.1)	1	(3.1)	1	(3.2)	0	(0)	0	(0)
Chest pain	1	(1.1)	0	(0)	1	(3.2)	0	(0)	0	(0)
Dizziness	1	(1.1)	1	(3.1)	0	(0)	0	(0)	0	(0)
Dyspepsia	1	(1.1)	0	(0)	1	(3.2)	0	(0)	0	(0)
Pharyngitis	1	(1.1)	1	(3.1)	0	(0)	0	(0)	0	(0)
Sinusitis	1	(1.1)	1	(3.1)	0	(0)	0	(0)	0	(0)

A small number of subjects were enrolled in this study, and there was a slightly higher total occurrence rate in fexofenadine-treated subjects. AEs noted were similar to those noted in the previous NDA and in other studies covered by this submission.

5.1.2. Serious adverse events in clinical studies

SAE findings in studies covered by this update are similar in type and frequency with those found in studies submitted in the original NDA. In summary, review of SAEs in the clinical studies update reveals no new safety concerns. Details of SAEs in the clinical studies update are discussed below.

There were no SAEs noted in the clinical pharmacology studies covered by this update or in the original NDA.

There were no SAEs noted in CIU study covered by this update.

SAEs were reported in 1 of the 3 PAR studies covered by this update, study M016455M/3097 (Volume 26.2, page 271-272, 365, 554). SAEs occurred in 3 fexofenadine-treated subjects, Patients 1162-0010, 1080-0028, and 1065-0016. Patient 1062-0010 was taking and was hospitalized with chest pain, cardiomegaly, hypertension, dyspnea, and lower respiratory congestion. This patient withdrew from the study (Volume 26.2, pages 554, 572). Patient 1080-0028 was taking fexofenadine 180 mg po QD and was hospitalized with a retinal detachment. The retinal detachment was considered a medically important AE. The patient withdrew from the study (Volume 26.2, page 554, 573). Patient 1065-0016 was taking and had a medically important AE which consisted of an accidental injury. The patient did not withdraw from the study (Volume 26.2, page 554). There were no deaths, overdoses, disabilities, congenital anomalies, or cancers in fexofenadine-treated subjects in PAR studies.

The total occurrence rate of SAEs for all fexofenadine-treated patients in PAR studies covered by this update was lower than the combined rate of SAEs for placebo-treated and cetirizine-treated patients. The rate of SAEs in fexofenadine-treated patients was 3/1422, or 0.21%. SAEs in placebo and cetirizine-treated patients had a combined occurrence rate of 5/865, or 0.58%. There were no PAR studies in the original NDA submission for comparison.

One SAE was noted in one of the multiple dose SAR studies covered by this update, Study M016455/4092 (Volume 26.2, pages 357-370). Patient 1141-0018 was taking fexofenadine 180 mg QD and was hospitalized with gastroenteritis. There were no deaths, overdoses, disabilities, congenital anomalies, or cancers in fexofenadine-treated subjects in multiple dose SAR studies.

The total occurrence rate of SAEs for all fexofenadine-treated subjects in all multiple dose SAR studies in this update was similar to that seen with placebo. SAEs were seen in 1/192, or 0.52% of fexofenadine-treated patients and in 1/198, or 0.50% of placebo-treated patients (Volume 26.2, pages 272, 370). In comparison, the overall rate of SAEs in the SAR studies covered by this update was higher than the rate in multiple dose studies in the original NDA. The occurrence rate for SAEs in fexofenadine-treated SAR patients in the original NDA was 4/1841 or 0.22%, compared with 2/1153, or 0.17% in cetirizine and placebo-treated patients combined.

There were no SAEs noted in the pollen chamber study covered by this update and there were no pollen chamber studies in the original NDA.

5.1.3. Early discontinuation from clinical studies

In summary, review of dropouts in the clinical studies update reveals no new safety concerns. Details of dropouts in the clinical studies update are discussed below.

There were no early discontinuations due to AEs in fexofenadine-treated subjects in the clinical pharmacology studies in this update. In comparison, there were 4 discontinuations from AEs in the clinical pharmacology studies in the original NDA (Volume 26.22, pages 273-274, 373-374).

There were 6 fexofenadine-treated patients that withdrew from the CIU study covered by this update because of AEs. None had SAEs. These included Patient 0027-0273 who was taking fexofenadine 10 mg BID and developed edema, increased LDH, and paresthesia. Patient 0030-0306 was taking fexofenadine 10 mg BID and developed erythema multiforme, pruritus, and vasodilation. Other patients withdrew from the study because of the following AEs: URI, stomatitis, paresthesia, and abdominal pain. The original NDA had 26 discontinuations in 713 fexofenadine-treated patients due to AEs and 7 discontinuations due to AEs in 178 placebo-treated patients in US CIU studies. There were 13 fexofenadine-treated patients who had early discontinuation in a total of 171, and 13 in 51 placebo-treated patients who had early discontinuation in non-US CIU studies (Volume 26.2, page 377).

There were 40 early discontinuations from AEs in fexofenadine-treated patients in 1422 subjects in PAR studies covered by this update. There were 21 early discontinuations from AEs in 539 placebo-treated patients in PAR studies (Volume 26.2, page 386). Patient 0481-0002, a 29 year-old white male taking fexofenadine 120 mg po QD, developed palpitations after taking 12 days of medication. He had a previous history of palpitations before entering the study. No treatment was required. The event resolved with no sequelae (Volume 29.1, pages 102-129). Patient 1062-0010, a 58 year-old white male taking fexofenadine 120 mg po was hospitalized with chest pain, cardiomegaly, and hypertension, dyspnea, and lower respiratory congestion. This patient required treatment with Atrovent MDI for the dyspnea. This patient withdrew from the study (Volume 26.2, pages 554, 572, Volume 29.1, page not numbered). Other AEs leading to withdrawal in the PAR studies include rash, dizziness, somnolence, worsened allergy symptoms, flu-like symptoms and dyspnea, and flu-like symptoms and chest tightness. The AEs causing early discontinuation and their associated rates were similar in drug and placebo-treated patients (Volume 26.2, pages 390-391) and were similar to those described in the AE section of this review. There were no PAR studies included in the original NDA submission.

There were dropouts due to AEs in 3 of 192 fexofenadine-treated patients and 3 of 198 placebo-treated patients in multiple dose SAR studies (Volume 26.2, pages 393, 568). Patient 1140-006, a 33 year-old white woman was taking fexofenadine 180 mg po QD and had postnasal drainage and stuffy ears. Patient 1123-0010 was taking fexofenadine 180 mg po QD and developed bronchitis. Patient 1147-0002 was taking fexofenadine 180 mg po QD and developed increased sweating. In comparison, the original NDA had 7 discontinuations in 569 fexofenadine-treated subjects and 4 discontinuations in 293 placebo-treated subjects in US SAR studies. (Volume 26.2, pages 394, 397-400). AEs causing early discontinuation in multiple dose SAR studies covered by this update were similar to those previously described (Volume 26.2, page 396).

There were no dropouts in the single pollen chamber study contained in this update due to AEs, and there were no pollen chamber studies in the original NDA submission.

CRFs were reviewed for selected subjects with AEs resulting in study dropout. Review of these CRFs did not reveal any new additional safety information (Volume 29.1, Aventis Pharmaceuticals response to IR dated 1/7/00).

