CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-909

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review
Final
(May 22, 2007)

NDA: 21-909	**Date of Submission:** September 28, 2006
Generic Name	Fexofenadine Hydrochloride
Brand Name:	**Allegra ODT**
Formulations:	**Orally Disintegrating Tablet (ODT)**
Strength:	30 mg
Route of Administration:	Oral
Indication:	Seasonal Allergic Rhinitis (SAR) and uncomplicated Chronic Idiopathic Urticaria (CIU) in Children 6 to 11 years of age
Dosage and Administration:	For children 6-11, 30 mg BI with or without water
Type of Submission:	New Formulation
Sponsor:	Sanofi-Aventis, Bridgewater, NJ
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader	Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.

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1.0 Executive Summary

1.1 Recommendation:

From the clinical pharmacology perspective, this NDA is acceptable. In addition, no biopharmaceutics data issues are pending per the DSI inspection report dated May 15, 2007.

1.2 Phase 4 Commitment

From the clinical pharmacology perspective, no phase 4 commitment is applicable to this NDA.

1.3 Summary of Important Clinical Pharmacology Findings:

Fexofenadine, the active ingredient of Allegra, is a histamine H_1-receptor antagonist that has been marketed in the US at recommended doses of 30 mg BID for children 6 to 11 years and 60 mg BID and 180 mg QD for adults. The sponsor has developed a new orally disintegrating tablet (ODT) formulation containing 30 mg fexofenadine. The main objective of this new formulation is to provide a more convenient method of administration in children ages 6 to 11 years of age. Therefore, the sponsor is seeking the same currently approved indications of the 30 mg IR tablet in children. These indications are: for the treatment of symptoms associated with seasonal allergic rhinitis (SAR) and the treatment of uncomplicated skin manifestation of chronic idiopathic urticaria (CIU) in pediatric patients 6 to 11 years of age. In addition, a dose of 15 mg BID as oral suspension is also indicated for CIU only in children 6 months to <2 years of age.

For the development of ODT product, the sponsor conducted a battery of *in vitro* dissolution experiments and three primary clinical pharmacology/PK studies. The first was a pilot/developmental study with four prototypes and two arms with and without food. The second was a pivotal bioequivalence study with 30 mg ODT tablet and 30 mg Allegra IR tablet. The final study was to determine the effect of water on ODT bioavailability.

The pilot study was designed as eight arms crossover in 35 healthy subjects with four prototypes for ODT and IR 30 mg Allegra tablet as a reference product. Only prototype I and Prototype II were administered with and without food. Based on this study, the sponsor selected prototype II formulation for further development. In the presence of food the exposure to fexofenadine on prototype II formulation was reduced by approximately 50% (Cmax 60 % and AUC 40%) and the Tmax was delayed by approximately 2 hours (Treatments D and E; **Figure 1.3.1 and Table 1.3.1**).

The same trend was seen for formulation I in which the Cmax was reduced by 43% and AUC by 64%. The AUC ratios for formulations I and II (Treatments C and E) in fed state were approximately 57% and 60%, respectively when compared to the same formulation in the fasted state. For Cmax, the ratios were approximately 36% and 40%

for formulation I and II in the fed and fasted states, respectively. In all formulation (I and II), the Tmax was reduced by approximately 2 hours when administered with food.

In terms of effect of water on prototype I, the bioavailability appears to be slightly reduced by approximately 2-3% (Treatments F and B). The ratio of Cmax and AUC was 98% and 97% when comparing treatments F and B, respectively.

Figure 1.3.1 Effect of Food on Fexofenadine (Study # 1004)

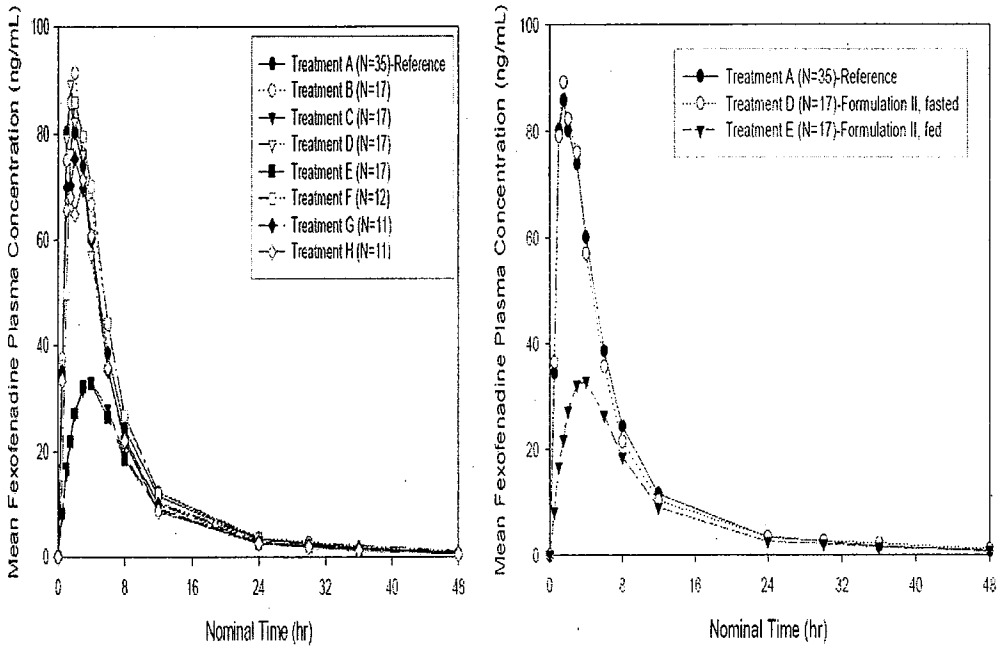


Table 1.3.1 Summary of PK Parameters From the Pilot and Effect of Food Study (Study # 1004)

Summary of analysis of variance of pharmacokinetic parameters

Parameter	Treatment[a]	N	Mean	CV (%)	Adjusted Mean[b]	Pairwise comparison[c] Pair[a]	Ratio (%)[b]	90% Confidence Interval[b]
AUC(0-∞)	A	33	672.0	39.9	615.5	-	-	-
(ng•h/mL)	B	17	707.2	29.8	674.9	B/A	109.65	(97.04, 123.89)
	C	16	391.4	27.6	386.3	C/B	57.24	(50.27, 65.18)
	D	17	655.4	34.4	630.4	D/A	102.42	(90.92, 115.37)
	E	16	390.8	38.7	380.6	E/D	60.37	(53.02, 68.74)
	F	12	681.3	32.5	657.1	F/B	97.36	(83.29, 113.81)
	G	11	600.6	38.9	563.4	G/A	91.53	(79.47, 105.42)
	H	11	571.2	29.9	560.6	H/A	91.08	(79.06, 104.92)
C_{max}	A	35	100.05	47.76	89.13	-	-	-
(ng/mL)	B	17	96.99	23.48	97.46	B/A	109.35	(92.44, 129.35)
	C	17	36.56	32.28	35.45	C/B	36.37	(30.39, 43.52)
	D	17	96.59	39.27	89.11	D/A	99.97	(84.57, 118.18)
	E	17	38.11	31.29	36.51	E/D	40.97	(34.24, 49.03)
	F	12	103.12	56.72	96.26	F/B	98.76	(79.34, 122.94)
	G	11	82.64	39.76	75.86	G/A	85.11	(69.93, 103.58)
	H	11	85.36	37.42	80.01	H/A	89.77	(73.81, 109.18)

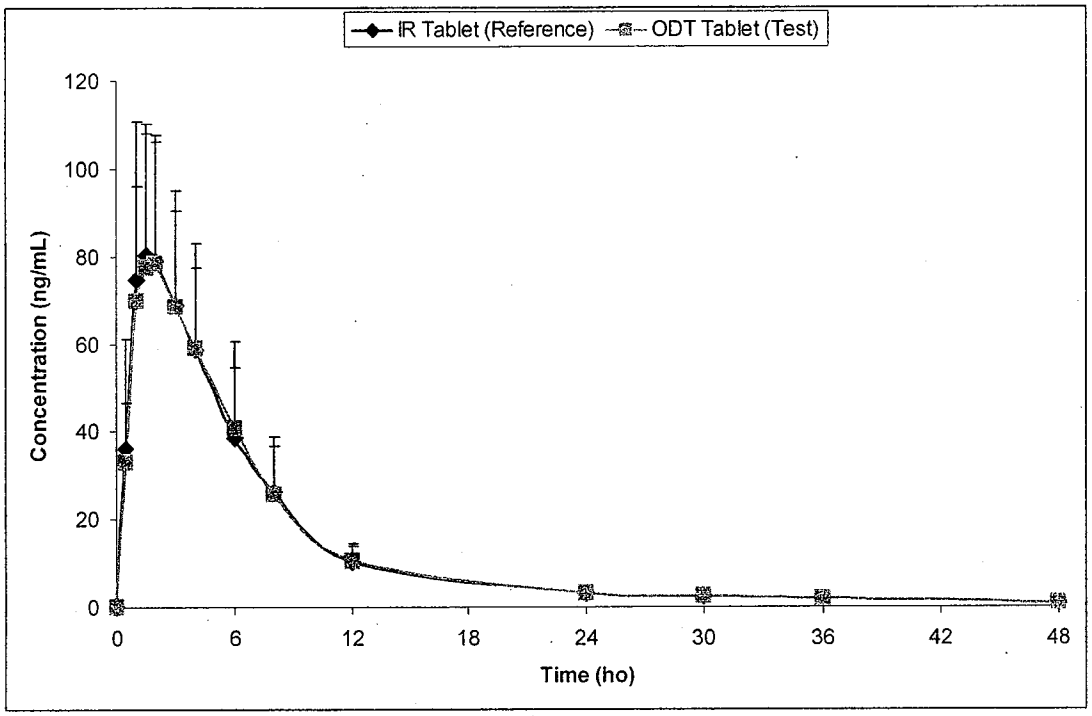
[a] Treatment A: 30 mg marketed lactose-free small tablet (fasted conditions); lot number 1045751
Treatment B: 30 mg prototype fast-disintegrating formulation I (fasted conditions); lot number C0067D
Treatment C: 30 mg prototype fast-disintegrating formulation I (fed conditions); lot number C0067D
Treatment D: 30 mg prototype fast-disintegrating formulation II (fasted conditions); lot number RA0206
Treatment E: 30 mg prototype fast-disintegrating formulation II (fed conditions); lot number RA0206
Treatment F: 30 mg prototype fast-disintegrating formulation I (fasted conditions with no water); lot number C0067D
Treatment G: 30 mg prototype fast-disintegrating formulation IV (fasted conditions); lot number C0070D
Treatment H: 30 mg prototype fast-disintegrating formulation V (fasted conditions); lot number C0071D

[b] Natural-log transformed results for the ANOVA were transformed to the original scale by exponentiation to obtain the adjusted mean, ratio, and 90% confidence interval.

