CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-909

CROSS DISCIPLINE TEAM LEADER REVIEW

CROSS-DISCIPLINARY TEAM LEADER'S MEMORANDUM

Date	July 10, 2007
From	Emmanuel O. Fadiran, Ph.D. , Clinical Pharmacology Team Leader
Subject NDA # Proprietary/Established (USAN) names	Cross-Disciplinary Team Leader's Memorandum 21-909 Allegra ODT/Fexofenadine HCl
Dosage form/strength	ODT (Orally Disintegrating Tablets), 30 mg
Proposed indications	1. Relief of symptoms associated with SAR 2. Treatment of uncomplicated skin manifestations of CIU 3. For children 6 to 11 years of age
Action	Approval is recommended

1. Introduction to Review

Sanofi-Aventis submitted a 505(b)(1) new drug application (NDA 21-909) on September 28, 2006, for fexofenadine 30 mg Orally Disintegrating Tablet (ODT) for the relief of symptoms associated with seasonal allergic rhinitis (SAR) and treatment of uncomplicated skin manifestations of chronic idiopathic urticaria (CIU) in children 6 to 11 years of age. The application is supported by comparison of the bioavailability (BA) and bioequivalence (BE) of the proposed ODT formulation to that of an approved reference product (Sanofi Aventis product, Allegra (fexofenadine HCl) Tablets, 30 mg). The PDUFA due date for this application is July 29, 2007.

The major issue during the review cycle was the ODT nomenclature for the dosage form because the disintegration time for the product meets the 30 second ONDQA specification, but the weight of the tablet exceeds the 500 mg size limit. These specifications for the nomenclature of ODT were published on April 6, 2007, in the draft Guidance for Industry: Orally Disintegrating Tablets, approximately five months after this NDA was submitted. Since the application was submitted prior to the publication of the draft guidance, ONDQA has decided that the ODT nomenclature is acceptable for proposed product. There are no other outstanding issues that may impact the approval of the application.

Pending agreed upon labeling, the recommendation for this NDA is **Approval.**

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

Fexofenadine HCl 60 mg twice daily and fexofenadine HCl 180 mg once daily were approved for the treatment of symptoms of SAR in adults and children 12 years of age

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

Fexofenadine HCl 30 mg tablets are approved in 74 countries other than the US, including countries in North, Central, and South America, the Caribbean, Asia, and Australia and New Zealand.

Fexofenadine HCl ODT 30 mg is not approved in any country.

3. CMC/Microbiology/Device

3.1 General product quality considerations: Fexofenadine HCl ODT, 30 mg were formulated as an alternative dosage form to the currently approved pediatric product/dosage strength and provide an immediate-release orally disintegrating tablet of a 30 mg dose of fexofenadine HCl. The fexofenadine HCl is [redacted] b(4)

[redacted] and [redacted] to produce the orally disintegrating tablets. An aluminum foil/aluminum foil blister container closure system will be used for the commercial packaging of the drug product.

Drug substance is manufactured by Aventis Pharma, Frankfurt, Germany, while drug product is manufactured by CIMA Labs Inc., Eden Prairie, Minnesota, United States.

The excipients in the proposed formulation include microcrystalline cellulose, sodium starch glycolate, povidone K-30 [redacted] magnesium stearate, mannitol, b(4)
crospovidone, sodium bicarbonate, citric acid anhydrous, aspartame, natural and artificial orange flavor, and artificial cream flavor.

The final drug product formulation was used in all pivotal BA/BE trials.

3.2. Facilities review/inspection:
The CMC review and the CMC TL's memo find the facilities for drug substance and drug product manufacturing acceptable.