5.2. Adverse events in other clinical and postmarketing studies (Volume 26.2, pages 277-279)

There are 5 other clinical and postmarketing studies that were included in addition to the studies covered above in this safety update. These studies are M016455/R010, M016455/R015, M016455/4073, AUS/96/16455A/001, and M016455/C087. Line listings for SAEs occurring in these studies were submitted for these studies. CRFs or study reports were not provided. These studies are displayed in Table 10.

Table 10. Foreign clinical studies in progress at time of NDA submission

Study number	Design	Duration of treatment	Treatment Groups	Number of subjects	Population
M016455/R010	Open label, Prospective, multiple dose Pharmacoepidemiology	3 months	Fexo 180 mg QD	Patients with CIU	225
M016455/R015	Open label, non-randomized, Not controlled, multiple dose Multicenter	2 weeks	Fexo 120 mg QD	Patients with SAR	2177
M016455/4073	Double-blind, randomized, Active controlled, Parallel group Multicenter	6 weeks	Fexo 180 mg QD, Loratadine 10 mg QD	Patients with CIU	50
AUS/96/16455A/001	Open label, randomized Prospective	7 days	Fexo BID, Fexo QD to BID prn for SAR symptoms	Patients with SAR	646
M016455/C087	Open label, non-randomized, Not controlled, multiple dose Multicenter	14 days	Fexo 60 mg BID	Patients with SAR	2925

5.2.1. Deaths in other clinical and postmarketing studies

There were no deaths in the 5 other clinical and postmarketing studies M016455/R010, M016455/R015, M016455/4073, AUS/96/16455A/001, and M016455/C087. However, a summary of deaths in patients receiving fexofenadine, submitted in response to an IR revealed one case not listed in theses studies or in the PSURs or the supplemental listings of spontaneous and clinical trial SAEs. This death was reported in a 38 year-old woman enrolled in a SAR trial, study PJPR0053, (NDA 20-625, Allegra capsules) who had a history of preexisting diabetes, hypertension, and obesity. She developed a bacterial pneumonia and fatal respiratory failure 7 weeks after completing the study (Aventis Pharmaceuticals Response to IR, 4/19/99).

5.2.2. Protocol M016455/R010

M016455/R010 was an open label, non-randomized, prospective pharmacoepidemiology surveillance study of fexofenadine 180 mg QD in CIU, with a treatment duration of 3 months. The study enrolled 225 patients. This study had one SAE, a 22 year-old woman who was taking fexofenadine 180 mg po QD who developed facial edema, vertigo, and dysphagia which was considered to be not associated with the fexofenadine.

5.2.3. Protocol M016455/R015

M016455/R015, was a SAR study, with a 2-week duration of treatment. The study enrolled 2177 patients. This study had 2 SAEs, one subject with sinus tachycardia, and another subject with hemolysis and epistaxis. A 36 year-old woman was taking 180 mg po QD and was switched to 120 mg po QD the day before she developed sinus tachycardia. The patient recovered and the SAE was considered to be not associated with fexofenadine. A 53 year-old male developed hemolysis and epistaxis. He was also being treated with an ACE inhibitor, isosorbide dinitrate, and phenprocoumon, an anticoagulant and a derivative of 4-hydroxycoumarin that is marketed in Europe (DRUGDEX Drug evaluations and Martindale). The patient recovered and the SAEs were considered not to be related to fexofenadine.

5.2.4. Protocol M016455/4073

M016455/4073 was a multinational double-blinded, randomized, loratadine-controlled parallel group study comparing the safety of fexofenadine 180 mg versus loratadine 10 mg in the treatment of CIU, with a 6 week duration of treatment in 50 patients. There was 1 patient in this study that developed a SAE. The patient was a 51 year-old female who was taking fexofenadine 180 mg po QD. Drinking alcohol to an excess was the SAE. The patient recovered and the SAE was considered not to be related to fexofenadine.

5.2.5. Protocol AUS/96/16455A/001

AUS/96/16455A/001 was a prospective, multicenter, open, randomized, comparative study of the efficacy of fexofenadine given BID daily versus QD- BID prn for the management of SAR, with a 7 day treatment duration. The study enrolled 646 patients. There was 1 patient in this study with a SAE. The patient developed a headache from which the patient recovered and which was not considered to be related to use of fexofenadine.

5.2.6. Protocol M016455/C087

M016455/C087 "The Allegra Research on Gaining Experience Trial," was of 14 days treatment duration and performed in 2925 patients. There were 2 SAEs in this study. One patient was a 66 year-old woman who developed atrial fibrillation, wheezing, respiratory distress, and congestive heart failure while taking fexofenadine 60 mg po BID. The listing indicates there were sequelae, but the nature of the sequelae are not reported. The congestive heart failure and the atrial fibrillation were considered to be associated with use of fexofenadine. A 42 year-old woman developed renal calculi while taking fexofenadine 60 mg po BID. The condition was ongoing at the time of the report, but the condition was considered not to be related to use of fexofenadine.

5.2.7. Comments on adverse events in other clinical and postmarketing studies

This reviewer's opinions on SAEs in other clinical and postmarketing studies are as follows. The only death that was reported occurred 7 weeks after completion of the study. This patient had other serious concomitant illnesses, and the death is not likely to be related to fexofenadine. The congestive heart failure and atrial fibrillation events occurred in a woman who was 66 years old and who had wheezing. These SAEs could also be attributed to preexisting cardiac disease. The other SAEs reported in these studies could be associated with other concomitant illness or have insufficient detail to interpret. Review of SAEs in other clinical and postmarketing studies reveal no new safety concerns.

6. Postmarketing and worldwide safety data

The sponsor submitted additional safety information based on:

- Supplemental listings of postmarketing spontaneous and clinical trial SAEs from 3/1/98-3/10/98
- PSURs
  - PSUR #5 for the period 3/11/98-9/10/98
  - PSUR #6 for the period 9/11/98-3/10/99
- Supplemental listings of postmarketing spontaneous and clinical trial SAEs from 3/11/99-7/16/99

The sponsor has made changes to the Core Safety Data Sheet for fexofenadine since the original NDA submission. The Core Safety Data Sheet lists AEs that the sponsor considers to be expected with use of a drug. The sponsor's changes to the fexofenadine Core Safety Data Sheet included the addition of dizziness to the list of frequently reported AEs (1%-3%), and the addition of various rare AEs which include insomnia, nervousness, nightmares, and hypersensitivity reactions (edema, chest tightness, flushing). The symptoms of overdose listed in the Core Safety Data Sheet also were amended to include dizziness, drowsiness, and dry mouth (Volume 26.3, pages 586, 656-657, 1383).

The estimated patient exposure from marketed use of fexofenadine was defined daily doses for years 1996 through 1998 (1 defined daily dose = 120 mg), and was defined daily doses in 1998 alone (Volume 26.5, page 1332).

There were 1161 individual AE cases included PSUR #5 (Volume 26.4, page 1064) and 805 individual AE cases in PSUR #6 (Volume 26.6 page 1651). There were 965 individual AE cases included in the supplemental listings for 3/1/98-3/10/98 and 3/11/99-7/16/99.

6.1. Cardiac AEs

Other nonsedating antihistamines may prolong the QT segment and produce ventricular arrhythmias. Fexofenadine is also a metabolite of terfenadine, which is known to cause QT segment prolongation and TdP. Therefore, cardiovascular AEs such as arrhythmia, atrial fibrillation, supraventricular tachycardia, QT prolongation, and Torsade de Points (TdP) are of particular importance with this product.