[c] Relative bioavailability is assessed by the comparison of Treatment A (reference) to Treatments B, D, G, and H (test). The effect of food is assessed by comparison of Treatments B and D (references) to Treatments C and E (tests), respectively. The effect of the coadministration of water is assessed by comparison of Treatment B (reference) to Treatment F (test).

The pivotal bioequivalence study was conducted as two-way crossover comparing the IR 30 mg FEX and the 30 mg ODT tablets in 54 healthy subjects (Study # 1007). All treatments were conducted after overnight fasting and with 240 mL water. The 90% CI for both treatments was within 80% to 125% (**Figure 1.3.2**). Therefore, the two products were bioequivalent.

Figure 1.3.2 . Mean Plasma Concentration Time Profiles for ODT and IR FEX Tablets in Healthy Subjects (Study # 1007).



Additional study with and without water was conducted (Study # 1008). The study was conducted in 54 healthy subjects after overnight fast of 30 mg FEX ODT tablets administered with and without 240 mL of water. The exposure (AUC) after both treatments was within the 90% CI limits (**Table 1.3.1**). However, the Cmax was slightly outside the limit (100%-127%). Therefore, the administration of FEX ODT tablet with water resulted in decrease of AUC and Cmax by 11.3% and 11.8%, respectively. Based on the standard bioequivalence criteria, the two treatments are not equivalent. From the clinical perspective, the impact of this small change in systemic exposure on the safety and efficacy of the product is negligible.

Table 1.3.1. Mean PK Parameters With and Without Water (Study # 1008)

Results - Pharmacokinetics and pharmacodynamics

Parameter (unit)	Treatment [a]	N	Arithmetic Mean (CV%) [b]	N	Geometric LS Mean [c]	Treatment Comparisons [d] Ratio [e] (%)	90% CI
AUC(0-∞) (ng·h/mL)	A	52	628 (34.3)	51	601	112	102 - 122
	B	53	699 (40.5)	51	671		
Cmax (ng/mL)	A	53	86.3 (50.9)	52	78.5	113	100 - 127
	B	53	96.5 (46.7)	52	88.5		
AUC(0-last) (ng·h/mL)	A	53	589 (38.4)	52	552	113	103 - 125
	B	53	668 (42.7)	52	625		
Tmax [f] (h)	A	53	2.0 (1.0-8.0)		-	-	-
	B	53	2.0 (1.0-8.0)		-		
t1/2 (h)	A	52	12.8 (52.9)		-	-	-
	B	53	12.0 (54.6)		-		
CLpo (L/h)	A	52	49.5 (31.8)		-	-	-
	B	53	46.8 (42.8)		-		

Notes: CV% = coefficient of variation; LS = least-squares; CI = confidence interval.
[a] Treatment A: single dose of 30 mg fexofenadine HCl as orally disintegrating tablet with 240 mL water (reference).
Treatment B: single dose of 30 mg fexofenadine HCl as orally disintegrating tablet without water (test).
[b] Arithmetic mean calculated from all subjects with evaluable data.
[c] Geometric mean calculated from balanced pair data.
[d] ANOVA with terms for sequence, period, and treatment as fixed effects and subject nested within sequence as random effect performed on the natural log-transformed AUC(0-∞), AUC(0-last), and Cmax.
[e] Ratio = geometric LS mean test/geometric LS mean reference (B/A).
[f] Tmax reported as median (range) values.

Conclusions:

- The sponsor conducted adequate studies to characterize the PK of Allegra ODT product.

- Considering the variability in the data with both products, ODT tablet is considered bioequivalent to Allegra IR 30 mg tablet under fasted condition.

- It is noted that in the pivotal BE study ODT was administered with 240 ml water. In a definitive study investigating the effect of water on the final to-be- marketed formulation II it was shown that the mean Cmax, but not on AUC, was slightly outside the BE goal post of 80-125% (100-127%). Thus, water appears to decrease the bioavailability of formulation II by approximately 11%. However, based on the pilot study with prototype I formulation (fast-disintegrating) the effect of water was negligible. The bioavailability was also lowered but only by approximately 2-3% (Pilot Study # 1004). The impact of the effect of water on the safety and efficacy of ODT product is negligible.

- The presence of food reduced the Cmax and AUC by approximately 60% and 40%, respectively for the prototype formulation II (the-to-be marketed) and also prototype formulation I (fast-disintegrating).

Reviewer

Sayed (Sam) Al Habet, R.Ph., Ph.D.
Office of Clinical Pharmacology
Division of Clinical Pharmacology 2
Final version signed by Emmanuel Fadiran, R.Ph., Ph.D., Team Leader----------

2. Question Based Review

2.1 General Attributes/Background:

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

Fexofenadine is the active ingredient of all allegro formulations. It is a histamine H_1-receptor antagonist with following chemical structure.

[redacted]

b(4)

ODT formulation was designed to rapidly disintegration in the mouth immediately following administration. The composition of the tablet will be presented in the Biopharmaceutic section of the review (Section 2.5).

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Mechanism of Action:

Fexofenadine is selective H_1-receptor antagonist anti-histamine. It inhibits antigen-induced bronchospasm in sensitized experimental animals.

Indications:

The general indications of Allegra are the following:

- Relief of symptoms associated with seasonal allergic rhinitis
- Treatment of uncomplicated skin manifestations of chronic idiopathic urticaria

However, ODT formulation will specifically be indicated for children 6 to 11 years of age.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

For children 6-11 years of age, ODT will be administered as one 30 mg tablet BID with and without water on empty stomach. However, in patients with renal impairment, the recommended dose is 30 mg ODT once daily.

2.1.4 What are the Core Studies Submitted in this NDA?

In this NDA, three main studies were submitted. The first study is a pilot/developmental study with an arm investigating the effect on food on the PK of FEX (Study #M016455H/1004). The second study is the pivotal BE study comparing ODT to Immediate Release (IR) tablets (Study #M016455H/1007). The third study was to investigate the effect of water on the absorption and bioavailability of ODT in which ODT was given with and without water (#M016455H/1008).

2.2 General Clinical Pharmacology

Based on the previous NDAs and the currently approved label, the PK of FEX is summarized below.

The PK of FEX in subjects with SAR and CIU were similar to those in healthy subjects. The plasma concentration-time profile of FEX is characterized by rapid absorption with Cmax occurring between 1 to 3 hours post-dose. The mean terminal elimination half-life is approximately 14 hours. FEX is moderately bound to plasma proteins (approximately 60%, depending on patients' status). A total of 80% and 11.5% of the ingested dose is excreted unchanged in the feces and urine, respectively. This indicated that drug undergoes minimal biotransformation. Biliary and renal excretions are considered to be the principal routes of elimination for FEX.

2.2.1 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

No biological biomarker was used in this NDA. All data in this NDA were presented as comparative PK.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

All data were based on measurement of the parent drug FEX. As stated earlier, FEX undergoes minimal metabolism in which it is excreted mainly unchanged in feces and urine.

2.2.3 Exposure Response

2.2.3.1 What are the characteristics of the dose-systemic exposure relationships for efficacy?

No formal PK/PD study was conducted in this NDA to establish the relationship between exposure and response/efficacy. However, in this relationship has been established in the previous NDAs for Allegra.

2.2.3.2 What are the characteristics of the dose-systemic exposure relationships for safety?

No formal PK/PD study was conducted in this NDA to establish the relationship between exposure and safety.

2.2.3.3 Does this Drug Prolong the QT or QTc Interval?

No formal QTc study was conducted in this NDA to establish the effect of 30 mg ODT QTc.

However, previous studies showed no significant effect on QTc was observed in over 700 adult patients at FEX doses ranging from 60 mg to 240 mg given daily for 2 weeks. Similarly, no effect was noted in over 800 pediatric patients at doses up to 60 mg BID.

2.2.4 What are the PK characteristics of the drug?

2.2.4.1 What are the single and multiple dose PK parameters of FEX and its metabolites? How do the PK parameters change with time following chronic dosing?

All the three studies conducted in this NDA were after single doses.

2.2.4.2 Are the PK of FF and its metabolites linear and dose-proportional?

As stated above, all the three studies conducted in this NDA were after single doses. However, in the previous NDAs it was noted that the FEX PK is dose proportional up to 120 mg.

2.2.4.3 What is the Extent of Systemic Exposure After ODT Administration?

As stated previously, only three single doses studies were conducted in this NDA to establish the PK and bioequivalency. Therefore, no data is available to determine the extent of systemic exposure after ODT administration.

2.3 Intrinsic factors

2.3.1 Does age, weight, race, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

Based on previous NDA and the current label, the Cmax of FEX in moderate and severe renal impairment patients is 87% and 111% higher than healthy subjects. Similarly, the Cmax was 99% higher in geriatric subjects (>65 years) compared to young adults (<65 years). Based on pop PK analysis, the exposure in pediatric subject's ages 6 to 12 years appears to be 40% higher than in 2 to 5 years of age. Furthermore, FEX exposure after 15 mg or 30 mg doses in pediatric subjects at ages ranging from 6 months to 11 years was comparable to that after 60 mg in adults.

No major differences were observed in the exposure between patients with hepatic impairment and healthy subjects. Similarly no gender–related differences were noted in FEX exposure.

2.4 Extrinsic factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The effects of herbal products, diet, smoking and alcohol on FEX use were not evaluated.

No specific studies were conducted with ODT to investigate the effect of extrinsic factors on the disposition of FEX. However, based on the previous NDAs and the current approved label the following is a summary of the major drug-drug interaction studies that were extracted from the current label.

- Ketoconazole increase the Cmax and AUC by 135% and 164% compared to placebo.
- Antacid decreases FEX Cmax and AUC by 43% and 41% compared to placebo, respectively.
- Based on pop PK data, grapefruit juice may reduce the bioavailability of FEX by 36%.

Therefore, ODT should be given on an empty stomach with or without water. The co administration with ketoconazole or grapefruit juice should be avoided.

2.5 General Biopharmaceutics

No biopharmaceutics data issues are pending per the DSI inspection report dated May 15, 2007.