3.3. Notable issues (resolved):

The Agency raised concerns at the End-of-Phase 2 and Pre-NDA meetings about using the ODT nomenclature because of the product's size and disintegration time. At the Pre-NDA meeting, the following issues about ODT were discussed:

- Agency's current thinking was that an ODT should be less than 500 mg in weight and should disintegrate within 30 seconds.
- ODT nomenclature and standards were currently under discussion in the Agency, and that decisions would be made on a case-by-case basis for products that had already been submitted or were close to being submitted to the Agency.
- ODT nomenclature for their product would be a review issue.

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

The CMC review for this NDA indicates that the tablet weight and disintegration time are acceptable [ONDQA Review, M. Haber, Ph.D., NDA 21-909, N-000, 9/28/06], and the ONDQA Branch Chief's memo finds the drug product satisfactory and recommends approval pending agreement on product labeling [ONDQA Memo, Ali Al-Hakim, Ph.D., NDA 21-909, 06/08/2007].

4. **Pharmacology and Toxicology**

Fexofenadine HCl has been reviewed and found to be safe and efficacious at doses up to 180 mg and is supported by data in NDA 20-625 and NDA 20-872. No new non-clinical toxicology studies were required or performed for this application. The Pharm Tox reviewer has recommended approval with some labeling changes (Pharm Tox Review, Lawrence Sancilio, Ph.D., NDA 21-909, 05/21/2007).

5. Clinical Pharmacology/Biopharmaceutics

The following information are included in the approved labeling for Allegra products with the addition of the information on Allegra ODT (*underlined and italicized*) in the proposed labeling for Allegra products.

5.1 General clinical pharmacology/biopharmaceutics considerations

Pharmacokinetics

The pharmacokinetics of fexofenadine hydrochloride in subjects with SAR and subjects with CIU were similar to those in healthy subjects.

Absorption:

ALLEGRA tablets: Fexofenadine hydrochloride was absorbed following oral administration of a single dose of two 60 mg capsules to healthy male subjects with a mean time to maximum plasma concentration occurring at 2.6 hours post-dose. After administration of a single 60 mg capsule to healthy adult subjects, the mean maximum plasma concentration (Cmax) was 131 ng/mL. Following single dose oral administrations

of either the 60 and 180 mg tablet to healthy adult male subjects, mean Cmax were 142 and 494 ng/mL, respectively. The tablet formulations are bioequivalent to the capsule when administered at equal doses. Fexofenadine hydrochloride pharmacokinetics are linear for oral doses up to a total daily dose of 240 mg (120 mg twice daily). The administration of the 60 mg capsule contents mixed with applesauce did not have a significant effect on the pharmacokinetics of fexofenadine in adults. Co-administration of 180 mg fexofenadine hydrochloride tablet with a high fat meal decreased the mean area under the curve (AUC) and (Cmax) of fexofenadine by 21 and 20% respectively.

ALLEGRA ODT: Fexofenadine hydrochloride was absorbed following single-dose oral administration of ALLEGRA ODT 30 mg to healthy adult subjects with a mean time to maximum plasma concentration occurring at approximately 2.0 hours post-dose. After single-dose administration of ALLEGRA 30 mg ODT to healthy adult subjects, the mean maximum plasma concentration (Cmax) was 88.0 ng/mL. ALLEGRA ODT 30 mg tablets are bioequivalent to the 30 mg ALLEGRA tablets. The administration of ALLEGRA ODT 30 mg with a high-fat meal decreased the AUC and Cmax by approximately 40% and 60% respectively and a 2-hour delay in the time to peak exposure (Tmax) was observed. ALLEGRA ODT should be taken on an empty stomach. The bioavailability of ALLEGRA ODT was comparable whether given with or without water

ALLEGRA oral suspension: A dose of 5 mL of ALLEGRA oral suspension containing 30 mg of fexofenadine hydrochloride is bioequivalent to a 30 mg dose of ALLEGRA tablets. Following oral administration of a 30 mg dose of ALLEGRA oral suspension to healthy adult subjects, the mean Cmax was 118 ng/mL and occurred at approximately 1 hour. The administration of 30 mg ALLEGRA oral suspension with a high fat meal decreased the AUC and the mean Cmax by approximately 30 and 47%, respectively in healthy adult subjects.