The most notable cardiovascular event covered by this update is the case reported in Lancet 1999; 353:980 (Volume 26.6, page 1791, Volume 26.6, pages 1777-1779). Case 199910471DDC was reported from the Netherlands. The patient was a 67 year old man with a history of hypertension and mild left ventricular hypertrophy who developed syncope and a prolonged QTc segment length while taking fexofenadine 180 mg po QD for treatment of generalized itching. The patient was taking a beta-blocker for hypertension. The beta-blocker was discontinued when the fexofenadine was started. The article reported that the patient was dechallenged and had a decrease in the QTc. The QTc did not normalize with dechallenge. The article reported that the patient was restarted on fexofenadine in the hospital, developed lengthening of the QTc, and developed ventricular tachycardia and TdP that progressed to ventricular fibrillation. He was successfully cardioverted. The patient had a coronary angiogram that showed 40% stenosis of the circumflex artery and right coronary artery wall irregularities. An infero-posterior defect was detected with myocardial scintigraphy which was interpreted as a false positive result. The patient was discharged on metoprolol and quinapril. The patient declined an implantable cardioversion defibrillator.

A recent abstract reports that this patient has a mutant HERG channel protein. The mutant HERG protein produced currents very similar to the wild-type in the *Xenopus* oocyte model. The currents were blocked by terfenadine but not by fexofenadine (NDA 20-625, D2, CDER stamp date 1/27/00, Biophysical Journal 2000; 78:342A).

Dr. Christian Funck-Brentano, consultant for Aventis Pharmaceuticals, points out that his reanalysis of the patient's ECGs supports preexisting cardiac disease. Dr. Funck-Brentano measured the QT interval in lead V1 to minimize bias due to repolarization in V4 and corrected the results by both the Bazett and Fridericia formulas. Dr. Funck-Brentano's reanalysis shows prolonged QT and QTc intervals and abnormal QTc dispersion in an ECG performed 5 months before the patient started fexofenadine. Reanalysis of ECGs using these criteria shows little change in the uncorrected QT interval. The variations in QTc during the course of treatment are found to fall into the normal range of spontaneous variation of 35 msec. Dr. Funck-Brentano cites Pratt CM, et. al., (Am Heart J 1996;131:472-480) as the reference for this range of spontaneous variation in QTc. Dr. Funck-Brentano points out that the patient's increased QTc dispersion in peripheral leads indicates preexisting cardiac disease and that the discontinuation of the beta-blocker would put the patient at a higher risk for arrhythmia if there was a preexisting cardiac problem (Volume 26.6, pages 1793-1803).

In the opinion of this medical reviewer, the most likely causative factor for the patient's arrhythmias is preexisting cardiac disease. The patient's prolonged QT, QTc, and QTc dispersion were present in an ECG performed 5 months before he started fexofenadine. The discontinuation of his beta-blocker one month before the event may also have been a provocative factor in his arrhythmias.

There are 4 other cases of either prolonged QT or QTc intervals or TdP noted in patients taking fexofenadine in this safety update. Each of these patients also had other possible causes, such as preexisting prolonged QT syndrome or other medications known to prolong QT interval (Volume 26.6, page 1806, Volume 26.7, page 1991, Aventis Pharmaceuticals letters and reports dated 7/22/99 and 7/30/99, and communication with C. Karwoski, DDRE I). Other cases of arrhythmia were associated with anatomical anomalies or other co-morbidities such as RV dysplasia or contained insufficient information to draw a conclusion (Volume 26.4, page 1120-1121, Volume 26.5, page 1352). None of these cardiovascular spontaneous reports represent a clean safety signal, but continued close monitoring of spontaneous events should continue.

6.2. Immediate hypersensitivity reactions

Immediate hypersensitivity reactions including rash, urticaria, pruritus, edema, flushing, dyspnea, anaphylaxis, chest tightness were noted in the spontaneous reports. Interpretation of these events are difficult, as patients may have been using fexofenadine to treat the early symptoms of an allergic reaction. One case was reported of a 40 year-old man with allergies who was taking no concomitant medications and who had anaphylaxis immediately after taking fexofenadine. Other spontaneous reports also indicate no new safety signal.

6.3. Rare AEs

Rare AEs noted in postmarketing surveillance included insomnia, sleep disorders, nightmares, drowsiness, fatigue, gastrointestinal symptoms such as nausea, abdominal pain, and diarrhea, dry mucous membranes, taste disturbance, elevated liver enzymes and hepatitis, hypertension, dysmenorrhea, headache, and dizziness. These AEs occurred in low numbers and were mostly non-serious. Concomitant medications and preexisting illness make interpretation difficult in many. The sponsor continues to monitor these events closely to detect patterns suggestive of a new safety signal (Volume 26.3, pages 591, 656-657, Volume 26.5, page 1383).

6.4. Overdoses

There were 31 cases of overdose reported in this update (Volume 26.3, page 655, Volume 26.5, page 1340). AEs from overdose included headaches, somnolence, loss of appetite, nausea, dizziness, hives, confusion, allergic reaction, palpitation, and increased blood pressure.

There were 11 deaths noted in both PSURs and supplemental listings from 3/1/98-3/10/98 and 3/11/99-7/16/99 (Volume 26.6, page 1805, Correspondence, Aventis Pharmaceuticals, 4/9/99). No death represents a clear safety signal. One death was from trauma in a 40 year-old man who fell from a scaffold (Volume 26.7, page 1923). Another death was in a neonate who had pulmonary artery stenosis, intrauterine growth retardation, and single umbilical

artery (Volume 26.7, page 1918). All other cases either occurred in patients with significant pre-existing morbidity or concomitant medications, or contained incomplete information.

6.5. Comments on postmarketing and worldwide safety data

In summary, review of both PSURs and the supplemental listings of spontaneous events do not reveal any new safety signal. Spontaneous reports will need to be monitored closely for the cardiovascular AEs such as arrhythmia, atrial fibrillation, supraventricular tachycardia, QT prolongation, and Torsade de Points (TdP). In addition close monitoring should continue for other reports that could represent a new safety signal. Labeling should reflect changes by the sponsor in the fexofenadine Core Safety Data Sheet, however.

7. Review of foreign labeling not previously submitted (Volume 26.7, pages 2045-2288)

Fexofenadine labeling approved for use in European, Asian and Pacific, Latin America, Canada, and Middle East and African countries is quite similar. Differences mainly reflect the 120 mg fexofenadine dose which is approved for use in most of these countries. No additional safety information is revealed.

8. Labeling comments

A preliminary review of the proposed label for Allegra® tablets was performed by the medical officer. The final product labeling will follow as a separate document.

Comments on the proposed label at this time include:

8.1. Adverse Reactions section

8.1.1. AEs occurring at rates > 2% are listed in Tables 1-3 (Volume 26.7, pages 2304-2306)

Tables 1, 2, and 3 list adverse experiences in U.S. clinical trials occurring at rates > 2% in SAR, SAR in pediatric patients, and CIU, respectively. The current label for Allegra 60 mg capsules lists adverse experiences occurring at rates > 1%.

Reviewer comment:

As a result of this change, the adverse event rates of nausea, dysmenorrhea, drowsiness, dyspepsia, fatigue are now no longer mentioned in the SAR table, Table 1, and are now listed in the text below this table. AEs occurring at rates > 1% should be listed in these tables.