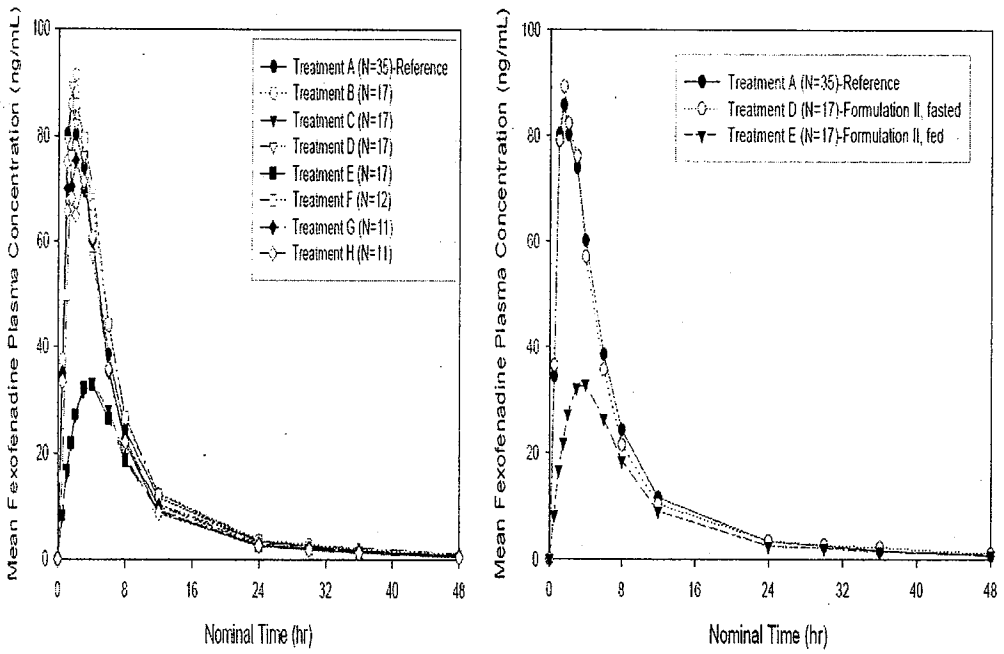
2.5.1 What is the BCS Class classification for FEX?

This information was not provided by the sponsor in this NDA.

2.5.2 What is the effect of food on the BA of FEX?

In a pilot study (Study # 1004) FEX ODT was administered with and without food. The exposure to FEX was reduced by approximately 50% (Cmax by 60%) and AUC by 40%) and the Tmax was delayed by approximately 2 hours (**Figure 2.5.2.1**).

Figure 2.5.2.1 Effect of Food on Fexofenadine (Study # 1004)



Based on the data from this study, ODT should be given on an empty stomach with or without water

2.5.3 Was the to-be-marketed formulation used in the PK/clinical trials?

Yes. The sponsor conducted a pilot /developmental study (Study # 1004) with four prototype formulations. The pivotal BE, food effect, and effect of water studies were conducted using formulation II. This formulation was chosen as the final to be marketed formulation.

2.5.4 What are the Biopharmaceutical Characteristics of the Products?

ODT 30 mg FEX formulation was developed to provide a more convenient method of administration in children ages 6 to 11 years of age. The formulation was designed to rapidly disintegration in the mouth immediately following administration. The composition of the tablet shown in **Table 2.5.4.1.**

Table 2.5.4.1 Composition of FEX 30 mg ODT (Clinical Formula, CA-162-00)

COMPONENTS	COMPOSITION		FUNCTION	REFERENCE TO STANDARDS (2)
	Proportion (% w/w)	Per Unit (mg)		
Fexofenadine HCl	[redacted]	[redacted]	Active Substance	Aventis
Microcrystalline Cellulose	[redacted]	[redacted]	[redacted]	USP/NF
Sodium Starch Glycolate	[redacted]	[redacted]	[redacted]	USP/NF
Povidone K-30	[redacted]	[redacted]	[redacted]	USP/NF
[redacted]	[redacted]	[redacted]	[redacted]	Ph. Eur./JPE[1]
Magnesium Stearate	[redacted]	[redacted]	[redacted]	USP/NF [2]
Alcohol [redacted]	[redacted]	[redacted]	[redacted]	CIMA[3]
Total	[redacted]	[redacted]		
[redacted] Fexofenadine HCl, [redacted]	[redacted]	[redacted]	Active Substance	CIMA
Mannitol[5]	[redacted]	[redacted]	[redacted]	USP/NF
[redacted] Mannitol[5]	[redacted]	[redacted]	[redacted]	USP/NF
Crospovidone	[redacted]	[redacted]	[redacted]	USP/NF
Microcrystalline Cellulose[6]	[redacted]	[redacted]	[redacted]	USP/NF
Sodium Bicarbonate, [redacted]	[redacted]	[redacted]	[redacted]	USP/NF
Citric Acid. Anhydrous. [redacted]	[redacted]	[redacted]	[redacted]	USP/NF
Aspartame	[redacted]	[redacted]	[redacted]	USP/NF
Magnesium Stearate	[redacted]	[redacted]	[redacted]	USP/NF
Natural and Artificial Orange Flavor	[redacted]	[redacted]	[redacted]	GRAS[7]
Artificial Cream Flavor	[redacted]	[redacted]	[redacted]	GRAS[7]
Total	[redacted]	[redacted]	[redacted]	

1. At the time of manufacture the [redacted] was tested as per the DAB(Deutsches Arzneibuch)/JPE compendial requirements. Since then the Ph. Eur. has added a monograph to [redacted] In the future, this excipient will be tested according to the Ph. Eur./JPE specifications.
2 [redacted]
3 Substituted alcohol as per USP. Complies to USP for [redacted] content. The alcohol [redacted] is a non-compendial excipient. Alcohol [redacted] which conforms to 27 CFR 21.35.
4. Removed during processing.
5. Amount adjusted based on the assay of the [redacted] fexofenadine HCl [redacted]
6 [redacted] microcrystalline cellulose is used for tablet manufacture.
7. Generally Recognized as Safe (GRAS).

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2.5.5 Are the method and dissolution specifications supported by the data provided by the sponsor?

The *in vitro* dissolution methods and data analysis will be covered in more details in the CMC review. The typical dissolution profiles for ODT (Test) and Allegra 30 mg IR (Reference) Tablets at pH 3.0 (0.001 M HCl) are show in **Figure 2.5.5.1 and Table 2.5.5.1**

Figure 2.5.5.1. Mean Dissolution Profiles of FEX ODT (Test) and Allegra 30 mg IR (reference) Tablets at pH 3.0 (0.001 M HCl)

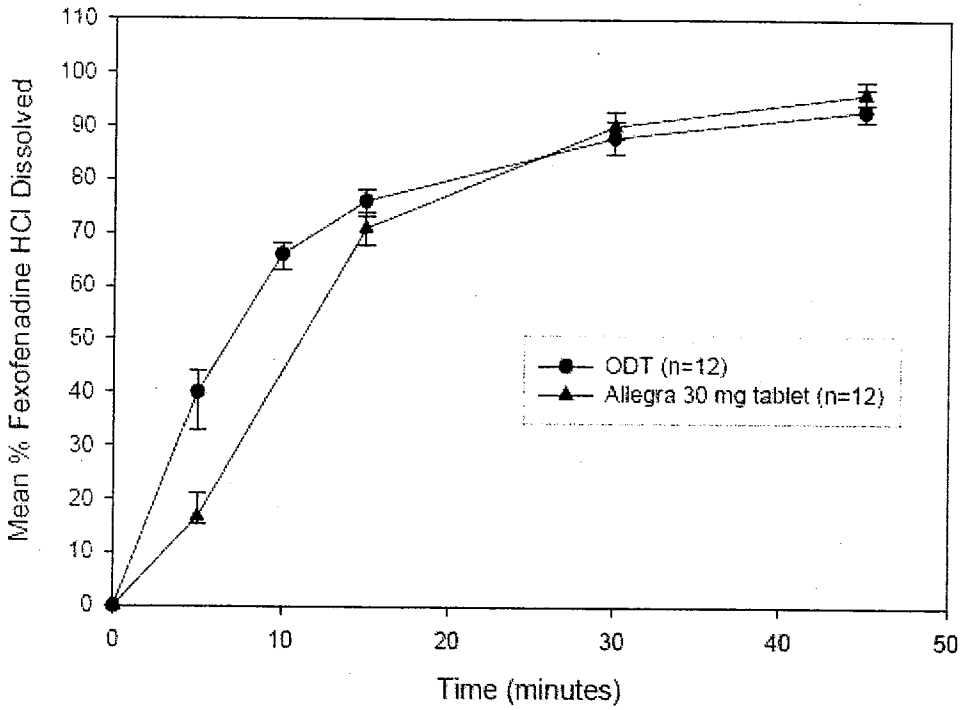

Figure 2.5.5.1. Mean Dissolution Data of FEX ODT (Test) and Allegra 30 mg IR (reference) Tablets at pH 3.0 (0.001 M HCl)

	Lot Number	Study	Mean % fexofenadine HCl dissolved (CV%)	
			10 min	30 min
Allegra® 30 mg tablet	1045751	M016455H/1004	69 (8.1)	91 (2.9)
	1070469	M016455H/1007	71 (2.6)	96 (0.7)
Orally disintegrating tablet (ODT)	RA0206	M016455H/1004	Not tested	99 (0.5)
	720583	M016455H/1007	66 (2.9)	88 (2.2)
		M016455H/1008		

The method used to generate the above data is as follow:

Apparatus: USP II (Paddle)
Media: 0.001 M HCl (pH 3.0)
Speed: 50 RPM
Sampling Times: 5, 10, 30, and 45 min for profiles and 10 and 30 min for dual time points
Specs: [redacted] at 10 min and [redacted] at 30 min b(4)

The data demonstrate that [redacted] of FEX was released from both tablets in 30 min. b(4)

2.6 Analytical Section

The plasma concentrations of FEX were determined by a validated high performance liquid chromatography coupled with solid phase extraction procedure. The assay was conducted at [redacted] in [redacted] The limit of quantitation of the assay is 1 ng/mL and a linear calibration ranging from11 to 150 ng/mL. The assay precession (% CV) ranges from approximately 3% to 11%% (**Table 2.6.1**). b(4)

Table 2.6.1. Summary of FEX Assay Validation

TABLE 1. Validation Summary for MDL-16,455 in Plasma - Method PJAY005A	
	Range
Quantitation range	1 - 150 ng/ml
Batch-to-batch accuracy (%) of validation QC samples	94.3 - 111.0%
Batch-to-batch precision (%CV) of validation QC samples	6.0 - 10.7%
Batch-to-batch accuracy (%) of calibration standards	92 - 111%
Batch-to-batch precision (%CV) of calibration standards	3.2- 8.4%
Within-batch accuracy (%) of validation QC samples	92 - 117%
Within-batch precision (%CV) of validation QC samples	2.4 - 13.0%

The assay validation data are satisfactory.

3.0 Labeling Comments

The labeling comments will be incorporated directly into the sponsor's proposed label after discussion with the review team.

The sponsor added statements specifically related to ODT. No other changes were made to the approved label. Overall, these statements are reasonable. However, they will be modified after the discussion with the review team after OCP briefing.

Based on the studies conducted in this NDA on ODT, the sponsor included general statement related to effect of food on the absorption of fexofenadine. Therefore, ODT and other fexofenadine products should be taken with water on empty stomach, with the exception of ODT that can be taken with and without water. [redacted] b(4)

[redacted] The joint edited version for clinical pharmacology and clinical studies labeling after discussion with the medical officer is posted in the DFS as a separate attachment. b(5)

21 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

4.2 **Individual Study Review:**

4.2.1. Study # 1004 (Pilot Study and Effect of Food)

Objective:

The primary objective of this study was to characterize the bioavailability of four prototypes of ODT tablets relative to the currently marketed 30 mg tablet.

Study Design:

This was a single dose, 4 periods, 8 treatments, partially balanced incomplete crossover design in healthy subjects as follows:

Treatment A (Reference): Single oral dose of 30 mg EEX Marketed tablet (Fasted)

Treatment B: Single oral dose of 30 mg of prototype ODT formulation I (Fasted)

Treatment C: Single oral dose of 30 mg of prototype ODT formulation I (Fed)

Treatment D: Single oral dose of 30 mg of prototype ODT formulation II (**Fasted**)

Treatment E: Single oral dose of 30 mg of prototype ODT formulation II (**Fed**)

Treatment F: Single oral dose of 30 mg of prototype ODT formulation I (Fasted, without water)

Treatment G: Single oral dose of 30 mg of prototype ODT formulation IV (Fasted)

Treatment H: Single oral dose of 30 mg of prototype ODT formulation V (Fasted)

Products Administration:

All treatments were conducted after overnight fasting followed by a high fat breakfast in the fed arms. In treatments B, C, D, E, G, and H the ODT tablets were placed on the tongue and allowed to be dissolved and swallowed within 1-2 minutes. The mouth was rinsed and content were swallowed with 20 mL water followed by the remaining portion of the 240mL water. However, in treatment F, ODT tablet was placed on tongue and allowed to dissolve/disintegrate and then swallowed without water. No water was allowed 2 hours post dose in treatment F. In treatment A, the marketed tablet was administered swallowed with 240 mL water.

Blood samples for PK analysis of FEX were collected at appropriate intervals over 48 hours. The following table shows the drug products used in each arm of the study:

Drug Code:	M016455	M016455	M016455	M016455	M016455
INN[a]:	Fexofenadine HCl	Fexofenadine HCl	Fexofenadine HCl	Fexofenadine HCl	Fexofenadine HCl
Treatment:	A	B, C, F[b]	D, E	G	H
Formulation:	Marketed lactose-free small tablet containing 30 mg fexofenadine	Prototype fast-disintegrating formulation I containing 30 mg fexofenadine	Prototype fast-disintegrating formulation II containing 30 mg fexofenadine	Prototype fast-disintegrating formulation IV containing 30 mg fexofenadine	Prototype fast-disintegrating formulation V containing 30 mg fexofenadine
Manufacturer:	Aventis	Ethypharm	CIMA labs	Ethypharm	Ethypharm
Batch/lot number:	1045751	C0067D	RA0206	C0070D	C0071D

[a] INN: International nonproprietary name
[b] Treatment F was changed from formulation III to formulation I administered without water, per protocol amendment 1.

Results:

- Based on the data from this study, formulation II was selected for further development (**Figure 4.2.1.1 and Table 4.2.1.1**).

- Food reduces the exposure by approximately 50% (Cmax by 40% and AUC by 60%) and Tmax was reduced by approximately 2 hours compared to fasting (**Table 4.2.1.1 and Figure 4.2.1.2**).

- The same trend was seen for formulation I in which the Cmax was reduced by 64% and AUC by 43% (Treatments B and C). The AUC ratios for formulations I and II (Treatments C and E) in fed state were approximately 57% and 60%, respectively when compared to the same formulation in the fasted state. For Cmax, the ratios were approximately 36% and 40% for formulation I and II in the fed and fasted states, respectively. In all formulation (I and II), the Tmax was reduced by approximately 2 hours when administered with food.

- In terms of effect of water on prototype I, the bioavailability appears to be slightly reduced by approximately 2-3% when ODT was given with water (Treatments F and B). The ratio of Cmax was 98% and for AUC was 97% for treatments F and B.

Figure 4.2.1.2 Mean Plasma Concentration-Time profiles of FEX (Study # 1004)

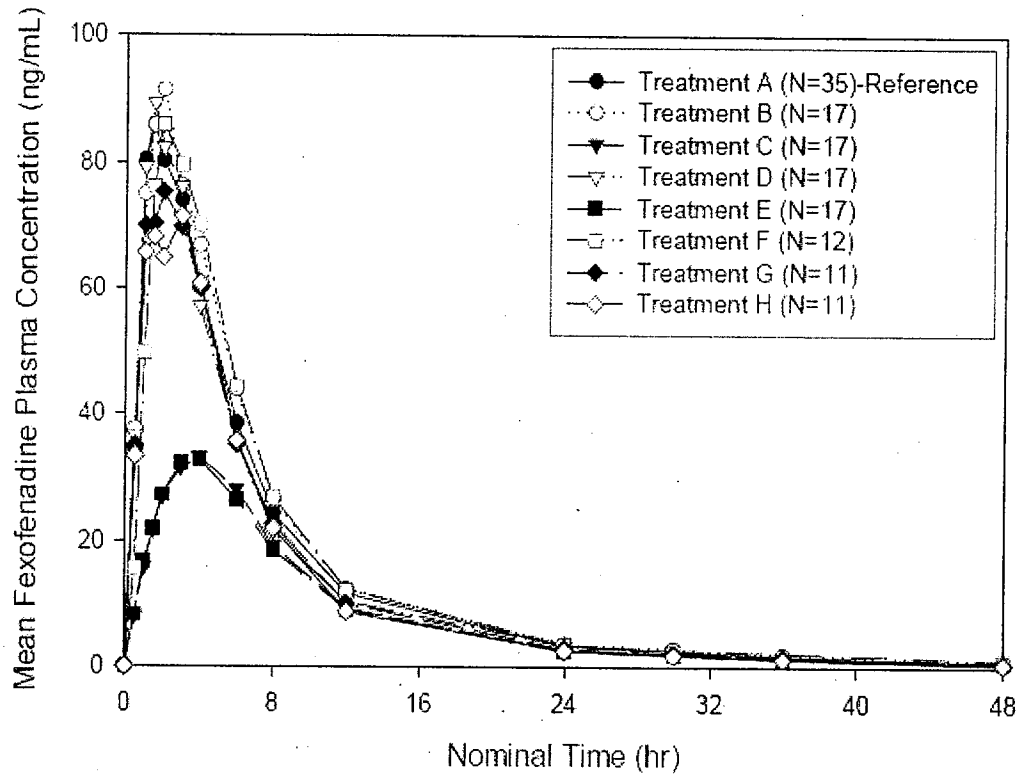

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Table 4.2.1.1. Summary of PK Parameters From the Pilot and Effect of Food Study (Study # 1004)

Summary of analysis of variance of pharmacokinetic parameters

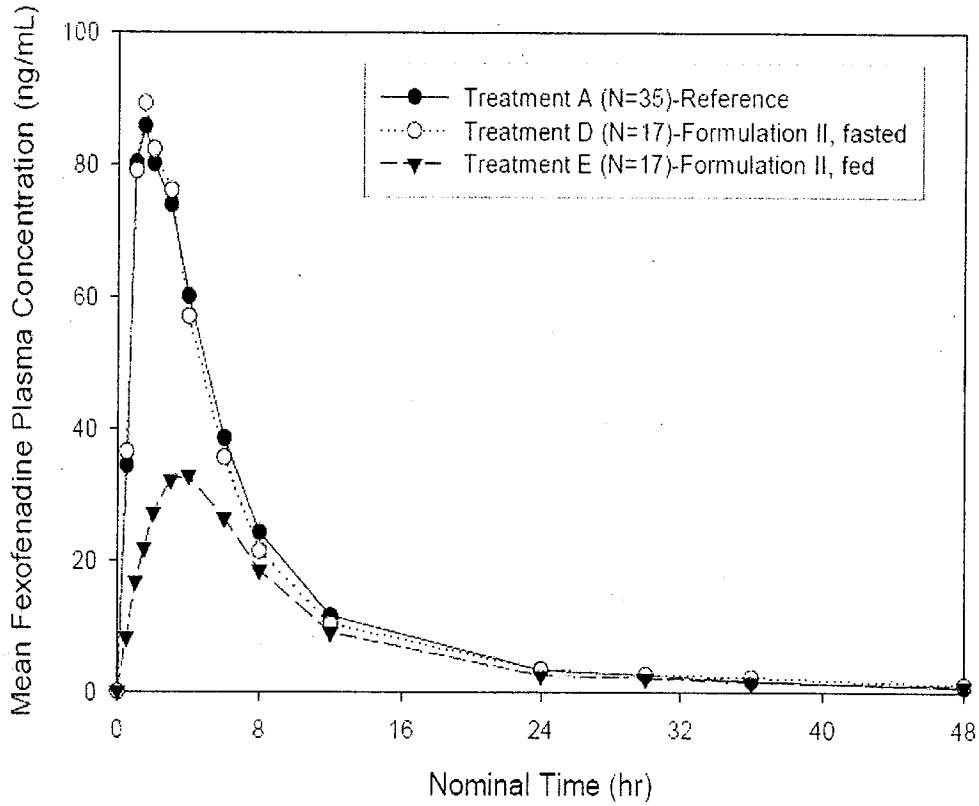
Parameter	Treatment[a]	N	Mean	CV (%)	Adjusted Mean[b]	Pair[a]	Pairwise comparison[c] Ratio (%)[b]	90% Confidence Interval[b]
AUC(0-∞)	A	33	672.0	39.9	615.5	-	-	-
(ng•h/mL)	B	17	707.2	29.8	674.9	B/A	109.65	(97.04, 123.89)
	C	16	391.4	27.6	386.3	C/B	57.24	(50.27, 65.18)
	D	17	655.4	34.4	630.4	D/A	102.42	(90.92, 115.37)
	E	16	390.8	38.7	380.6	E/D	60.37	(53.02, 68.74)
	F	12	681.3	32.5	657.1	F/B	97.36	(83.29, 113.81)
	G	11	600.6	38.9	563.4	G/A	91.53	(79.47, 105.42)
	H	11	571.2	29.9	560.6	H/A	91.08	(79.06, 104.92)
C_{max}	A	35	100.05	47.76	89.13	-	-	-
(ng/mL)	B	17	98.99	23.48	97.46	B/A	109.35	(92.44, 129.35)
	C	17	36.56	32.28	35.45	C/B	36.37	(30.39, 43.52)
	D	17	96.59	39.27	89.11	D/A	99.97	(84.57, 118.18)
	E	17	38.11	31.29	36.51	E/D	40.97	(34.24, 49.03)
	F	12	103.12	56.72	96.26	F/B	98.76	(79.34, 122.94)
	G	11	82.64	39.76	75.86	G/A	85.11	(69.93, 103.58)
	H	11	85.36	37.42	80.01	H/A	89.77	(73.81, 109.18)

[a] Treatment A: 30 mg marketed lactose-free small tablet (fasted conditions); lot number 1045751
Treatment B: 30 mg prototype fast-disintegrating formulation I (fasted conditions); lot number C0067D
Treatment C: 30 mg prototype fast-disintegrating formulation I (fed conditions); lot number C0067D
Treatment D: 30 mg prototype fast-disintegrating formulation II (fasted conditions); lot number RA0206
Treatment E: 30 mg prototype fast-disintegrating formulation II (fed conditions); lot number RA0206
Treatment F: 30 mg prototype fast-disintegrating formulation I (fasted conditions with no water); lot number C0067D
Treatment G: 30 mg prototype fast-disintegrating formulation IV (fasted conditions); lot number C0070D
Treatment H: 30 mg prototype fast-disintegrating formulation V (fasted conditions); lot number C0071D

[b] Natural-log transformed results for the ANOVA were transformed to the original scale by exponentiation to obtain the adjusted mean, ratio, and 90% confidence interval.

[c] Relative bioavailability is assessed by the comparison of Treatment A (reference) to Treatments B, D, G, and H (test). The effect of food is assessed by comparison of Treatments B and D (references) to Treatments C and E (tests), respectively. The effect of the coadministration of water is assessed by comparison of Treatment B (reference) to Treatment F (test).

Figure 4.2.1.2. Effect of Food on FEX Bioavailability Following Administration of ODT (Study # 1004).



Reviewer's Comment:

Since food reduces the bioavailability of FEX by approximately 50% from ODT, it should be given on empty stomach with or without water.

4.2.2. Study # M016455H/1007 (Pivotal BE Study):

Objective:

The primary objective of this study was to establish the bioequivalence (BE) of FEX when administered as an ODT relative to the marketed 30 mg FEX tablet under fasted conditions.

Study Design:

This was a single dose, two-way crossover study in 54 healthy subjects with a washout period of al least 6 days between each treatment as follows:

Treatment A (Reference): Single dose 30 mg FEX currently marketed IR tablet

Treatment B (Test): Single dose 30 mg FEX ODT tablet

All treatments were conducted after overnight fasting with 240 mL water. ODT tablets were placed on the tongue and allowed to be dissolved and swallowed within 1-2 minutes. The mouth was rinsed and content were swallowed with 20 mL water followed by the remaining portion of the 240mL water.

Blood samples for PK analysis of FEX were collected at appropriate intervals over 48 hours.

Results:

- Out of 54 subjects, 52 completed the study per the protocol.
- The 90% CI for both treatments fall within 80-125% (**Table 4.2.2.1 and Figure 4.2.2.1**).

Table 4.2.2.1. Summary of PK Parameters (Study # 1007)

Parameter (unit)	Treatment [a]	Arithmetic Mean (CV%) [b]	Geometric LS Mean [c]	Treatment Comparisons [d] Ratio [e] (%)	90% CI
AUC(0-∞) (ng·h/mL)	A	637 (29.2)	612	98.9	92.3 - 106
	B	635 (31.2)	606		
Cmax (ng/mL)	A	93.8 (33.3)	88.9	93.2	85.3 - 102
	B	88.0 (35.5)	82.9		
AUC(0-last) (ng·h/mL)	A	607 (30.7)	582	99.4	92.3 - 107
	B	608 (32.9)	579		
Tmax [f] (h)	A	2.0 (1.0-4.0)	-	-	-
	B	2.0 (0.5-6.0)	-		
t1/2 (h)	A	11.6 (27.8)	-	-	-
	B	11.8 (31.8)	-		
CLpo (L/h)	A	47.4 (27.4)	-	-	-
	B	48.3 (32.2)	-		

Notes: CV% = coefficient of variation; LS = least-squares; CI = confidence interval.

[a] Treatment A: single dose of 30 mg fexofenadine HCl as marketed tablet (reference).
Treatment B: single dose of 30 mg fexofenadine HCl as orally disintegrating tablet (test).

[b] Arithmetic mean calculated from all subjects with evaluable data; N = 52 for all Treatment B parameters and AUC(0-last), Cmax, and Tmax for Treatment A; N = 51 for Treatment A AUC(0-∞) t1/2, and CLpo.

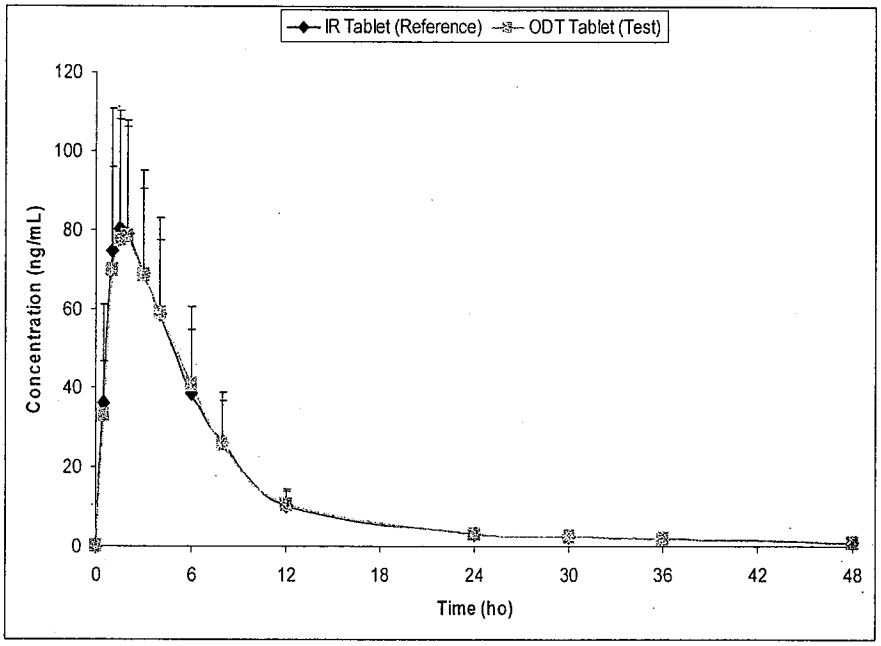
[c] Geometric mean calculated from balanced pair data; N = 52 for AUC(0-last) and Cmax; N = 51 for AUC(0-∞).

[d] ANOVA with terms for sequence, period, and treatment as fixed effects and subject nested within sequence as random effect performed on the natural log-transformed AUC(0-∞), AUC(0-last), and Cmax.

[e] Ratio = geometric LS mean test/geometric LS mean reference (B/A).

[f] Tmax reported as median (range) values.

Figure 4.2.2.1. Mean (SD) of FEX Plasma Concentration-Time Profiles (Graph Constructed by the Reviewer, Source Study # 1007, Appendix, Table T5, Page 70)



Reviewer's Comments:

The data from this study was very tight with 90% CI of 92.3-106% and 85.3-101.9% for $AUC_{(0-\infty)}$ and Cmax, respectively. In addition, the intra-subject variability was relatively low with a CV of <35%.

Conclusion:

Based on this study, 30 mg ODT tablet is bioequivalent to the currently marketed 30 mg IR tablet.

4.2.3. Study # 1008 (Effect of Water)

Objective:

The primary objective of this study was to compare the bioavailability of the FEX ODT when administered with and without water.

Study Design:

This was a single dose, two-way crossover study in 54 healthy subjects with a washout period of al least 6 days between each treatment as follows:

Treatment A (Reference): Single dose 30 mg FEX ODT with 240 mL water

Treatment B (Test): Single dose 30 mg FEX ODT tablet without water

All treatments were conducted after overnight fasting with 240 mL water. ODT tablets were placed on the tongue and allowed to be dissolved and swallowed within 1-2 minutes. The mouth was rinsed and content were swallowed with 20 mL water followed by the remaining portion of the 240mL water.

Blood samples for PK analysis of FEX were collected at appropriate intervals over 48 hours.

Results:

- There was wide variability in the data in both treatment arms (**Figure 4.2.3.1**). The CV is over 40% for most of the parameters (**Table 4.2.3.1**).
- The 90% CI for AUC was withibn 80-125% (**Table 4.2.3.1**). However, for Cmax it was slightly outside the boundaries (100-127%).

Figure 4.2.3.1. FEX PK Plasma Concetration-Time Profiles of ODT With and Without Water (Study # 1008).

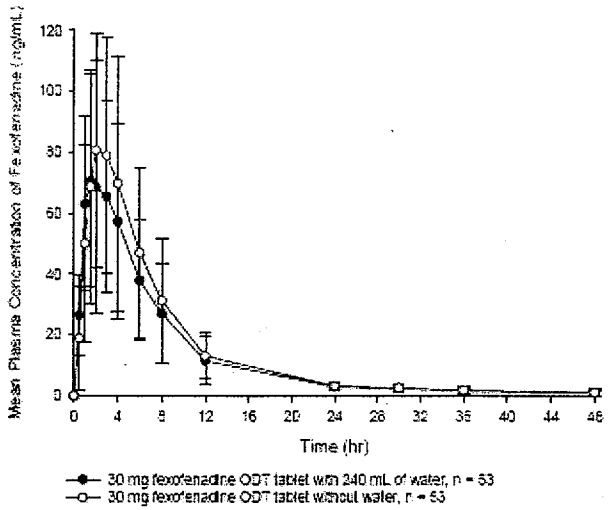


Table 34.2..2. FEX Mean PK Parameters for ODT With and Without Water (Study # 1008).