Distribution:

Fexofenadine hydrochloride is 60% to 70% bound to plasma proteins, primarily albumin and α_1-acid glycoprotein.

5.2. Drug-drug interactions

Erythromycin and Ketoconazole

Fexofenadine has been shown to exhibit minimal (ca. 5%) metabolism. However, co–administration of fexofenadine hydrochloride with either ketoconazole or erythromycin led to increased plasma concentrations of fexofenadine in healthy adult subjects. Fexofenadine had no effect on the pharmacokinetics of either erythromycin or ketoconazole. In 2 separate studies in healthy adult subjects, fexofenadine hydrochloride 120 mg twice daily (240 mg total daily dose) was co-administered with either erythromycin 500 mg every 8 hours or ketoconazole 400 mg once daily under steady-state conditions to healthy adult subjects (n=24, each study). No differences in adverse events or QT_c interval were observed when subjects were administered fexofenadine hydrochloride alone or in combination with either erythromycin or ketoconazole. The findings of these studies are summarized in the following table:

Effects on steady-state fexofenadine pharmacokinetics
after 7 days of co-administration with fexofenadine hydrochloride
120 mg every 12 hours in healthy adult subjects (n=24)

Concomitant Drug	C_{maxSS} *(Peak plasma concentration)*	$AUC_{ss(0\text{-}12h)}$ *(Extent of systemic exposure)*
Erythromycin (500 mg every 8 hrs)	+82%	+109%
Ketoconazole (400 mg once daily)	+135%	+164%

The changes in plasma levels were within the range of plasma levels achieved in adequate and well-controlled clinical trials.

The mechanism of these interactions has been evaluated in *in vitro, in situ*, and *in vivo* animal models. These studies indicate that ketoconazole or erythromycin co-administration enhances fexofenadine gastrointestinal absorption. This observed increase in the bioavailability of fexofenadine may be due to transport-related effects, such as p-glycoprotein. *In vivo* animal studies also suggest that in addition to enhancing absorption, ketoconazole decreases fexofenadine gastrointestinal secretion, while erythromycin may also decrease biliary excretion.

b(4)

Fruit Juices

Fruit juices such as grapefruit, orange and apple may reduce the bioavailability and exposure of fexofenadine. This is based on the results from 3 clinical studies using histamine induced skin wheals and flares coupled with population pharmacokinetic analysis. The size of wheal and flare were significantly larger when fexofenadine hydrochloride was administered with either grapefruit or orange juices compared to water. Based on the literature reports, the same effects may be extrapolated to other fruit juices such as apple juice. The clinical significance of these observations is unknown. In addition, based on the population pharmacokinetics analysis of the combined data from grapefruit and orange juices studies with the data from a bioequivalence study, the bioavailability of fexofenadine was reduced by 36%. Therefore, to maximize the effects of fexofenadine, it is recommended that ALLEGRA tablets should be taken with water.

ALLEGRA ODT can be taken with or without water.

5.3. Pathway of Elimination (hepatic/renal – effects of impairment)

Metabolism:

Approximately 5% of the total dose of fexofenadine hydrochloride was eliminated by hepatic metabolism.

Elimination:

The mean elimination half-life of fexofenadine was 14.4 hours following administration of 60 mg twice daily in healthy adult subjects.

Human mass balance studies documented a recovery of approximately 80% and 11% of the [^{14}C] fexofenadine hydrochloride dose in the feces and urine, respectively. Because the absolute bioavailability of fexofenadine hydrochloride has not been established, it is unknown if the fecal component represents primarily unabsorbed drug or is the result of biliary excretion.