8.1.2. AEs more common in placebo-treated patients than in fexofenadine-treated patients are consistently listed

The label consistently includes AEs that were more common in placebo-treated patients than in fexofenadine-treated patients.

Reviewer comment:
This information is of limited information to the clinical practitioner. In comparison, the current Claritin (loratadine) label includes no listing of AEs that were more common in placebo. The current Zyrtec (cetirizine) label does list headache and nausea as occurring more commonly in placebo-treated patients.

8.1.3. Symptoms identified by the sponsor for closer monitoring

Insomnia, nervousness, nightmares, and hypersensitivity reactions were identified by the sponsor for closer monitoring. These symptoms were added to the sponsor's Core Safety Data Sheet. Alopecia, photosensitivity, dry mucous membranes, taste disturbance, elevated liver enzymes and hepatitis, and hypertension were identified by the sponsor for closer monitoring, but were not added to the sponsor's Core Safety Data Sheet.

Reviewer comment:
Consideration should be given to listing these AEs as rare, but possibly drug-related adverse events that have been noted in postmarketing surveillance reports.

9. Executive summary and recommendations

This document is a review of a response to approvable letter for Allegra® tablets. The approvable letter included chemistry, marketing, and controls and clinical deficiencies. The sponsor was also asked to submit a safety update for fexofenadine and revised product labeling for Allegra. The sponsor withdrew

to meet the clinical deficiencies. The sponsor submitted a safety update covering 9 clinical trials in progress at the time of the original NDA submission, adverse event reports in other clinical and postmarketing studies, postmarketing and worldwide safety data, and proposed product labeling. The safety update and the product labeling are the focus of this review.

Review of clinical studies for AEs, SAEs, and early discontinuations reveals no new safety signal for fexofenadine. There was one death in a subject with other concomitant serious illnesses. This death occurred 7 weeks after conclusion of the study. There were no other deaths in clinical studies covered by this update. Review of both PSURs and the supplemental listings of spontaneous events do not reveal any new safety signal. Spontaneous reports will need to be monitored closely for rare AEs such as arrhythmia, atrial fibrillation, supraventricular tachycardia, QT prolongation, TdP, or immediate hypersensitivity reactions and for any other report that could represent a new safety signal.

The sponsor's response to the approvable letter reveals no new safety concerns. This application is recommended for approval.

/S/ 2/18/00

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MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

Application #:	**20-872**	**Application Type:**	**NDA**
Sponsor:	**Hoechst Marion Roussel, Inc.**	**Product/Proprietary Name:**	**ALLEGRA Tablets (30, 60, and 180 mg)**
Principal Investigator:	**Not Applicable**	**USAN/Established Name:**	**Fexofenadine HCl 30, 60, and 180 mg Tablets-lactose-free formulation.**
Category of Drug:	**Histamine H_1 Receptor Antagonist**	**Route of Administration:**	**Oral**
Reviewer:	**Alexandra S. Worobec, M.D.**	**Review Date:**	**05/20/99, revised 07/01/99**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
July 17, 1998	July 17, 1998	NDA 20-872	Clinical Data Section for NDA 20-872
August 13, 1998	August 14, 1998	NDA 20-872	Correspondence addressing pivotal trial data without Dr. Edwards' site
October 12, 1998	October 13, 1998	NDA 20-872	Correspondence addressing DSI Audit: Copies of patient diary cards for study 0077 (pediatric SAR), 0039 and 0067 (adult CIU), and 3081 (adult SAR).
October 28, 1998	October 30, 1998	NDA 20-872	Report of Fexofenadine HCl dissolution data.
November 10, 1998	November 12, 1998	NDA 20-872	120 Day Safety Update
May 24, 1998	May 27, 1998	NDA 20-872	Correspondece regarding 'corrected data' for Study 0032.

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
July 31, 1995	NDA 20-625	NDA Application for ALLEGRA
January 2, 1997	NDA 20-786	NDA Application for ALLEGRA-D

Overview of Application/Review: This is an NDA for ALLEGRA tablets (in several dosage strengths: 30 mg, 60 mg and 180 mg) for 3 clinical indications: (1) once daily treatment of adult nasal SAR symptoms or 180 mg qd), (2) twice daily treatment of pediatric nasal SAR symptoms (30 mg), and (3) twice daily treatment of adult (60 mg bid) and pediatric (30 mg or' CIU symptoms. For the adult SAR indication, 3 trials were reviewed (3081, 0032, and 0061) in which 1 trial was pivotal-3081. Two of these 3 trials evaluated dosing with fexofenadine 120 mg qd and 180 mg qd. Review of both the end-of-dosing interval (the 8 a.m. instantaneous TSS) and change from baseline in the 24 hour reflective total nasal symptom score (TSS) revealed a numerically small but statistically significant decrease in symptoms over the 2-week double-blind treatment period over placebo, though a slightly greater numerical decrease in scores was seen with the fexofenadine 180 mg dose. In the pivotal study 3081, onset of action was evaluated by a.m. and p.m. scores on a daily basis, using the 8 a.m. instantaneous TSS and demonstrated onset of action by 24 hours, which is consistent with the current labeling for ALLEGRA capsules.

Two pediatric SAR studies were reviewed and consisted of 2 identical studies 0066 and 0077, combined by the sponsor into 1 large study in order to obtain adequate numbers of patients to maintain powering in the study which was not achievable in the separate studies due to poor patient enrollment. Statistical review of this pooling found the sponsor's methods and rationale for pooling the 2 pediatric studies to be inappropriate from the data analysis perspective because of discordant directions of the treatment effects in the 2 studies. Review of efficacy for the end-of-dosing interval (the change from baseline in average daily 7 a.m. and 7 p.m. instantaneous TSS) and the change from baseline in the average 7 p.m. reflective TSS over the 2 week double-blind treatment period, only showed a statistically significant difference for all 3 fexofenadine doses tested: 15 mg bid, 30 mg bid, and 60 mg bid for study 0077 but study 0066 nor the study combination (0066/0077). In these latter 2 studies, none of the fexofenadine doses (even the highest, at 60 mg bid) demonstrated greater efficacy than placebo. While a number of explanations were sought to explain this discrepancy in clinical response between the 2 identical pediatric studies, a greater placebo response was seen in study 0066 which would have impacted efficacy for both this individual trial and combined trials 0066/0077. Onset of action was likewise evaluated in the combined pediatric studies 0066/0077 on a daily basis, using change from baseline in the 7 p.m. reflective TSS, and a statistically significant difference compared to placebo was seen for the fexofenadine 15 mg bid and 60 mg bid doses after 24 hours of dosing, which did not appear to be maintained after this time point. Hence, fexofenadine 30 mg bid dose was chosen as the most appropriate dose from a clinical and PK standpoint by the medical reviewer, since no significant dose response was seen between the 30 mg and 60 mg dose of fexofenadine in children that would justify marketing a higher dose and a 30 mg dose in children was comparable to a 60 mg dose in adults in terms of PK. In addition to review of clinical data from combined studies 0066 and 0077 and separate studies 0066 and 0077, the basis for extrapolation of efficacy for the pediatric population was also based on the Pediatric Rule under the supposition that the pathophysiology of SAR is similar in adults and children (which they are) and comparable plasma fexofenadine levels to those of adults (similar or somewhat higher levels) were shown in children age 7-11 years treated with a single dose of fexofenadine 30 mg [V1.63:209].