Parameter (unit)	Treatment [a]	N	Arithmetic Mean (CV%) [b]	N	Geometric LS Mean [c]	Treatment Comparisons [d] Ratio [e] (%)	90% CI
AUC(0-∞) (ng·h/mL)	A	52	628 (34.3)	51	601	112	102 - 122
	B	53	699 (40.5)	51	671		
Cmax (ng/mL)	A	53	86.3 (50.9)	52	78.5	113	100 - 127
	B	53	96.5 (46.7)	52	88.5		
AUC(0-last) (ng·h/mL)	A	53	589 (38.4)	52	552	113	103 - 125
	B	53	668 (42.7)	52	625		
Tmax [f] (h)	A	53	2.0 (1.0-8.0)		-	-	-
	B	53	2.0 (1.0-8.0)		-		
t1/2 (h)	A	52	12.8 (52.9)		-	-	-
	B	53	12.0 (54.6)		-		
CLpo (L/h)	A	52	49.5 (31.8)		-	-	-
	B	53	46.8 (42.8)		-		

Notes: CV% = coefficient of variation; LS = least-squares; CI = confidence interval.
[a] Treatment A: single dose of 30 mg fexofenadine HCl as orally disintegrating tablet with 240 mL water (reference).
Treatment B: single dose of 30 mg fexofenadine HCl as orally disintegrating tablet without water (test).
[b] Arithmetic mean calculated from all subjects with evaluable data.
[c] Geometric mean calculated from balanced pair data.
[d] ANOVA with terms for sequence, period, and treatment as fixed effects and subject nested within sequence as random effect performed on the natural log-transformed AUC(0-∞), AUC(0-last), and Cmax.
[e] Ratio = geometric LS mean test/geometric LS mean reference (B/A).
[f] Tmax reported as median (range) values.

Reviewer's Comments:

- From this study it can be concluded that the absorption profile and systemic exposure of FEX following administration of ODT with and without water are comparable. However, the Cmax FEX was slightly higher when ODT was given without water (96.5 ng/mL) than with water (86.3 ng/mL). The reason of this difference is unknown.

- Examining the individual data and absorption profiles shows there was a consistent pattern of lower exposure when ODT is given with water. In addition, there were about 5 subjects that could be considered outliers, at least two with very low exposure when given without water and two with very high exposure when given with water. However, considering all the data collectively, there is little difference between both treatments.

- The effect of water on formulation I (fast-disintegrating) that was seen in the pilot Study # 1004 was somewhat negligible comparing to that seen in this study for prototype II formulation. In the pilot study, the bioavailability was also slightly lowered by approximately 2-3% when ODT was given with water (Treatments F and B in Study # 1004). The ratio of Cmax was 98% and for AUC was 97% for treatments F and B.

Conclusions:

Overall, considering the observed variability in the data at both treatments, the absorption of FEX following ODT with water or without water is comparable. The observed difference in Cmax may not have any significant clinical impact.

4.3 Consult Review (Pharmacometric Review)

No pharmacometric consult was needed for this NDA.

4.4 Filing Memo:

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-909	Brand Name	N/A
OCP (I, II, III)	II	Generic Name	Fexofenadine
Medical Division	DPADP	Drug Class	Anti Allergy
OCPB Reviewer	Sayed (Sam) Al Habet, RP.h, Ph.D.	Indication(s)	Seasonal Allergic Rhinitis and Chronic Idiopathic Urticaria
OCPB Team Leader	Emmanuel (Tayo) Fadiran, RP.h., Ph.D.	Dosage Form	Oral Disintegrating Tablets
PM Reviewer		Dosing Regimen	Once or Twice daily in children 6 to 11 years of age
Date of Submission	September 28, 2006	Route of Administration	Oral
Estimated Due Date of OCP Review	April 28, 2007	Sponsor	Sanofi-Aventis
PDUFA Due Date	July 28, 2007	Priority Classification	Standard
Division's Due Date	May 28, 2007		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	3		
multiple dose:	X			

Patients-				
single dose:	x			
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4	4	
Filability and QBR comments				

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	**No Comments at this time.**	Comments have been sent to firm (or attachment included) FDA letter date if applicable **NONE at this time**
QBR questions (key issues to be considered)	**The sponsor conducted adequate PK/BE studies (see attached filing slides for detisl). The three main studies are:** **1) BE study with ODT and marketed allegro 30 mg.** **2) Effect of food study** **3) Effect of water (ODT with and without water)**	
Other comments or information not included above	**Inspection Recommendation:** DSI inspection is recommended for the pivotal BE study # M016455H/1007. This BE study was for 30 mg ODT and 30 mg Allegra marketed tablets. The study was conducted at the following site: **Clinical Site:** [redacted] b(4) PI: [redacted] Dates: August 31, 2004 Last Subject Completed: October 4, 2004 **Analytical Site:** [redacted] b(4) Study Manager: [redacted] Phone [redacted] Fax [redacted]	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Clinical Pharmacology Filing Meeting
(November 17, 2006)

Sayed (Sam) Al Habet, R.Ph., Ph.D.
and
Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.

11/21/2006 12:42 PM 1

Product Summary

NDA#:	21-909
Date of Submission:	September 28, 2006
Generic Name:	Fexofenadine
Trade Name:	ALLEGRA® Orally Disintegrating Tablet (ODT)
Formulation:	30 mg ODT
Route of Administration:	Oral
Indications:	Seasonal Allergic Rhinitis (SAR) Chronic Idiopathic Urticaria (CIU)
Type of Submission:	NDA
Sponsor:	Sanofi-Aventis Pharmaceuticals
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D
Team Leader:	Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.

11/21/2006 12:43 PM 2

What Studies Were Submitted in the Current NDA?

In vitro Dissolution:

- Two lots of ODT
- Two lots of reference

Clinical Pharmacology Studies:

- Pilot/Formulation development study and food effect study (#1004)
  - Four prototypes
  - Fed/fasted on one prototype (formulation II)
- Pivotal BE study (#1007):
  - 30 mg single dose of ODT vs 30 mg reference Allegra
- Effect of water:
  - ODT with and without water

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Pilot Study (Formulation Development and Food Effect) Study # 1004

Crossover in 35 healthy subjects:

Treatment A: 30 mg reference (Allegra)
Treatment B: 30 mg ODT prototype I (fasting)
Treatment C: 30 mg ODT prototype I (fed)
Treatment D: 30 mg ODT prototype II (fasting)
Treatment E: 30 mg ODT prototype II (fed)
Treatment F: 30 mg ODT prototype I (without water)
Treatment G: 30 mg ODT prototype IV (fasting)
Treatment H: 30 mg ODT prototype V (fasting)

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Results of the Pilot Study (#1004)

Summary of analysis of variance of pharmacokinetic parameters

Parameter	Treatment[a]	N	Mean	CV (%)	Adjusted Mean[b]	Pairwise comparison[c] Pair[c]	Ratio (%)[d]	90% Confidence Interval[d]
AUC(0-∞)	A	33	672.0	39.9	615.5	Reference		
(ng•mL/mL)	B	17	707.3	29.4	674.6	B/A	109.65	(97.04, 123.88)
	C	16	391.4	27.6	389.3	C/B	57.24	(50.27, 65.18)
Fasted →	D	17	645.4	34.4	630.4	D/A	102.42	(90.92, 115.37)
→	E	17	379.8	38.7	380.1	E/D	60.37	(53.02, 68.74)
	F	12	481.5	32.5	457.1	F/D	72.36	(63.29, 83.01)
	G	11	420.6	38.4	421.4	G/A	91.53	(79.47, 105.47)
	H	11	571.2	29.5	560.7	H/A	91.08	(79.06, 104.92)
C_{max}	A	33	103.06	47.76	89.19			
(ng/mL)	B	17	98.99	23.44	97.46	B/A	109.35	(92.44, 129.35)
	C	16	39.56	32.24	39.48	C/B	36.37	(30.39, 43.52)
→	D	17	96.59	39.22	89.11	D/A	99.97	(84.57, 118.16)
→	E	17	39.11	31.26	35.51	E/D	40.97	(34.24, 49.03)
	F	12	102.12	54.72	96.26	F/E	98.76	(79.34, 122.94)
	G	11	82.64	39.76	79.86	G/A	85.11	(69.93, 103.58)
	H	11	85.46	37.42	83.01	H/A	89.27	(73.81, 109.16)

[a] Treatment A: 30 mg marketed sucrose free small tablet (fasted conditions), lot number 1048Fb1
Treatment B: 30 mg prototype fast-disintegrating formulation I (fasted conditions), lot number C00670
Treatment C: 30 mg prototype fast-disintegrating formulation I (fed conditions), lot number C00670
Treatment D: 30 mg prototype fast-disintegrating formulation I, (fasted conditions), lot number RA0206
Treatment E: 30 mg prototype fast-disintegrating formulation I (fed conditions), lot number RA0206
Treatment F: 30 mg prototype fast-disintegrating formulation I (fasted conditions) with no wafers, lot number C00670
Treatment G: 30 mg prototype fast-disintegrating formulation II, (fasted conditions), lot number C00700
Treatment H: 30 mg prototype fast-disintegrating formulation II (fasted conditions), lot number C00710

[b] Natural log transformed results for the AUC(0-∞) were transformed to the original scale by exponentiation to obtain the adjusted mean, ratio, and 90% confidence interval.

[c] Relative bioavailability is assessed by the comparison of Treatment A (reference) to Treatments B, D, G and H (test). The effect of food is assessed by comparison of Treatments H and D (reference) to Treatments C and E (fed), respectively. The effect of the orodispersibility of water is assessed by comparison of Treatment E (reference) to Treatment F (test).

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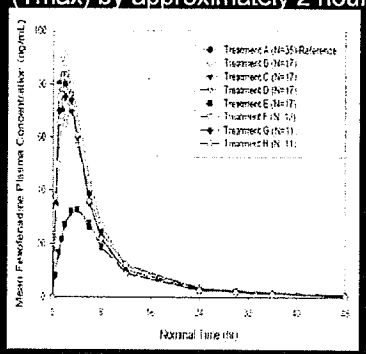
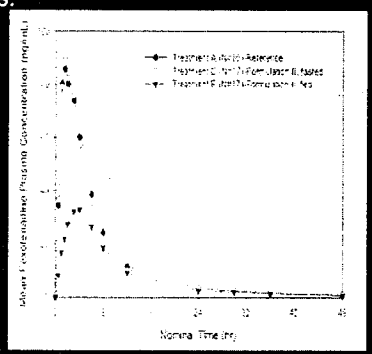
5

Conclusions from Study #1004

- Formulation II goes forward for further development
- Food reduce exposure by approximately 50% and delays Cmax (Tmax) by approximately 2 hours.





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6

Pivotal BE Study (#1007)

Crossover in 54 healthy subjects:

Treatment A: 30 mg reference (Allegra) (fasting)

Treatment B: 30 mg ODT prototype II (fasting)

Note: A and B were given in fasted condition with 240 ml water.

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Results of Pivotal BE Study (#1007)

Parameter (unit)	Treatment [a]	Arithmetic Mean (CV%) [b]	Geometric LS Mean [c]	Treatment Comparisons [d] Ratio [e] (%)	90% CI
AUC(0-∞) (ng·h/mL)	A	637 (29.2)	612	98.9	92.3 - 106
	B	635 (31.2)	606		
Cmax (ng/mL)	A	93.6 (33.3)	88.9	93.2	85.3 - 102
	B	88.0 (35.5)	82.9		
AUC(0-last) (ng·h/mL)	A	607 (30.7)	582	99.4	92.3 - 107
	B	608 (32.9)	579		
Tmax [f] (h)	A	2.0 (1.0-4.0)	-	-	-
	B	2.0 (0.5-8.0)	-		
t1/2 (h)	A	11.6 (27.6)	-	-	-
	B	11.8 (31.8)	-		
CLpo (L/h)	A	47.4 (27.4)	-	-	-
	B	48.3 (32.2)	-		

Notes: CV% = coefficient of variation; LS = least-squares; CI = confidence interval.

[a] Treatment A: single dose of 30 mg fexofenadine HCl as marketed tablet (reference).
Treatment B: single dose of 30 mg fexofenadine HCl as orally disintegrating tablet (test)

[b] Arithmetic mean calculated from all subjects with evaluable data; N = 52 for all Treatment B parameters and AUC(0-last), Cmax, and Tmax for Treatment A; N = 51 for Treatment A AUC(0-∞), t1/2, and CLpo

[c] Geometric mean calculated from balanced pair data; N = 52 for AUC(0-last) and Cmax; N = 51 for AUC(0-∞)

[d] ANOVA with terms for sequence, period, and treatment as fixed effects and subject nested within sequence as random effect performed on the natural log-transformed AUC(0-∞), AUC(0-last), and Cmax.

[e] Ratio = geometric LS mean test/geometric LS mean reference (B/A).

[f] Tmax reported as median (range) values.

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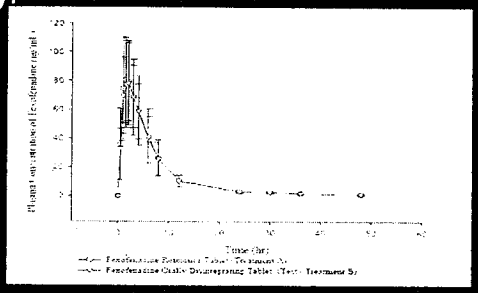
Comments on Pivotal Study (#1007)

- ODT is bioequivalent to the reference when given with water under fasting condition.
- ODT should have been administered without water in this study.



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Effect of Water (Study #1008)

Crossover in 54 healthy subjects:

Treatment A: ODT 30 mg (fasting with 240 ml water) (reference)

Treatment B: ODT 30 mg (fasting without water) (Test)

11/21/2006 12:45 PM 10

Results Summary of Effect of Water (Study # 1008)

Results - Pharmacokinetics and pharmacodynamics

Parameter (unit)	Treatment [a]	N	Arithmetic Mean (CV%) [b]	N	Geometric LS Mean [c]	Treatment Comparisons [d] Ratio [e] (%)	90% CI
AUC(0-∞) (ng·h/mL)	A	52	628 (34.3)	51	601	112	102 - 122
	B	53	699 (40.5)	51	671		
Cmax (ng/mL)	A	53	86.3 (50.9)	52	78.5	113	100 - 127
	B	53	96.5 (46.7)	52	88.5		
AUC(0-last) (ng·h/mL)	A	53	589 (38.4)	52	552	113	103 - 125
	B	53	668 (42.7)	52	625		
Tmax [f] (h)	A	53	2.0 (1.0-8.0)		-	-	-
	B	53	2.0 (1.0-8.0)		-		
t1/2 (h)	A	52	12.8 (52.9)		-	-	-
	B	53	12.0 (54.6)		-		
CLpo (L/h)	A	52	49.5 (31.8)		-	-	-
	B	53	46.8 (42.8)		-		

Notes: CV% = coefficient of variation; LS = least-squares; CI = confidence interval
[a] Treatment A: single dose of 30 mg fexofenadine HCl as orally disintegrating tablet with 240 mL water (reference).
Treatment B: single dose of 30 mg fexofenadine HCl as orally disintegrating tablet without water (test).
[b] Arithmetic mean calculated from all subjects with evaluable data.
[c] Geometric mean calculated from balanced pair data.
[d] ANOVA with terms for sequence, period, and treatment as fixed effects and subject nested within sequence as random effect performed on the natural log-transformed AUC(0-∞), AUC(0-last), and Cmax.
[e] Ratio = geometric LS mean test/geometric LS mean reference (B/A)
[f] Tmax reported as median (range) values.

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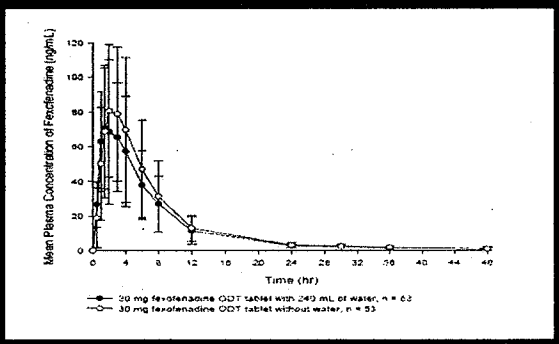
Comments On Effect of Water (Study # 1008)

- Cmax was slightly outside 80-125%
- Wide variability in the data



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General Comments

- The sponsor conducted adequate studies to characterize the PK of Allegra ODT product.
- It is noted that in the pivotal BE study ODT was administered with 240 ml water. The study should have been conducted without water. Alternatively, the sponsor should have conducted the study as three arms with and without water.
- Water appears to have some effect on the Cmax, but not on AUC. The Cmax was slightly outside the 80-125% (100-127%).
- Considering the variability in the data with both products, ODT is considered bioequivalent to the reference.

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Recommendation

Fileable

(from OCP Perspective)

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/s/

Sayed Al-Habet
5/23/2007 05:04:07 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
5/23/2007 05:09:38 PM
BIOPHARMACEUTICS
I concur.

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-909	Brand Name	N/A
OCP (I, II, III)	II	Generic Name	Fexofenadine
Medical Division	DPADP	Drug Class	Anti Allergy
OCPB Reviewer	Sayed (Sam) Al Habet, RP.h, Ph.D.	Indication(s)	Seasonal Allergic Rhinitis and Chronic Idiopathic Urticaria
OCPB Team Leader	Emmanuel (Tayo) Fadiran, RP.h., Ph.D.	Dosage Form	Oral Disintegrating Tablets
PM Reviewer		Dosing Regimen	Once or Twice daily in children 6 to 11 years of age
Date of Submission	September 28, 2006	Route of Administration	Oral
Estimated Due Date of OCP Review	April 28, 2007	Sponsor	Sanofi-Aventis
PDUFA Due Date	July 28, 2007	Priority Classification	Standard
Division's Due Date	May 28, 2007		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	3		
multiple dose:	X			
Patients-				
single dose:	x			
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				

Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	**No Comments at this time.**	Comments have been sent to firm (or attachment included). FDA letter date if applicable. NONE at this time
QBR questions (key issues to be considered)	**The sponsor conducted adequate PK/BE studies (see attached filing slides for detisl). The three main studies are:** **1) BE study with ODT and marketed allegro 30 mg.** **2) Effect of food study** **3) Effect of water (ODT with and without water)**	

Other comments or information not included above	**Inspection Recommendation:** DSI inspection is recommended for the pivotal BE study # M016455H/1007. This BE study was for 30 mg ODT and 30 mg Allegra marketed tablets. The study was conducted at the following site: **Clinical Site:** [redacted] PI: [redacted] Dates: August 31, 2004 Last Subject Completed: October 4, 2004 **Analytical Site:** [redacted] Study Manager [redacted] Phone [redacted] Fax [redacted]
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

Clinical Pharmacology Filing Meeting
(November 17, 2006)

Sayed (Sam) Al Habet, R.Ph., Ph.D.
and
Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.

11/21/2006 12:42 PM 1

Product Summary

NDA#:	21-909
Date of Submission:	September 28, 2006
Generic Name:	Fexofenadine
Trade Name:	ALLEGRA® Orally Disintegrating Tablet (ODT)
Formulation:	30 mg ODT
Route of Administration:	Oral
Indications:	Seasonal Allergic Rhinitis (SAR) Chronic Idiopathic Urticaria (CIU)
Type of Submission:	NDA
Sponsor:	Sanofi-Aventis Pharmaceuticals
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D
Team Leader:	Emmanuel (Tayo) Fadiran, R.Ph., Ph.D.

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What Studies Were Submitted in the Current NDA?

In vitro Dissolution:

- Two lots of ODT
- Two lots of reference

Clinical Pharmacology Studies:

- Pilot/Formulation development study and food effect study (#1004)
  - Four prototypes
  - Fed/fasted on one prototype (formulation II)
- Pivotal BE study (#1007):
  - 30 mg single dose of ODT vs 30 mg reference Allegra
- Effect of water:
  - ODT with and without water

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Pilot Study (Formulation Development and Food Effect) Study # 1004

Crossover in 35 healthy subjects:

Treatment A: 30 mg reference (Allegra)
Treatment B: 30 mg ODT prototype I (fasting)
Treatment C: 30 mg ODT prototype I (fed)
Treatment D: 30 mg ODT prototype II (fasting)
Treatment E: 30 mg ODT prototype II (fed)
Treatment F: 30 mg ODT prototype I (without water)
Treatment G: 30 mg ODT prototype IV (fasting)
Treatment H: 30 mg ODT prototype V (fasting)

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Approved This Way
On [illegible]

Results of the Pilot Study (#1004)

Summary of analysis of variance of pharmacokinetic parameters

Parameter	Treatment[1]	N	Mean	CV (%)	Adjusted Mean[2]	Pair[3]	Ratio (%)[4]	90% Confidence Interval[4]
AUC(0-∞)	A	33	672.0	29.9	615.5		Reference	
ng•h/mL)	B	17	707.3	29.8	674.9	B/A	109.65	(97.64, 123.09)
	C	16	391.4	27.6	346.3	C/B	51.34	(45.27, 58.18)
Fasted	D	17	655.4	34.4	630.4	D/A	102.42	(90.92, 115.37)
	E	16	395.6	38.7	380.6	E/D	60.37	(53.02, 68.74)
	F	12	681.3	32.6	667.1	F/B	97.36	(83.29, 113.81)
	G	11	600.6	38.9	563.4	G/A	91.53	(79.47, 105.37)
	H	11	571.2	36.9	560.6	H/A	91.08	(79.06, 104.92)
C_{max}	A	33	150.06	47.76	69.13			
(ng/mL)	B	17	94.89	23.48	97.46	B/A	109.35	(92.44, 129.30)
	C	17	35.56	32.28	35.45	C/B	36.37	(30.38, 43.57)
	D	17	96.53	39.27	89.11	D/A	99.97	(84.57, 118.18)
	E	17	38.11	31.29	35.61	E/D	40.07	(34.24, 49.02)
	F	12	103.12	34.72	95.26	F/B	95.79	(79.34, 122.04)
	G	11	82.64	39.78	75.86	G/A	85.11	(69.93, 103.58)
	H	11	85.46	37.43	80.91	H/A	89.77	(73.83, 109.18)

[1] Treatment A: 50 mg marketed tablets from scout tablet (fasted conditions), lot number 1045751
Treatment B: 50 mg prototype fast-disintegrating formulation I (fasted conditions), lot number C00670
Treatment C: 50 mg prototype fast-disintegrating formulation I (fed conditions), lot number C00670
Treatment D: 50 mg prototype fast-disintegrating formulation II (fasted conditions), lot number R40209
Treatment E: 50 mg prototype fast-disintegrating formulation II (fed conditions), lot number RA0209
Treatment F: 50 mg prototype fast-disintegrating formulation I (fasted conditions with no water), lot number C00670
Treatment G: 50 mg prototype fast-disintegrating formulation IV (fasted conditions), lot number C00700
Treatment H: 50 mg prototype fast-disintegrating formulation V (fasted conditions), lot number C00710

[2] Natural log transformed results for the ANOVA were transformed to the original scale by exponentiation to obtain the adjusted mean, ratio and 90% confidence interval.

[3] Relative bioavailability is assessed by the comparisons of Treatment A (reference) to Treatments B, D, G, and H (test). The effect of food is assessed by comparison of Treatments B and D (references) to Treatments C and E (tests), respectively. The effect of the coadministration of water is assessed by comparison of Treatment B (reference) to Treatment F (test).

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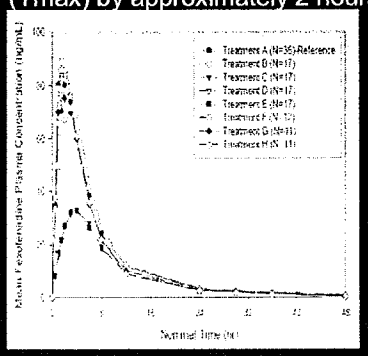
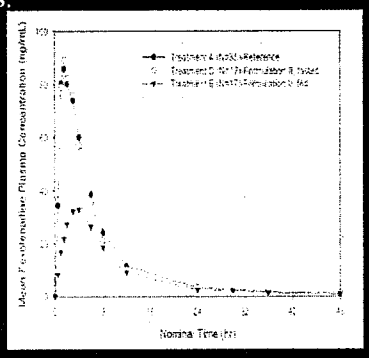
Conclusions from Study #1004

- Formulation II goes forward for further development
- Food reduce exposure by approximately 50% and delays Cmax (Tmax) by approximately 2 hours.





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Pivotal BE Study (#1007)

Crossover in 54 healthy subjects:

Treatment A: 30 mg reference (Allegra) (fasting)

Treatment B: 30 mg ODT prototype II (fasting)

Note: A and B were given in fasted condition with 240 ml water.

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Results of Pivotal BE Study (#1007)

Parameter (unit)	Treatment [a]	Arithmetic Mean (CV%) [b]	Geometric LS Mean [c]	Treatment Comparisons [d] Ratio [e] (%)	90% CI
AUC(0-∞) (ng·h/mL)	A	637 (29.2)	612	98.9	92.3 - 106
	B	635 (31.2)	606		
Cmax (ng/mL)	A	93.8 (33.3)	88.9	93.2	85.3 - 102
	B	88.0 (35.5)	82.8		
AUC(0-last) (ng·h/mL)	A	607 (30.7)	582	99.4	92.3 - 107
	B	608 (32.9)	579		
Tmax [f] (h)	A	2.0 (1.0-4.0)	-	-	-
	B	2.0 (0.5-6.0)	-		
t1/2 (h)	A	11.6 (27.8)	-	-	-
	B	11.8 (31.6)	-		
CLpo (L/h)	A	47.4 (27.4)	-	-	-
	B	48.3 (32.2)	-		

Notes: CV% = coefficient of variation; LS = least-squares; CI = confidence interval.

[a] Treatment A: single dose of 30 mg fexofenadine HCl as marketed tablet (reference).
Treatment B: single dose of 30 mg fexofenadine HCl as orally disintegrating tablet (test).

[b] Arithmetic mean calculated from all subjects with evaluable data; N = 52 for all Treatment B parameters and AUC(0-last), Cmax, and Tmax for Treatment A; N = 51 for Treatment A AUC(0-∞), t1/2, and CLpo.

[c] Geometric mean calculated from balanced pair data; N = 52 for AUC(0-last) and Cmax; N = 51 for AUC(0-∞).

[d] ANOVA with terms for sequence, period, and treatment as fixed effects and subject nested within sequence as random effect performed on the natural log-transformed AUC(0-∞), AUC(0-last), and Cmax.

[e] Ratio = geometric LS mean test/geometric LS mean reference (B/A).

[f] Tmax reported as median (range) values.

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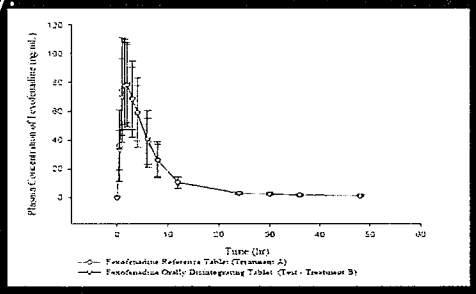
Comments on Pivotal Study (#1007)

- ODT is bioequivalent to the reference when given with water under fasting condition.
- ODT should have been administered without water in this study.



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Effect of Water (Study #1008)

Crossover in 54 healthy subjects:

Treatment A: ODT 30 mg (fasting with 240 ml water) (reference)

Treatment B: ODT 30 mg (fasting without water) (Test)

11/21/2006 12:45 PM 10

Results Summary of Effect of Water (Study # 1008)

Results - Pharmacokinetics and pharmacodynamics

Parameter (unit)	Treatment [a]	N	Arithmetic Mean (CV%) [b]	N	Geometric LS Mean [c]	Treatment Comparisons [d] Ratio [e] (%)	90% CI
AUC(0-∞) (ng·h/mL)	A	52	628 (34.3)	51	601	112	102 - 122
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Tmax [f] (h)	A	53	2.0 (1.0-8.0)		-	-	-
	B	53	2.0 (1.0-8.0)		-		
t1/2 (h)	A	52	12.8 (52.9)		-	-	-
	B	53	12.0 (54.6)		-		
CL/F (L/h)	A	52	49.5 (31.8)		-	-	-
	B	53	46.8 (42.8)		-		

Notes: CV% = coefficient of variation; LS = least-squares; CI = confidence interval

[a] Treatment A: single dose of 30 mg fexofenadine HCl as orally disintegrating tablet with 240 mL water (reference)
Treatment B: single dose of 30 mg fexofenadine HCl as orally disintegrating tablet without water (test)

[b] Arithmetic mean calculated from all subjects with evaluable data.

[c] Geometric mean calculated from balanced pair data.

[d] ANOVA with terms for sequence, period, and treatment as fixed effects and subject nested within sequence as random effect performed on the natural log-transformed AUC(0-∞), AUC(0-last), and Cmax.

[e] Ratio = geometric LS mean test/geometric LS mean reference (B/A).

[f] Tmax reported as median (range) values.

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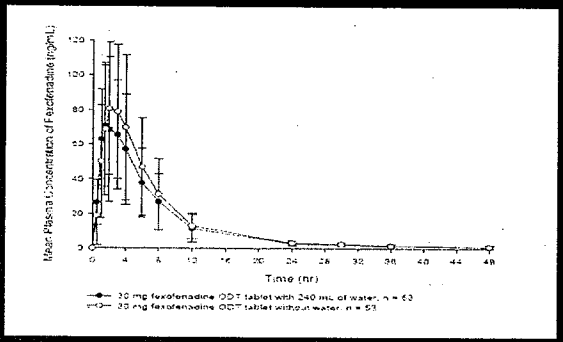
Comments On Effect of Water (Study # 1008)

- Cmax was slightly outside 80-125%
- Wide variability in the data



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General Comments

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- It is noted that in the pivotal BE study ODT was administered with 240 ml water. The study should have been conducted without water. Alternatively, the sponsor should have conducted the study as three arms with and without water.
- Water appears to have some effect on the Cmax, but not on AUC. The Cmax was slightly outside the 80-125% (100-127%).
- Considering the variability in the data with both products, ODT is considered bioequivalent to the reference.

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Recommendation

Fileable

(from OCP Perspective)

11/21/2006 12:46 PM 14

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/s/

Sayed Al-Habet
11/21/2006 02:40:33 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
11/21/2006 02:46:42 PM
BIOPHARMACEUTICS
I concur.