Renally Impaired:

In subjects with mild to moderate (creatinine clearance 41-80 mL/min) and severe (creatinine clearance 11-40 mL/min) renal impairment, peak plasma concentrations of fexofenadine were 87% and 111% greater, respectively, and mean elimination half-lives were 59% and 72% longer, respectively, than observed in healthy subjects. Peak plasma concentrations in subjects on dialysis (creatinine clearance ≤10 mL/min) were 82% greater and half-life was 31% longer than observed in healthy subjects. Based on increases in bioavailability and half-life, a dose of 60 mg once daily is recommended as the starting dose in adult patients with decreased renal function. For pediatric patients with decreased renal function, the recommended starting dose of fexofenadine is 30 mg once daily for patients 2 to 11 years of age and 15 mg once daily for patients 6 months to less than 2 years of age.

Hepatically Impaired:

The pharmacokinetics of fexofenadine hydrochloride in subjects with hepatic impairment did not differ substantially from that observed in healthy subjects.

5.4. Demographic interactions/special populations

Geriatric Subjects: In older subjects (≥65 years old), peak plasma levels of fexofenadine were 99% greater than those observed in younger subjects (<65 years old). Mean fexofenadine elimination half-lives were similar to those observed in younger subjects.

Pediatric Subjects: A population pharmacokinetic analysis was performed with data from 77 pediatric subjects (6 months to 12 years of age) with allergic rhinitis and 136 adult subjects. The individual apparent oral clearance estimates of fexofenadine were on average 44% and 36% lower in pediatric subjects 6 to 12 years (n=14) and 2 to 5 years of age (n=21), respectively, compared to adult subjects.

Administration of a 15 mg dose of fexofenadine hydrochloride to pediatric subjects 6 months to less than 2 years of age and a 30 mg dose to pediatric subjects 2 to 11 years of age produced exposures comparable to those seen with a dose of 60 mg administered to adults.

Effect of Gender: Across several trials, no clinically significant gender-related differences were observed in the pharmacokinetics of fexofenadine hydrochloride

5.5. Thorough QT study or other QT assessment
No statistically significant increase in mean QTc interval compared to placebo was observed in 714 adult subjects with SAR given fexofenadine hydrochloride capsules in doses of 60 to 240 mg twice daily for 2 weeks. Pediatric subjects from 2 placebo-controlled trials (n=855) treated with up to 60 mg fexofenadine hydrochloride twice daily demonstrated no significant treatment- or dose-related increases in QTc. In addition, no statistically significant increase in mean QTc interval compared to placebo was observed in 40 healthy adult subjects given fexofenadine hydrochloride as an oral solution at doses up to 400 mg twice daily for 6 days, or in 230 healthy adult subjects given fexofenadine hydrochloride 240 mg once daily for 1 year. In subjects with CIU, there were no clinically relevant differences for any ECG intervals, including QTc, between those treated with fexofenadine hydrochloride 180 mg once daily (n = 163) and those treated with placebo (n = 91) for 4 weeks.

5.6. Notable issues (resolved or outstanding)
This application is based on clinical pharmacology/biopharmaceutics program and the Sponsor submitted the results of three BA/BE studies (Study M016455H/1004, Study M016455H/1007, and Study M016455H/1008) in support of the application. Detailed review of these studies can be found in the clinical pharmacology review (Clinical Pharmacology Review, S. Al Habet, Ph.D., NDA 21-909, N-000, 05/23/2007).

The studies are described briefly below.

Study M016455H/1004: This was a pilot BA and food effect study designed to identify the ODT formulation for the pivotal BE study and to characterize the effect of food on the chosen formulation. It was an open label, randomized, single-dose, four-period, eight-treatment, partially balanced, incomplete crossover study conducted in 35 healthy male and female adult subjects between 18 and 45 years of age. Study treatments included the marketed 30 mg fexofenadine HCl tablet administered under fasted conditions, two prototype ODT formulations (Prototype I and Prototype II) of fexofenadine HCl 30 mg administered under fasted and fed conditions, two additional prototype ODT formulations of fexofenadine HCl 30 mg (Prototype IV and Prototype V) administered under fasted conditions, and a prototype ODT formulation (Prototype I) of fexofenadine HCl 30 mg administered under fasted conditions with and without water. Blood samples were taken immediately before dosing (0 hours) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36, and 48 hours during each study period for plasma fexofenadine levels.