For the CIU indication, a total of 3 trials were evaluated in adult patients (0039, 0067, and 0019), the 1st two of which were pivotal and examined twice daily dosing of fexofenadine: 20 mg, 60 mg, 120 mg, and 240 mg bid vs. placebo for 4 weeks. One non-pivotal trial (0019) evaluated once daily (qd) dosing of fexofenadine (60 mg, 120 mg, and 240 mg). Review of the primary efficacy endpoint for the 2 pivotal studies (the change from baseline in the mean pruritus score (MPS)) revealed a statistically significantly greater improvement in pruritus for all fexofenadine 4 treatment groups compared to placebo, with the smallest numerical change from baseline evident in the 20 mg bid group. The end-of-dosing interval was not evaluated in these trials. Based on these findings and results of non-pivotal study 0019 which showed efficacy of fexofenadine at the 180 mg qd and 240 mg qd doses compared to placebo, the most appropriate dose of fexofenadine for the treatment of adult CIU would appear to be the 60 mg bid dose, given that the 120 mg bid and 240 mg bid doses, and the 180 mg qd and 240 mg qd doses did not afford a significantly greater decrement in symptoms than did the 60 mg bid dose. Choice of the appropriate pediatric dose of fexofenadine for treatment of CIU at 30 mg bid by the medical reviewer was established by the Pediatric Rule since CIU is comparable in terms of pathophysiology, symptoms and treatment in both adults and children and since similar drug exposures were seen for the 30 mg dose in children and 60 mg dose in adults. Hence, no specific clinical trials were performed in children for the CIU indication.

The safety database for ALLEGRA tablets consisted of 1886 safety evaluable patients in the 3 adult SAR trials, 646 safety evaluable patients in the 2 pediatric SAR trials, and 884 safety evaluable patients in the 3 adult CIU trials. Overall, ALLEGRA tablets were safe and well-tolerated given at doses of ranging from 30 mg bid-240 mg bid. Similar to placebo treatment, headache was the most common adverse event, followed by upper respiratory infection, and pharyngitis for the adult population (SAR and CIU) and coughing, injury accident, and fever were the most common AEs in the pediatric population (SAR studies). No clinically significant trends in 12-lead ECG findings (i.e. QT_c) or laboratory abnormalities were demonstrable in fexofenadine treated patients and no obvious difference in outlier values was noted between the various treatment groups for both adult and pediatric populations, and in adults--even when fexofenadine was given for up to 1 year (in healthy volunteers) at a dose of 240 mg qd (no pediatric trials at these doses.

Outstanding Issues: None

Recommended Regulatory Action: Approvable | **N drive location:c:\NDA\20872\clin\99-06-18.rev**

New Clinical Studies: NA **Clinical Hold** NA **Study May Proceed**

NDAs:

Efficacy/Label Supp.: NA **Approvable** NA **Not Approvable**

Signed: Medical Reviewer: /S/ **Date:** 07/01/99

Medical Team Leader: /S/ **Date:** 7/2/99

Medical Officer's Review

NDA #:	20-872	Submission Date: July 17, 1998
Medical Officer Review:	20-872	Filing Date: September 1, 1998
		Review Completed: June 18, 1999

1.2. Drug Name:

1.2.1. Generic Name: Fexofenadine HCl 30 mg, 60 mg, 180 mg

1.2.2. Proposed Trade Name: ALLEGRA™ Tablet

1.2.3. Chemical Name: Fexofenadine HCl: (±)-4-[1[Hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α-α-dimethylbenzenacetic acid HCl (MDL 16,455A)

1.3. Sponsor: Hoechst Marion Roussel, Inc.

1.4. Pharmacologic Category: Histamine H_1-receptor antagonist

1.5. Proposed Indications: Treatment of symptoms due to seasonal allergic rhinitis and chronic idiopathic urticaria in adults (≥ 12 years of age) and children (6-11 years of age).

1.6. Dosage form and route of administration: Fexofenadine HCl 30 mg tablet twice a day, fexofenadine HCl 60 mg tablet (or capsule) twice a day, fexofena-dine HCl 180 mg tablet once a day.

1.7. NDA Drug Classification: S

1.8. Related Drugs: NDA 20-625: ALLEGRA™ (Fexofenadine 60 mg capsules), Approved July 25, 1996.
NDA 20-786: ALLEGRA-D™ (Fexofenadine 60 mg plus pseudoephedrine hydrochloride, 120 mg extended release tablet), Approved January 2, 1998.

1.9. Related Reviews: Chemistry reviews dated:
Pharmacology/Toxicology review-none
Statistical review dated: 06/18/99
Biopharmaceutics review dated: 07/17/99
DDMAC Consult Response: 05/15/99

2.0. TABLE OF CONTENTS

(BID Dosing, Pivotal Trials 0066/0077 combined and separate)
Protocol No. PJPR0066/0077: A double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of 3 dosage strengths of fexofenadine HCl 15 mg, 30 mg, and 60 mg bid in pediatric patients (ages 6-11 years) in the treatment of seasonal allergic rhinitis.

8.3. CHRONIC IDIOPATHIC URTICARIA IN ADULTS (BID Dosing, Pivotal Trial):
Protocol No. PJPR0039: A multicenter, double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of 4 dosage strengths of fexofenadine HCl 20 mg, 60 mg, 120mg, and 240 mg bid in adult patients (age 12-65 years) in the treatment of chronic idiopathic urticaria.

8.4. CHRONIC IDIOPATHIC URTICARIA IN ADULTS (BID Dosing, Pivotal Trial):

Protocol No. PJPR0067: A multicenter, double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of 4 dosage strengths of fexofenadine HCl 20 mg, 60 mg, 120mg, and 240 mg bid in adult patients (age 12-65 years) in the treatment of chronic idiopathic urticaria.

8.5. CHRONIC IDIOPATHIC URTICARIA IN ADULTS (BID Dosing, Non-pivotal Trial):

Protocol No. PJPR0019: A multicenter, double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of 4 dosage regimes of fexofenadine HCl (20 mg, 60 mg, 120mg, and 240 mg qd) in the treatment of chronic idiopathic urticaria.

3.0. CONDUCT OF THE REVIEW

The clinical review of NDA 20-872 (ALLEGRA Tablets) was conducted using volume 1.1 to volume 1.351 of the NDA submission [S2-V1.1 to S2-V1.351], along with volume S9-V1 of the 120 Day Safety Update for NDA 20-872 (dated 11/10/98). A number of additional submissions provided by the sponsor addressing specific questions were reviewed by the medical officer and these included correspondences dating: 07/09/98, 08/13/98, 10/12/98, 10/28/98, 11/16/98, 11/23/98, and 05/24/99.

A total of 4 pivotal clinical studies (1 for adult qd SAR, 1 large combined study for pediatric SAR, and 2 adult chronic idiopathic urticaria (CIU) studies) were reviewed for approvability. Four clinical indications for ALLEGRA tablets were sought in this NDA submission: (1) the once daily treatment of the symptoms of SAR in adults and adolescents age 12 years and older, (2) the twice daily treatment of the symptoms of SAR in children 6-11 years of age, and (3) treatment of the cutaneous manifestations (pruritus and wheals) of CIU in adults age 12 years and older, and (4) in children 6-11 years of age.

Line listings were reviewed for all efficacy endpoints, demographic subgroups, and the efficacy results for the intent-to-treat population were compared to the efficacy evaluable population in order to evaluate any potential discrepancies. The safety review also consisted of a review of all adverse events by summary tables and line listings. Particular importance was placed on cardiac adverse events and electrocardiographic evaluation of patients' ECG tracings before and after treatment with study medication and placebo, respectively, where performed. Laboratory tests were likewise reviewed, with special attention to trends in mean values post-treatment with study medication, compared with placebo and patient outlier values for liver function tests, white blood count and absolute neutrophil count. 'Clinically significant' or 'outlier' liver function elevations or white blood cell count changes were defined as falling outside the 'normal' range values for the clinical parameter by a specified amount defined in the study report by the sponsor.

Pertinent positive and negative safety and efficacy findings are discussed in the clinical study review, with the appropriate volumes indexed from the NDA or 120 Day Safety Update [Volume of Submission-pages]. A summary of relevant study site audit findings at designated centers (for each of the pivotal clinical trials) are presented in the DSI Audit section (section 11.0), along with a discussion of clinical issues involving the one disqualified investigator-Dr. Edwards (who participated in 3 out of 4 pivotal clinical trials reviewed in this NDA). An integrated summary of efficacy and safety follows analysis of the individual studies, and efficacy and safety results of the entire NDA, along with recommendations for approval are summarized in the Conclusion: 'Executive Summary of Efficacy and Safety' section (section 12.0).

4.0. CHEMISTRY, MANUFACTURING, AND CONTROLS

ALLEGRA tablets are immediate release products containing: 30 mg, 60 mg, 120 mg or 180 mg of fexofenadine HCl and the following excipients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and pregeletanized starch. The aqueous tablet film coating is made from hydroxypropyl methylcellulose, iron oxide blends, polyethylene glycol, povidone, silicone dioxide, and titanium dioxide [V1.1:86-90]. The composition of each tablet is presented in Tables 2-2 to 2-5 of the clinical section of NDA 20-872 [V1.1:86-90]. Quantitative composition of investigational fexofenadine HCl batches, including all of those used in the pivotal clinical studies for NDA 20-872 is presented in Table 2-6 [V1.1:91]. The sponsor has provided information demonstrating that the 30, 60, 120, and 180 mg tablets are compositionally proportional. Additionally, they have provided mean tablet data showing similar in vitro behaviour in 4 dissolution media. Critical CMC issues relating to the approvability of ALLEGRA tablets include: (1) release specifications on the polymorphisms in the drug substance, (2) specifications with respect to impurities and (3) specification issues related to the hardness of the tablet. These issues are further discussed in the CMC review.

5.0. ANIMAL PHARMACOLOGY/TOXICOLOGY

As fexofenadine HCl capsule, 60 mg (NDA 20-625) is an already approved drug by the oral route and its pharmacology and toxicology is well known, preclinical data was not required for the approval of ALLEGRA tablets. However, re-calculation of the AUC for fexofenadine in adults and children using the maximum 'to-be-marketed' dose was performed and is included in the product labeling.

The toxicity profile of fexofenadine HCl in animals was based on that of its pro-drug, terfenadine, during the approval of ALLEGRA (approved July 26, 1996).

6.0. CLINICAL BACKGROUND

Relevant Human Experience

Two adequate and well-controlled efficacy and safety phase 3 clinical trials were not required for each respective clinical indication in this submission (adult qd SAR, pediatric bid SAR, adult and pediatric CIU) by the Agency as a basis for approval of ALLEGRA tablets, as fexofenadine HCl was approved for the SAR indication in adults and adolescents ≥ 12 years of age with established priors with respect to efficacy for the SAR indication and overall safety. Based on the 1992 FDA Guidance 'Statistical Procedures for Bioequivalence Studies Using the Standard Two-Treatment Crossover Design', the sponsor elected to follow the bioequivalence approach as the basis for linking the fexofenadine tablet and capsule formulations. The sponsor also elected to utilize the 'Pediatric Rule' in order to link the adult PK and pediatric PK data for fexofenadine given the clinical similarity of SAR and CIU in adults and children, as the basis for

pediatric approval of fexofenadine for these 2 clinical indications. Use of the pediatric rule was especially important for the pediatric SAR indication since the combined SAR study 0066/0077 failed to demonstrate a statistically greater decrease in SAR symptoms in fexofenadine treated patients compared to placebo treated patients.

Important Information from related INDs and NDAs

Information about the safety and efficacy of fexofenadine HCl was provided in the medical officer review of NDA 20-625 (ALLEGRA) in which 4 adequate and well-controlled phase 3 trials provided evidence of efficacy of fexofenadine HCl in the reduction of SAR related symptom scores, as compared with placebo. The safety database for ALLEGRA includes data available in NDA 20-625 from over 2800 patients with allergic rhinitis and normal volunteers treated with doses of ALLEGRA up to 690 mg po bid. Since fexofenadine HCl (MDL 16,455) is the major human metabolite of terfenadine (Seldane, NDA 18-949 and Seldane-D, NDA 19-664), the safety database also includes the extensive clinical exposure to fexofenadine HCl which has occurred in patients treated with terfenadine. Furthermore, additional safety information with respect to fexofenadine HCl was provided in the ALLEGRA-D NDA (# 20-786), although this application was for a combination product with pseudoephedrine HCl and relied heavily on the original ALLEGRA NDA as the basis for much of the long-term safety data.

Foreign Experience

A substantial amount of information exists regarding the efficacy and safety of fexofenadine HCl tablets, ranging in doses from 60 mg bid to 180 mg qd, as the drug product has been approved for marketing in numerous countries [V1.1:85]. For the 60 mg, 120 mg, and 180 mg strengths of ALLEGRA tablets, as of 02/28/87, 21 countries (in Europe and South America) have approved this formulation of ALLEGRA. The fexofenadine HCl tablet has also been approved for marketing in Canada (60 mg bid for SAR) as a non-prescription product. ALLEGRA capsules, 60 mg were approved for the treatment of SAR in adults and adolescents 12 years of age and older in the U.S. on 07/25/96 (NDA #20-625). ALLEGRA-D (fexofenadine HCl and pseudoephedrine HCl 120 mg extended release tablets) was approved in the U.S. for the treatment of symptoms of SAR, including nasal congestion on 01/02/98 (NDA #20-786). Neither ALLEGRA nor ALLEGRA-D has not been approved for the pediatric age group (6-11 years) in any country. There have been no withdrawals of this product from marketing for any reason related to safety or effectiveness. At this time, the maximum recommended daily dose is not to exceed 180 mg qd.

Human Pharmacology, pharmacokinetics, pharmacodynamics

A number of pharmacokinetic studies were submitted by the sponsor in support of ALLEGRA tablets at the time of filing of the NDA but 2 studies were critical for supporting the bioequivalence of the fexofenadine tablets to capsules:

(1) an open label 2-period, 2-treatment, randomized, complete crossover, single dose trial in which 60 mg tablets were compared to the 60 mg capsule (0094) in 50 healthy volunteers between 18-45 years of age (47 subjects completed) and (2) an open label 6-period, 3-treatment, randomized, complete crossover trial in which the comparability of the maximum 'to-be-marketed' dose of fexofenadine in this NDA application (180 mg qd) was compared to the same dose in capsule formulation (3 x 60 mg capsules) in 27 healthy volunteers between 20-37 years of age (25 subjects completed); with extrapolation of results to lower doses of fexofenadine using a 'downward waiver' for bioequivalence (study 0045) [V1.63:227].