Results for the selected prototype formulation (II) and the reference product are summarized in Table 1.
The chosen formulation (Prototype II) demonstrated bioequivalence to the marketed reference product (Allegra tablet, 30 mg). Food caused a 59% decrease in Cmax, a 40% decrease in $AUC_{0-\infty}$, a 66% increase in oral clearance (CLpo), and a prolongation in the

Tmax by 1.7 hours for the chosen formulation (II). The ODT formulation is to be taken on empty stomach to avoid the food effect on its bioavailability. The other prototypes did not meet the bioequivalence criteria for rate and extent of systemic exposure comparison with Allegra tablets.

Table 1. Mean (%CV) PK parameters for fexofenadine from pilot BA Study M016455H/1004

PK Parameter	Trt A Fexofenadine HCl Tablet 30 mg single dose Reference Fasting State	Trt D Fexofenadine HCl ODT 30 mg single dose Prototype II Fasting State	Trt E Fexofenadine HCl ODT 30 mg single dose Prototype II Fed State	Pair Comparison	Geometric Mean Ratio (%)	90% CI
$AUC_{0-\infty}$ (ng.h/ml)	672.0 (39.9)	655.4 (34.4)	390.8 (38.7)	D/A E/D	102.4 60.4	91-115 53-69
Cmax (ng/ml)	100.1 (47.7)	96.6 (39.3)	38.1 (31.29	D/A E/D	100.0 41.0	85-118 34-49
Tmax (h)	2.1	2.0	3.7	-	-	-
$T_{1/2}$ (h)	14.2	17.1	17.6	-	-	-
CLpo (L/h)	49.1	48.6	80.9	-	-	-

Study M016455H/1007: This was an open label, randomized, single dose, two-period, two-way crossover study conducted in were 54 healthy adult male and female subjects, 18 to 45 years of age, designed to demonstrate the bioequivalence of Allegra ODT to Allegra tablet. Each subject received the marketed 30 mg fexofenadine HCl tablet and the selected prototype ODT formulation (II) of fexofenadine HCl 30 mg administered under fasted conditions with 240 ml of water. Blood samples were collected over a 48-hour period after each treatment. There was a six-day washout between study periods. Samples were taken at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36, and 48 hours post-dose. The data obtained from the study showed that fexofenadine HCl 30 mg ODT formulation was bioequivalent to the marketed 30 mg tablet (Table 2). The time to maximum concentration (Tmax), elimination half-life ($T_{1/2}$) and oral clearance (CLpo) are similar for both treatments.

Table 2. Mean (%CV) PK parameters for fexofenadine from pivotal BE Study M016455H/1007

PK Parameter	Trt A Fexofenadine HCl Tablet 30 mg single dose Reference Fasting State	Trt B Fexofenadine HCl ODT 30 mg single dose Prototype II Fasting State	Geometric Mean Ratio (%) B/A	90% CI of the ratio
$AUC_{0-\infty}$ (ng.h/ml)	637.0 (29.2)	635.0 (31.2)	98.9	92-106
Cmax (ng/ml)	93.8 (33.3)	88.0 (35.5)	93.2	85-102
$AUC_{0\text{-last}}$ (ng.h/ml)	607.0 (30.7)	608.0 (32.9)	99.4	92-107
Tmax (h)	2.0	2.0	-	-
$T_{1/2}$ (h)	11.6	11.8	-	-
CLpo (L/h)	47.4	48.3	-	-