Plasma concentrations of fexofenadine in pediatric SAR patients 7-12 years of age were assessed in 1 PK trial (0037)—a double-blind, single oral dose, randomized, 2-period complete crossover study performed in 15 patients (13 completed) in which 2, 30 mg fexofenadine capsules were compared to 1, 30 mg capsule and to placebo capsule (study 0037). Results from the pediatric PK trial were subsequently linked to the adult PK data seen in study 0094 for fexofenadine 60 mg capsules and tablets in order to demonstrate comparability of doses between children and adults such that one, 30 mg tablet in children yielded a similar plasma fexofenadine AUC as did one, 60 mg tablet in adults. Children were found to have a lower plasma clearance of fexofenadine (approximately 50-60% lower) than adults. Sub-analysis of pediatric PK data by age, weight, and height failed to show any correlation between plasma AUC for fexofenadine and either of these 3 parameters (although it was noted that there was little variability in weight in the pediatric age group). Plasma fexofenadine clearance however, was found to be proportional to height, indicating that size should be taken into account in pediatric dosing. Furthermore, pediatric population PK analysis in combined pediatric SAR studies 0066/0077 revealed an AUC (ng•h/ml) of: 356 ± 162 for the fexofenadine 15 mg dose (n=198), 679 ± 282 for the fexofenadine 30 mg dose (n=196), and 1425 ± 480 (n=199) for the fexofenadine 60 mg dose, a clearance (l/h) of: 45.6 ± 10.0 for the fexofenadine 15 mg dose (n=198), 47.9 ± 10.9 for the fexofenadine 30 mg dose (n=196), and 66.0 ± 35.1 (n=199) for the fexofenadine 60 mg dose, and a volume of distribution (l) of: 61.1 ± 31.3 for the fexofenadine 15 mg dose (n=198), 66.0 ± 35.1 for the fexofenadine 30 mg dose (n=196), and 58.4 ± 33.6 (n=199) for the fexofenadine 60 mg dose. Based on these data, the biopharmaceutics reviewer also recommended analysis of the adult population PK (from pivotal SAR study 3081) and comparison with the pediatric population PK data.

Pediatric PK data was used in the support of clinical efficacy for both the SAR and CIU indications ~~via~~ extension of the Pediatric Rule and bioequivalence for the 30 mg tablet was substantiated by dose compositional proportionality from the ALLEGRA 60 mg tablet strength. Marketed capsules and 'to-be-marketed' lactose-free tablets were used in each of these 3 pivotal PK trials. Plasma fexofenadine levels were measured via with an assay range of ng/mL [V1.63:251].

Results of these 3 trials are presented below in Tables 1-3 and demonstrate bioequivalence between the marketed fexofenadine capsule formulation and the 'to-be-marketed' fexofenadine tablet formulation. Of note, results from study 0094 indicated that the time to maximum exposure for fexofenadine tablets was faster than that of the capsules. One additional study (PJPR0068) in which comparison of the fexofenadine PK after qd and bid dosing of ALLEGRA revealed that the C_{min} following administration of fexofenadine 180 mg qd vs. 90 mg bid was 21.67 ng/ml vs. 36.28 ng/ml (90% CI: 53.1, 67.9), suggesting that if extrapolated to the 120 mg qd dose vs. 60 mg bid doses, respectively, the 120 mg qd dose might not offer as high an end-of-dosing interval level of plasma fexofenadine as would the bid dosing regimen. Comparability between adult and pediatric exposure was likewise shown, in which children age 7-12 demonstrated a 56% greater $AUC_{(0-\infty)}$ than adults for equal mg doses of fexofenadine.

Additional important points from the biopharmaceutics review included a drug-drug interaction study using Maalox in which administration of 120 mg of fexofenadine (2 x 60 mg capsules) within 15 minutes of an aluminum and magnesium containing antacid (Maalox) decreased fexofenadine AUC by 41% and C_{max} by 43%. This interaction was deemed to be primarily due to binding of fexofenadine HCl to Maalox rather than due to the increased pH [Biopharmaceutics Review, NDA 20-872, Dr. Young-Moon Choi, 07/17/99, p. 24]. The T_{max} was found to change very little, consistent with findings of no significant delay in absorption.

Table 1: Study 0045: Treatment Comparisons for Key PK Parameters Calculated from Plasma Fexofenadine Concentrations Following 180 mg doses of Fexofenadine HCl to Healthy Male Volunteers [V1.63:253]

PK Parameter	*Treatment	Mean	% CV	Adjusted Mean	Pairwise Comparison		
					Pair	Ratio (%)	90% CI
$AUC_{(0-\infty)}$ (ng•h/mL)	A	3330.08	39.49	3091.31	A/C	95.17	86.0, 105.3
	B	3192.02	36.84	3153.29	B/C	97.08	87.7, 107.5
	C	3396.65	32.60	3248.20	-	-	-
T_{max} (h)	A	2.0	34.15	1.8	A/C	76.17	67.1, 86.4
	B	2.5	53.70	2.1	B/C	90.04	79.3, 102.3
	C	2.6	38.77	2.3	-	-	-
C_{max} (ng/mL)	A	494.24	55.24	443.75	A/C	100.02	87.3, 114.6
	B	453.64	44.27	415.79	B/C	93.72	81.7, 107.5
	C	476.32	40.98	443.66	-	-	-

*Treatment A=1 x 180 mg fexofenadine HCl lactose-free tablet.
Treatment B=1 x 180 mg fexofenadine HCl lactose-gelatin tablet.
Treatment C=3 x 60 mg fexofenadine HCl capsules.
Adjusted means and pairwise comparisons are based on statistical analysis of natural-log transformed data.

Table 2: Study 0094: Treatment Comparisons for Key PK Parameters [V1.63:260]

PK Parameter	*Treatment	Mean	% CV	Adjusted Mean	Pairwise Comparison		
					Pair	Ratio (%)	90% CI
$AUC_{(0-\infty)}$ (ng•h/mL)	A	973.77	33.36	926.07	A/B	100.29	93.3, 107.8
	B	958.98	30.39	923.37	-	-	-
T_{max} (h)	A	141.89	49.07	1.54	A/B	66.48	57.3, 76.5
	B	131.25	34.04	2.32	-	-	-
C_{max} (ng/mL)	A	1.72	34.84	134.41	A/B	109.57	100.1, 120.0
	B	2.49	42.23	122.68	-	-	-

*Treatment A=1 x 60 mg fexofenadine HCl lactose-free tablet (lot # RD9723).
Treatment B=1 x 60 mg fexofenadine HCl capsules.
Adjusted means and pairwise comparisons are based on statistical analysis of log transformed data.

Table 3: Study 0037: Treatment Comparisons for Key PK Parameters [V1.63:286]

PK Parameter	*Treatment	Mean	% CV	[I]Dose Normalized Mean
Cl_{po} (L/h)	A	31.57	29.0	N/A
	B	29.05	36.3	N/A
$AUC_{(0-\infty)}$ (ng•h/mL)	A	1899.87	26.1	949.94
	B	1090.67	36.7	1090.67
$T_{1/2}$ (h)	A	9.05	38.8	N/A
	B	8.78	34.5	N/A
T_{max} (h)	A	2.54	26.3	N/A
	B	2.24	38.3	N/A
C_{max} (ng/mL)	A	280.12	43.3	140.06
	B	183.52	48.1	183.52

*Treatment A=2 x3 0 mg fexofenadine HCl capsules (n=13).
Treatment B=1 x 30 mg fexofenadine HCl capsules (n=14).
[I]Dose normalized means are based on parameters normalized to the 30 mg dose.
N/A=Not applicable.