Study M016455H/1008: This was a phase 1, open label, randomized, single-dose, two-period, two treatment, complete crossover study conducted in 54 healthy male and female patients, 18-45 years of age designed to compare the PK of the proposed ODT formulation administered under fasted conditions, both with and without water . Each subject received the proposed ODT formulation of fexofenadine HCl 30 mg administered under fasted conditions with and without 240 mL of water with a six-day washout between the treatments. Blood samples were taken at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36, and 48 hours post-dose. Results obtained from this study indicate that the BA of the ODT formulation are comparable when taken with and without water (Table 3). The two treatments are equivalent with respect to $AUC_{0-\infty}$ but not with Cmax. The Cmax of the ODT formulation when administered without water is 13% higher than when administered with water and the 90% CI for the geometric mean ratio of 100-127 is slightly outside the BE range is 80-125. However, the observed difference in the Cmax should not have any significant clinical impact because of the large therapeutic index for fexofenadine. The time to maximum concentration (Tmax), elimination half-life ($T_{1/2}$) and oral clearance (CLpo) are similar for both treatments.

Table 3. Mean (%CV) PK parameters for fexofenadine from pivotal BA/BE Study M016455H/1008

PK Parameter	Trt A Fexofenadine HCl ODT 30 mg single dose with water Reference Fasting State	Trt B Fexofenadine HCl ODT 30 mg single dose without water Test Fasting State	Geometric Mean Ratio (%) B/A	90% CI of the ratio
$AUC_{0-\infty}$ (ng.h/ml)	628.0 (34.3)	699.0 (40.5)	112	102-122
Cmax (ng/ml)	86.3 (50.9)	96.5 (46.7)	113	100-127
AUC_{0-last} (ng.h/ml)	589.0 (38.4)	668.0 (42.7)	113	103-125
Tmax (h)	2.0	2.0	-	-
$T_{1/2}$ (h)	12.8	12.0	-	-
CLpo (L/h)	49.5	46.8	-	-

The results obtained from these clinical pharmacology studies support the efficacy of Allegra ODT for the treatment of symptoms of SAR and CIU in children 6 to less than 12 years of age. Study M016455H/1007 confirmed that Allegra ODT is bioequivalent to Allegra tablets (the reference product) under fasting conditions (conditions recommended in the General BA/BE Guidance BE studies). Study M016455H/1004 showed that co-administration of Allegra ODT with a high fat meal led to a significant decrease in the rate and extent of exposure of Allegra ODT and the proposed labeling appropriately recommends that it should be taken on an empty stomach. Study M016455H/1008 showed that the bioavailability of Allegra ODT is comparable when taken with or without water and the product has been proposed to be labeled accordingly. Therefore there is no need for clinical efficacy studies to support the approval of the application. Additionally, the medical officer's review of the safety data from the three BA/BE studies as well as the safety update submitted by the Sponsor showed that the application supports the safety of Allegra ODT for the treatment of symptoms of SAR and CIU in children 6 to 11 years of age (Clinical Review, Charles E Lee, M.D., NDA 21-909, 05/29/2007).

6. Clinical/Statistical

This submission is supported by a clinical pharmacology program. The application is supported by comparison of the BA and BE of the proposed ODT formulation to that of

an approved reference product (Sanofi Aventis product, Allegra (fexofenadine HCl) Tablets, 30 mg). No clinical efficacy studies were required to support this application. The clinical pharmacology studies in this application support the efficacy of the applicant's product. The clinical pharmacology studies in this application confirmed that under fasting conditions, the proposed product is bioequivalent to the reference product. The medical officer reviewed the safety data from the three BA/BE studies as well as the safety update submitted by the Sponsor and concluded that the application supports the safety and efficacy of Allegra ODT for the treatment of symptoms of SAR and CIU in children 6 to 11 years of age (Clinical Review, Charles E Lee, M.D., NDA 21-909, 05/29/2007).

Pediatrics
Allegra ODT is proposed for use in children from 6 to 11 years of age and is the subject of this review. Accordingly, this section of this review will deal only with the applicant's requirements under the Pediatric Research Equity Act (PREA). The applicant previously submitted studies designed to assess the effectiveness and safety of fexofenadine HCl in pediatric patients from 6 months to less than 6 years of age (NDA 20-872 SE8-011, 11/18/02, NDA 21-963, 12/15/05]. In this application, the applicant requested a deferral of pediatric studies in patients less than 6 years of age for Allegra ODT. The Agency previously determined that the applicant fulfilled the requirements under PREA for patients 6 months of age and older. The requirement for pediatric studies for patients less than 6 months of age was waived because SAR does not exist in this age group and CIU is extremely rare and the drug does not represent a meaningful therapeutic benefit over existing therapies for this condition [NDA Acknowledgement Letter, dated 1/11/06, NDA 20-963, 12/15/05]. At the End-of-Phase 2 meeting on January 10, 2003, the Division advised the applicant that additional support from a pharmacokinetics study of the ODT would be required to support approval in children from 2 to less than 6 years of age. The data supporting the approval of NDA 21-963 included a study of the oral suspension formulation in children of this age group [Medical Officer Review, Charles E. Lee, M.D., NDA 21-963, 12/15/05]. Although we now have data on the bioavailability of fexofenadine administered without applesauce in this age group, we do not have data on the bioavailability of the ODT in this age group.
The applicant has requested a deferral of pediatric studies for the ODT formulation in children from 2 to less than 6 years of age. An alternative fexofenadine HCl formulation (Allegra Oral Suspension) is currently marketed and liquid formulations of other antihistamines, both prescription and non-prescription, are available. The ODT dosage form of fexofenadine HCl does not represent a meaningful therapeutic benefit over existing therapies for this condition. The medical officer concluded that pediatric studies for the ODT formulation should therefore be waived in children less than 6 years of age [Clinical Review, Charles E. Lee, M.D., NDA 21-909, 05/29/2007].

6.4. **Clinical Microbiology** (*where relevant*)
This is not relevant to this application.

7. **Advisory Committee Meeting**
There was no need for an advisory committee meeting for this application.

8. Risk Minimization Considerations (*where relevant*)
There was no need for risk minimization consideration for Allegra ODT.

10. Financial Disclosure
The applicant certified that there was no financial arrangement with the clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study. The applicant stated that the clinical investigators in the pivotal studies in this application certified that they did not have a proprietary interest in the proposed product or a significant equity in the applicant. The clinical investigators also certified that they were not a recipient of significant payments.

11. **Labeling**
Detailed labeling review was performed by all review disciplines. The labeling was submitted in Physician's Labeling Rule (PLR) format. Recommended changes in the proposed labeling were made to the Sponsor and agreement was made on most of the recommendations. The Sponsor sent in their revised draft labeling on June 29, 2007 and this is currently been reviewed. It was noted that the Sponsor accepted most of the recommendations from the Division and there are no major areas of disagreement.

12. **DSI Audits**
The Division of Scientific Investigations conducted an audit of the clinical and the analytical portions of pivotal BA/BE studies MO16455H/1007 and MO16455H/1008 and concluded that the inspections did not reveal any significant deficiencies (DSI Memo, Jagan Rarepally, Ph.D. 05/15/2007).

13. **Conclusions and Recommendations**
The clinical pharmacology studies in this application support the efficacy of Allegra ODT, 30 mg. These studies confirmed that under fasting conditions, Allegra ODT is bioequivalent to the reference product (Allegra tablets, 30 mg). Administration of Allegra ODT with a high fat meal significantly decreased both the rate and extent exposure to fexofenadine. Labeling appropriately notes this significant decrease in bioavailability of fexofenadine in the fed state and recommends that Allegra ODT should be taken on an empty stomach. Absorption of the ODT formulation is comparable when taken with and without water and this has been reflected in the proposed labeling accordingly.

The application is recommended for approval.

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/s/

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