Additionally, for pediatric PK study 0037, pharmacodynamic assessments were performed that evaluated wheal and flare inhibition 10 minutes after subcutaneous injections of 1 mg and 10 mg histamine, in children age 7-12 years who were pre-treated with fexofenadine 30 mg and 60 mg (compared to pre-treatment). Somewhat greater inhibition was seen with the 60 mg dose of fexofenadine for both the histamine 1 mg and 10 mg doses. The mean maximum observed inhibition of wheal and flare areas ranged from 84.76% to 93.26%, and 76.84% to 91.18% following the 1 mg and 10 mg histamine injections, respectively [V1.63:286]. The sponsor noted that the decline in wheal and flare inhibition did not occur as rapidly as decline in plasma fexofenadine concentrations for either the 30 mg or 60 mg dose [V1.63:287-288]. Over the entire 24 hour observation period, the mean inhibition of wheal and flare area ranged from 44.55% to 72.16%, and 37.70% to 62.58% following the 1 mg and 10 mg histamine injections, respectively [V1.63:286]. In summary, fexofenadine 30 mg and 60 mg were able to inhibit histamine-induced wheal and flare responses in pediatric patients.

Directions for use

ALLEGRA tablets are indicated for the relief of symptoms associated with SAR in adults and children 12 years of age and older and 6-11 years, respectively. Symptoms treated effectively include sneezing, rhinorrhea, itchy nose/palate/throat, and itchy/watery/red.

The recommended dose of ALLEGRA tablets for the treatment of SAR symptoms in adults and adolescents ≥ 12 years of age is 60 mg bid, 120 mg qd, or 180 mg. A dose of one, 60 mg tablet once daily is recommended as the starting dose in patients with decreased renal function. The recommended pediatric dose (age 6-11 years) of ALLEGRA tablets for the treatment of SAR symptoms is 30 mg bid.

ALLEGRA tablets are also indicated for the treatment of cutaneous manifestations of chronic idiopathic urticaria (CIU) in adults and children, 12 years of age and older and 6-11 years, respectively. The recommended adult dose of ALLEGRA tablets is 60 mg bid and in children, 30 mg bid.

7.0. DESCRIPTION OF CLINICAL DATA SOURCES

The clinical data sources for NDA #20-872 comprised the efficacy and safety data for fexofenadine HCl (ALLEGRA NDA #20-625 and ALLEGRA-D NDA #20-786), along with post-marketing safety data for fexofenadine HCl capsules (Medical Officer Review of Adverse Events for the first-fourth quarterly periods), Dr. Alexandra Worobec, ALLEGRA (NDA #20-625) and the wealth of published literature on fexofenadine HCl.

Aside from the clinical trials submitted to the ALLEGRA tablet NDA (#20-872) which include a 1 year safety study of 240 mg fexofenadine vs. placebo in healthy volunteers (study 0027) and the human safety data from the PK studies with ALLEGRA tablets, no additional human clinical studies of safety or efficacy for the combination product were reviewed for the approval of this application.

8.0. CLINICAL STUDIES:

SEASONAL ALLERGIC RHINITIS IN ADULTS (QD Dosing, Pivotal Trial):

8.1. Protocol No. M016455B/3081: A double-blind, randomized, placebo-controlled, parallel study comparing the efficacy and safety of fexofenadine HCl 120 mg and 180 mg qd in the treatment of autumn seasonal allergic rhinitis.

Principal Investigator: None, multi-center study.

Participating Centers: 40 U.S. centers

8.1.1. Objective

The primary objective of this study was to investigate the safety and efficacy of fexofenadine HCl 120 mg po qd and fexofenadine HCl 180 mg po qd compared to placebo treatment in patients age 12-65 years for the treatment of symptoms of autumnal seasonal allergic rhinitis (SAR).

A secondary objective of the study was to characterize the population pharmacokinetics of fexofenadine QD in adult SAR patients.

8.1.2. Study Design

The study was a phase III, multi-center, randomized, double-blind, parallel group, with a 5-7 day single-blind placebo lead-in, safety and efficacy study of the treatment of fexofenadine HCl 120 mg po qd, vs. fexofenadine HCl 180 mg po qd, and vs. placebo in 861 autumnal seasonal allergic patients. The study consisted of 4 subject visits: 2 screening/baseline visits (visits 1 and 2; weeks 1 and 2), and 2 treatment visits (visits 3 and 4; weeks 3 and 4) such that patients received study medication for approximately 2 weeks. Patients participated in the study for a total of 16-26 days [V1.64:283, 285, Amendment 3]. A total of approximately 750 patients were to be randomized to the 3 treatment groups, with approximately 40 study sites and approximately 20 patients per study site [V1.64:44, Amendment 1]. A table of study procedures is provided in Appendix 1 [V1.64:65, 187].

8.1.3. Protocol

8.1.3.1.a. Population: Male or female patients, 12-65 years of age, with SAR documented by a positive response to at least 1 autumnal allergen indigenous to the study site at Visit 1 or during the previous 15 month period [V1.64:47, 165].

(I) Inclusion Criteria [V1.64:47-48, 165-167]:

1. History of seasonal allergies due to autumnal allergens (not specified in protocol) for at least 2 seasons. The specific type of pollen the patient was allergic to must have been indigenous to the study site area.
2. A positive skin prick test to an autumnal allergen (diluent not specified in the protocol) performed within the previous 15 months at the investigator's site and recorded in the patient's medical record. A positive skin test was defined as a wheal diameter at least 3 mm greater than diluent within 15 minutes after placement of the allergen.
3. Patients ≥ 12 years and ≤ 65 years of age.
4. Clinical evidence of active SAR symptoms at both screening and baseline. At visit 1 (=screening visit), the patient's reflective total symptom score (TSS) for the previous 12 hours had to be ≥ 6 (excluding nasal congestion), 2 or more additional SAR symptoms (excluding nasal congestion) were to be rated as 'moderate' or 'severe', and no SAR symptom was to be rated as 'very severe'.
5. At visit 2 (=baseline/randomization visit), the 8 a.m. instantaneous allergy symptom assessment (excluding nasal congestion) had to meet the following criteria: (1) for 5, 8 a.m. instantaneous assessments completed, at least 4 assessments must have had: a total symptom score (TSS) ≥ 5, and 2 or more symptoms with a score of "2" or "3", (2) for 6, 8 a.m. instantaneous assessments completed, at least 4 assessments must have had: a total symptom score (TSS) ≥ 5, and 2 or more symptoms with a score of "2" or "3", and (3) for 7, 8 a.m. instantaneous assessments completed, at least 5 assessments must have had: a total symptom score (TSS) ≥ 5, and 2 or more symptoms with a score of "2" or "3". No symptom, including nasal congestion was to be rated as 'very severe' at any a.m. or p.m. assessment.
6. Sexually active females or females of childbearing potential were expected to use an effective form of birth control throughout the study, (defined as: continuous use of oral or long-acting injected contraceptives for at least 2 months prior to study entry, use of an IUD, use of an implantable contraceptive, or use of a barrier method) and were to have a negative serum pregnancy test prior to study enrollment (visit 1, week 1).

(II) Exclusion Criteria [V1.64:49-50, 168-169]: