CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20872

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Cobbs
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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA Number:	NDA 20-872
Drug:	Fexofenadine HCl 30, 60, 120 and 180 mg tablet (Allegra ®)
Sponsor:	Hoechst Marion Roussel, Inc., 10236 Marion Park Drive, P.O. Box 9627, Kansas City, MO 64134-0627
Submission Date:	8/26/99, 10/15/99, 1/25/00
Type of Submission:	NDA amendment
Reviewer:	Young Moon Choi, Ph.D.

1. SYNOPSIS

Fexofenadine HCl, the active ingredient of Allegra ®, is an H1-receptor antagonist. The free base of fexofenadine HCl is an active metabolite of terfenadine.

On 7/25/96, FDA approved fexofenadine HCl 60 mg B.I.D. in a capsule dosage form indicated for the treatment of symptoms associated with seasonal allergic rhinitis (SAR) in patients greater than 12 years of age. As an alternative to the capsule, the sponsor has newly developed 30 mg, 60 mg, 120 mg, and 180 mg lactose-free fexofenadine HCl tablets.

On 7/17/98, the sponsor submitted NDA 20-872 to support (1) new dosage regimens using new tablet formulations, i.e., 120 mg QD and 180 QD, (2) new indication, i.e., chronic idiopathic urticaria (CIU) and (3) new target population:

- SAR (Age over 12 years): 120 or 180 mg QD; 60 mg QD as a starting dose for renal patients
- SAR (Age 6-11 years): 30 or 60 mg B.I.D.
- CIU (Age over 12 years): 60 mg B.I.D.; 60 mg QD as a starting dose for renal patients
- CIU (Age 6-11 years): 30 or 60 mg B.I.D.

After completing the review, the Division of Pulmonary and Allergy Drug Products (DPADP) issued an approvable letter including clinical pharmacology and biopharmaceutics (CPB) comments. (Please refer to the agency's letter dated 7/16/99 for full comments/requests).

The present amendment submitted on 8/26/99 is a full response to the above Agency's letter.

The sponsor's response related to the CPB comments are:

(1)

(2) Population pharmacokinetic comparison between adults and children
(3) Reanalysis of bioequivalence study (PJPR0045)
(4) Revised proposal for dissolution specification

With respect to the above comment #1, the sponsor responded as

Therefore, the present review is focused on the responses to the comments (2), (3), and (4).

2.REVIEW ON THE SPONSOR'S RESPONSES

2-1-1. Agency's original comment on the population pharmacokinetics

"Our analysis of the combined data from the two trials K-98-0093-D and K-98-0119-D using populations methods indicates no difference between adults and children. Since our estimate of clearance from this analysis is different from your results, the population pharmacokinetic approach should be utilized to compare the pharmacokinetics of fexofenadine in adults with that in children using the data from K-98-0093-D and K-98-0119-D."

2-1-2. Sponsor's response

The sponsor analyzed the combined data set using NONMEM. Three separate NONMEM jobs were processed:

(1) Base two compartment, first order absorption, pharmacokinetic model
(2) Two-compartment, first order absorption, pharmacokinetic model with separate estimates for apparent oral clearance for the two population groups.
(3) Two-compartment, first order absorption, pharmacokinetic model with apparent oral clearance expressed as a function of subject height, Clpo=X·hgt (cm).

Table I. Sponsor's results of population pharmacokinetics

Parameter/ Factor	Base two compartment model	Separate apparent oral clearance estimate for the two populations	Apparent oral clearance as a function of height
Clpo (L/h)	50.1 (3.17)	For adult : 52.1 (4.44) For children: Clpo x 0.930=48.5	0.329 x height For adult: 55.3 For children: 45.4
Intersubject CV (%) for Clpo	53.0 %	52.3 %	54.4 %
Intrasubject CV (%) for Clpo	95.0 %	95.9 %	94.9 %

2-1-3. Reviewer's comment

The sponsor's population pharmacokinetic analysis appeared to be appropriate. It should be noted that the sponsor's clearance values are slightly different from the values generated by the pharmacometrics scientist (47 l/h either for adult or children; refer to the following Table II). This difference is expected since the pharmacometric scientist used one-compartment model, while the sponsor used two-compartment model.

The population pharmacokinetic (pop pk) analysis using combined data does not support the conclusion that the clearance of fexofenadine in children is different from that in adults. However, it should be noted that the modeled intersubject and intrasubject variability was 53 and 95 %, respectively. With this level of variability in fexofenadine population clearance estimation, the conclusions will not be as robust as the ones derived from the population analysis of the data-rich pharmacokinetic studies, in which the inter- and intrasubject variability are 34 and 20 %, respectively (Refer to the following Table II).

In conclusion, this reviewer is of the opinion that the oral clearance of fexofenadine in children (6-11 years old) is 1.7 times less than that in adults. This conclusion is also supported by the analyses of the 13 available conventional sample-rich pharmacokinetic studies (Refer to the following Table II).

From the clinical efficacy study in this pediatric population, it is apparent that there is no increase in efficacy when dose increased from 30 to 60 mg bid. Therefore, 30 mg bid seems to be an appropriate dose for children 6-11 years of age, compared to the approved adult dose of 60 mg bid.

Table II. Comparison of the oral clearance values of fexofenadine in adult and children

Method	Adult Clearance (l/h)	Children Clearance (l/h)	Remarks
Pop pk by pharmacometric scientist	47.0	47.0	One compartment model as a base model. No covariates effect.
Pop pk by the sponsor One or two samples from each subject	64.3 Intersubject variability= 68 % Intrasubject variability=103 %	42.6 Intersubject variability= 37.1 % Intrasubject variability=69.6 %	Analyzed using not combined data, i.e., adult and children separately
	52.1	48.5	Analyzed using combined data Intersubject variability= 52.3 % Intrasubject variability=95.9 %
	55.3	45.4	Estimated using POP PK model (i.e., height as a covariate; CL=0.329 X height) Intersubject variability= 54.4 % Intrasubject variability=94.9 %
Pop pk by the sponsor (2-stage method) 8 – 15 blood samples per subjects	50.7	30.3	Clearance values were estimated by model independent method and then the covariate effects were analyzed using pop pk technique. Intersubject variability= 34 % Intrasubject variability=20 %
Conventional PK 14-15 blood samples per subject	58.5	30.3	Adult data were extracted from 13 plasma concentration rich, controlled PK studies

2-2-1. Agency's original comment on the bioequivalence study (PJPR0045)

"The analysis of variance with terms of sequence was not performed for each pharmacokinetic parameter in Study PJPR0045. Re-analyze the data including sequence and provide the results for the study."

2-2-2. Sponsor's response

The sponsor's results are shown in the following table.

Table III. Analysis of variance results for log $AUC_{0\text{-}Inf}$

Source	Original Results		With Sequence*Trt	
	Type III F	Pr > F	Type III F	Pr > F
Sequence	2.99	0.0346	2.99	0.0345
Period	0.81	0.5459	1.03	0.3819
Treatment	0.38	0.6822	0.18	0.8384
Seq*Trt	NA	NA	0.91	0.5084

The test for a sequence effect demonstrated significant differences among the six sequences at the 0.05 level, with Type III F statistic of 2.99 and p=0.0346.

The sponsor performed further examination on the sequence effect and found that the significance effect is due mainly to one subject, Subject 13. The following table shows the adjusted means for the six sequences based on the original results.

Table IV. Adjusted sequence means for AUC $_{0\text{-}inf}$

Sequence Number	Subjects	Mean AUC
Sequence 1; CBA ABC	1,8,10, 14, 21, 22, 23, 25	3141
Sequence 2; BACCAB	2, 4, 5, 9, 11, 12, 18, 24	3271
Sequence 3; ACB BCA	3, 6, 7, 1 6, 19, 20, 26, 27	3295
Sequence 4; BCA ACB	13	1601
Sequence 5; CAB BAC	15	2330
Sequence 6; ABC CBA	17	4345

Note: The means are log-scale least square means transformed back to the original scale by exponentiation

It is noted that for Sequence 1-3, there are eight subjects per sequence; for Sequence 4-6, there is only one subject per sequence. Therefore, the subject-to-subject variation associated with only one subject has contributed to the sequence sum of squares. It appeared that the only one subject's variation, especially Subject 13, created the apparent sequence effect. Without Subject 13, there is no evidence of a sequence effect (p=0.3784). Therefore, it is considered that the sequence effect is an artifact of the data caused by the very low absorption of a single subject (Subject 13).

A test was also conducted for a sequence by treatment (seq*trt) interaction. The interaction is not significant with p value of 0.5084.

Either with or without the interaction term included in the model, the confidence interval for the ratios were within the 80 –125 %.

Table V. Adjusted treatment means and ratios for AUC $_{0\text{-}inf}$

	Original				With Seq*Trt included			
Treatment	Mean	Pair	Ratio	90 % CI	Mean	Pair	Ratio	90 % CI
A	2793	A/C	95 %	86-105	2944	A/C	103 %	88-120
B	2849	B/C	97 %	87-107	2783	B/C	97 %	83-114
C	2944				2860			

The means are the log-scale least squares means transformed back to the original scale by exponentiation; the rations are the log scale least squares differences transformed back to the original scale by exponentiation.

Treatment A: a single oral dose of a 180 mg fexofenadine HCl lactose free tablet; to-be marketed formulation
Treatment B: a single oral dose of a 180 mg fexofenadine HCl lactose-gelatin tablet
Treatment C: a single oral dose of 3x60 mg fexofenadine HCl hard-gelatin capsules; reference

2-2-3. Reviewer's comment

The sponsor responded appropriately.
This reviewer agrees with the sponsor's conclusion that the sequence effect on the estimation of AUC in the Study PJPR0045 is artifact due to one subject. It is noted that the reanalyzed results indicate that the to-be-marketed formulation is bioequivalent to the reference (3 x 60 mg capsule).

It should be also noted that all the pivotal safety and efficacy trials utilized the to-be-marketed formulation manufactured at a scale that was representative of full-scale. Therefore, this study is, while useful, not a pivotal bioequivalence study.

No more comments need to be forwarded to the sponsor.

2-3-1. Agency's original comment on the dissolution specification
"The dissolution method proposed is acceptable. However, the proposed dissolution specifications of Q % at 15 minutes and Q % at 45 minutes are not sufficiently discriminatory to adequately characterize the dissolution profiles of the tablets. The following acceptance criteria are acceptable:

Q % at 10 minutes and Q % in 30 min.

2-3-2. Sponsor's response
The sponsor responded that HMR agrees to change the time points for dissolution testing to 10 and 30 minutes. However, the proposed Q values are problematic since they would require HMR to have a high level of S1 dissolution failures both at the time of manufacture and for tablets stored through the expiry period. Based on teleconference dated 10/6/99 (with reviewing chemist), HMR has evaluated the data and would like the FDA to consider the following three proposals. Any of these alternatives would be acceptable to HMR:

Option 1:	Q	% at 10 min
	Q	% at 30 min
Option 2:	Q	% at 10 min
	Q	% at 45 min
Option 3:	Release limit Q	% at 10 min
	Q	% at 30 min
	Shelf life limit Q	% at 10 min
	Q	% at 30 min

2-3-3. Reviewer's comment
Option 3 is acceptable based on the following:

(1) Option 3 seems to have enough discriminatory power and to warrant the sameness of the new batches at initial release with the biobatches as originally suggested by the Agency.

(2) The % reduction in dissolution at shelf life (i.e., Q % at 30 min as opposed to Q % at release) may not have much impact on the in vivo absorption due to following factors, i.e.,

- the physiological factors that affect dissolution and absorption in vivo, e.g., pH range of the stomach (1-3) and the intestine (5-7), gastric emptying time and intestinal transit time,
- the solubility of fexofenadine vs. pH (Solubility increases with pH >3), and
- the slow and variable absorption (e.g., Tmax 1-6 hours) indicating that the dissolution is not a rate limiting step for the absorption.

3. RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics completed the review of the amendment to the NDA 20-872 submitted on 8/26/99, 10/15/99 and 1/25/00 and found that the sponsor's responses to the Agency's comments are acceptable from a clinical pharmacology and biopharmaceutics perspective. The following comment on the dissolution specification needs to be forwarded to the sponsor.

4. COMMENT TO THE SPONSOR

The following dissolution specification should be used for fexofenadine HCl tablets:

Apparatus: USP apparatus II (Paddle)
Speed: 50 rpm
Temperature: 37 °C
Medium: 0.001 M HCl
Volume: 900 ml (30 and 60 mg tablet) or 1800 ml (180 mg tablet)
At release Q: at 10 min, and Q: % at 30 min
At shelf life Q: at 10 min, and Q: % at 30 min.

/S/ 2/10/00

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Concurrence:

/S/ 02/10/2000

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JUL 13 1999

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA Number:	NDA 20-872
Drug:	Fexofenadine HCl 30, 60, 120 and 180 mg tablet (Allegra ®)
Sponsor:	Hoechst Marion Roussel, Inc., 10236 Marion Park Drive, P.O. Box 9627, Kansas City, MO 64134-0627
Submission Date:	7/17/98, 10/28/98
Type of Submission:	New NDA
Code:	3 S
Reviewer:	Young Moon Choi, Ph.D.

1. SYNOPSIS

Fexofenadine HCl, the active ingredient of Allegra ®, is an H1-receptor antagonist. The free base of fexofenadine HCl is an active metabolite of terfenadine.

On 7/25/1996, FDA approved fexofenadine HCl 60 mg B.I.D. in a capsule dosage form indicated for the treatment of symptoms associated with seasonal allergic rhinitis (SAR) in patients greater than 12 years of age. As an alternative to the capsule, the sponsor has newly developed 30 mg, 60 mg, 120 mg, and 180 mg lactose-free fexofenadine HCl tablets.

The purpose of the present application is to support (1) new dose regimens using new tablet formulations, i.e., 120 mg QD and 180 QD, (2) new indication, i.e., chronic idiopathic urticaria (CIU) and (3) new target population:

- SAR (Age over 12 years): 120 or 180 mg QD; 60 mg QD as a starting dose for renal patients
- SAR (Age 6-12 years): 30 or 60 mg B.I.D.
- CIU (Age over 12 years): 60 mg B.I.D.; 60 mg QD as a starting dose for renal patients
- CIU (Age 6-12 years): 30 or 60 mg B.I.D.

The sponsor has conducted a complete safety and efficacy program for SAR and CIU patients of age over 12 years. For patients of age 6-12 years, the pediatric rule is utilized to support registration in that population. The sponsor conducted two clinical trials for SAR patients (children of age 6-12 years). For CIU indication for children, clinical trial is not conducted.

Therefore, the primary focus of the present review was on the following questions:

(1) Is the pharmacokinetics of fexofenadine after administration of new tablet formulation comparable to that of the already approved capsule formulation?

(2) Whether the pharmacokinetics of new dosage regimen (120 or 180 mg tablet QD) is comparable to the current dosage regimen (60 mg capsule BID)?

(3) Is the pharmacokinetics in children (age 6-12 years) described appropriately? What is the systemic exposure in the new target population? Is a dose adjustment for that population warranted based on the systemic exposure?

(4) Is the pharmacokinetics of fexofenadine in SAR patients comparable to that in CIU patients? Is the pharmacokinetics of fexofenadine similar or different from healthy volunteers?

These questions were answered upon reviewing a total of 15 clinical pharmacology studies/analyses reported in item 6 of the current NDA. It is noted that all four different strengths of Allegra tablets have been used in clinical pharmacokinetic studies.

2. COMMENTS TO THE MEDICAL OFFICER

2-1. Bioequivalency between tablet and capsule

Two pivotal bioequivalence studies showed that the tablet is bioequivalent to the capsule. The two strengths of 60 mg and 180 mg tablets appeared bioequivalent to a reference (capsule) formulation. These two bioequivalence studies support the approval of other two tablet strengths (30 and 120 mg strengths) since they are proportional in composition and the dissolution profiles of all four tablets are similar. The population pharmacokinetic analysis also showed that the in vivo performance of the 30 and 60 mg tablet strengths is similar. (Please refer to the individual study review and dissolution review.) Further all strengths have been evaluated in bio-studies.

2-2. Comparison of systemic exposure pediatric patients and adults

Based on the controlled pharmacokinetic studies, 56 % greater AUC, 84 % higher Cmax, and 40% lower oral clearance has been shown in children than those in adults. A proposed dose of 30 mg bid in children appeared to result in similar systemic exposure compared to a 60 mg bid in adults. Oral clearance of fexofenadine in children is comparable with that of adult when normalized by body weight based on the controlled pharmacokinetic studies. The systemic exposure in children for 60 mg bid regimen may be reasonably predicted based on the linear pharmacokinetics of fexofenadine.

On the contrary, in a population pharmacokinetic analysis conducted by pharmacometrics reviewer of the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation-II (OCPB, DPE-II) using the pooled data from two phase 3 studies (K-98-0093-D for adult and K-980119-D for children), there was no substantial difference in clearance values of fexofenadine in adult and children. However, it should be noted that there was marked difference in clearance values of fexofenadine in adults based on the present analysis (47 l/h reported by the pharmacometrics reviewer) using pooled data vs. that based only on the adult (64 l/h as reported by the sponsor). The reason of this discrepancy is not known. Therefore, the sponsor will be asked to reanalyze the data from the above two phase III studies.

However, the proposed 60 mg bid for children seems to be inappropriately high based on the review of the effect of fexofenadine on the inhibition of histamine-induced flare and wheal in children. The 30 mg dose appeared to produce almost similar degree of extent and duration of effect as the 60 mg dose. In this context, the sponsor will be asked the rationale for 60 mg BID for children.

Overall, a dose of 30 mg bid in children is recommended as a starting dose from a pharmacokinetic perspective.

2-3.Comparison of pharmacokinetics of fexofenadine in healthy volunteers, SAR patients, and CIU patients.

The population analyses showed that the oral clearance values of SAR patients appeared to be comparable to that of CIU patients as well as healthy volunteers: 64.3 ± 12.3 l/h, 55.3 ± 14.7 l/h, and 47.9 – 59.1 l/h for SAR patients, CIU patients, and normal healthy volunteers, respectively.

2-4. Comparison of systemic exposure of fexofenadine after QD and BID

The AUC of fexofenadine after 90 mg BID and 180 QD was not equivalent, however, the degree of the difference may not be clinically significant. On average, 11.8 % larger AUC has been observed after 180 QD.

Linearity in pharmacokinetics of fexofenadine was exhibited at the 120 mg qd regimen, but not in 180 qd. At 180 qd regimen, the steady state AUC 0-24h were 21 % larger than that after single dose. It should be noted that these results of dose proportionality are similar with that reported after administration of capsule 20, 60, 120 and 240 mg BID (NDA 20-625). The oral clearance appeared to be 24 % less at 180 mg QD than 120 QD. Dose adjustment may not be warranted based on this difference due to the large therapeutic index of fexofenadine.

It should be noted that the minimum concentration at the steady state (Cmin) following 180 QD (21.67 ng/ml) appeared to be similar to that following the approved dose of 60 mg BID (24 ng/ml). However, the Cmin following 120 QD is expected to be lower than that following 60 mg BID. The clinical efficacy data needes to be evaluated to see if there is end of efficacy with the 120 mg QD dose.

2-5. Food effect

The degree of food effect i.e., reduction of AUC (16-21 %) and Cmax (14-20 %) on the PK of fexofenadine after administration of tablet appeared highly comparable to that after capsule (21 % of AUC and 14 % of Cmax reduction). It should be noted that dose adjustment has not been warranted based on the food effect for previous capsule formulation (NDA 20-625).

2-6. Gender difference

Population analysis suggests that oral clearance is larger in male CIU adult patients (56.2 l/h in female and 87.4 l/h in male. It should be noted dose adjustment has not been warranted for the capsule formulation based on the gender difference.

2-7. Drug –Drug Interaction

Administration of omeprazole with 120 mg fexofenadine HCl (2x60 mg capsule) did not affect fexofenadine pharmacokinetics.

Administration of 120 mg of fexofenadine HCl (2x60 mg capsule) within 15 min of an aluminum and magnesium containing antacid (Maalox) decreased AUC by 41% and Cmax by 43 %.

Dosage adjustment may not be warranted based on the Maalox coadministration. However, it is recommended that a precautionary statement with respect to the decreased AUC that may result upon concomitant administration of Maalox with Allegra may need to be included in the labeling. It should be recommended that antacids and Allegra should not be coadministered at the same time.

3. COMMENTS TO THE CHEMIST

3-1. The effect of surface area of the drug substance on bioavailability

The effect of surface area of raw material on the bioavailability has been reviewed. There appears to be no correlation between the AUC or Cmax vs. surface area of raw material (Please refer to the individual study review Protocol on PJPR0098)

3-2. The effect of hydration of the drug substance on bioavailability

Tablets manufactured from anhydrous and hydrated material are bioequivalent to each other.

Please refer to the review of the Office of Clinical Pharmacology and Biopharmaceutics of NDA 20-786 submitted 7/21/97 and reviewed on 9/2/97)

3-3. Dissolution specification

In establishing the dissolution method, the sponsor conducted dissolution test in selected media to include pH 1, pH 2, pH 3, and pH 6.8 buffer.

Dissolution behavior was considerably slow and incomplete in pH 1 due to the salting out effect of chloride ion. The dissolution profile of pH 2 and 3 are comparable. The selection of dissolution medium of pH 3 is acceptable.

Fexofenadine released fast from the tablets and the dissolution profile appeared to be similar for 30, 60, 120, and 180 mg.

The sponsor's proposed dissolution specifications are as following:

Apparatus: USP apparatus II (Paddle)
Speed: 50 rpm
Temperature: 37 °C
Medium: 0.001 M HCl
Volume: 900 ml (30 and 60 mg tablets) or 1800 ml (120 and 180 mg tablets)
Q: Two time points at 30 min Q , at 45 min Q

Upon reviewing the dissolution data of bio-batches including full production scale batches, this reviewer recommends a dissolution specification of Q % at 30 min for all strengths of Allegra tablets. (Please refer to the Dissolution review section of the present review.)

4. LABELING COMMENTS

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information

5. COMMENTS TO THE SPONSOR

5-1. It is recommended that a precautionary statement with respect to the decreased AUC that may result upon concomitant administration of Maalox with Allegra may need to be included in the labeling under the section of drug interaction.

5-2. It is recommended that the sponsor further analyze the data obtained from the protocol PJPR 0037 entitled "Pharmacokinetics and pharmacodynamics of fexofenadine HCl in 6-12 year old

pediatric patients with allergic rhinitis" utilizing PK-PD modeling technique to establish the fexofenadine concentration vs. effect relationship.

5-3. It appeared that the analysis of variance with terms of sequence was not done for each pharmacokinetic parameter in PJPR0045. Please re-analyze the data including sequence and submit the result for the study.

5-4. The dissolution method proposed by the sponsor is acceptable. However, the dissolution specification should be changed to Q % in 30 min.

5-5. Based on all the pharmacokinetic data, 30 mg BID appears to be an appropriate starting dose in children 6-11 years old. Therefore, the sponsor is asked to provide the sponsor's rationale for the proposed 60 mg BID dosage regimen for the children. Analysis of the combined data from the two trials, K-98-0093-D and K-98-0119-D, by our pharmacometrics reviewer, indicates no difference in clearance between adults and children. This conclusion is different from the sponsor's conclusion. Therefore, the sponsor is also requested to utilize population pharmacokinetic approach and compare the pharmacokinetics of fexofenadine in adults with that in children using the data from K-98-0093-D and K-98-0119-D.

6. RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed and found NDA 20-872 to be acceptable provided that the above "Labeling comments" and "Comments to the sponsor" are addressed satisfactorily and dissolution specifications are agreed by the sponsor. Please forward the above "Labeling comments" and "Comment to the sponsor" to the sponsor, as appropriate.

/S/ 7/13/99

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Concurrence /S/ 07/13/99

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7. TABLE OF CONTENTS

8. BACKGROUND

Fexofenadine is a nonsedating, long-acting antihistamine with highly selective peripheral histamine H1-receptor antagonist activity. Fexofenadine (HCl 60 mg b.i.d.) in a capsule dosage form was approved in the US for the treatment of symptoms associated with seasonal allergic rhinitis (SAR) in patients greater than 12 years of age, by the Division of Pulmonary Drug Products on July 25, 1996 (NDA 20-625). The free base of fexofenadine HCl (MDL 16,455) is an active acid metabolite of terfenadine.

The sponsor developed fexofenadine HCl in lactose-free tablet formulations (Allegra 30 mg, 60 mg, and 180 mg tablets) as alternatives to the approved fexofenadine HCl capsule.

The purpose of the present application is to support following indications and dosage regimens:

- SAR (Age over 12 years): 180 mg QD; 60 mg QD as a starting dose for renal patients
- SAR (Age 6-12 years): 30 or 60 mg B.I.D.
- Chronic idiopathic urticaria (CIU) (Age over 12 years): 60 mg B.I.D.; 60 mg QD as a starting dose for renal patients
- CIU (Age 6-12 years): 30 or 60 mg B.I.D.

In support of the new tablet, new indication, new dosage regimen, and new population, the sponsor has conducted a complete safety and efficacy program for SAR and CIU patients age of over 12 years. For patients of age 6-12 years, the pediatric rule is being utilized to support registration in that population. The sponsor conducted two clinical trials for SAR children patients. For the CIU indication for children, clinical trial is not conducted.
In addition to the clinical trials, a total of 15 clinical pharmacology studies/analyses have been reported. (Please refer to the Appendix VI. Biopharmaceutic study summary tables). One study, protocol PJPR0033, has not been reviewed, since the study is only a pilot study for formulation development purpose.

9. DRUG SUBSTANCE AND DRUG PRODUCT

9-1. Drug substance

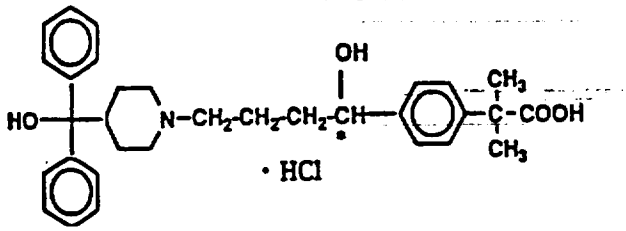


Figure. Chemical structure of fexofenadine HCl

Chemical Name: benzeneacetic acid,
4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]-a,a-dimethyl hydrochloride, (±)

Other Name: Fexofenadine HCl
Empirical Formula: $C_{32}H_{39}NO_4$ HCl
Molecular Weight: 538.13

Physical properties
Appearance: Crystalline fine white to off-white powder

Solubility: Slightly soluble in water (3.6 mg/mL) Freely soluble in methanol Soluble in ethanol. Slightly soluble in chloroform and in hexane.

Fexofenadine HCl contains a basic amine and an acidic carboxylic acid group. As a result, the aqueous solubility is pH sensitive, showing a maximum at pH 3 (cationic), a minimum from pH 4-8 (zwitterionic), and another maximum at pH 9 (anionic).

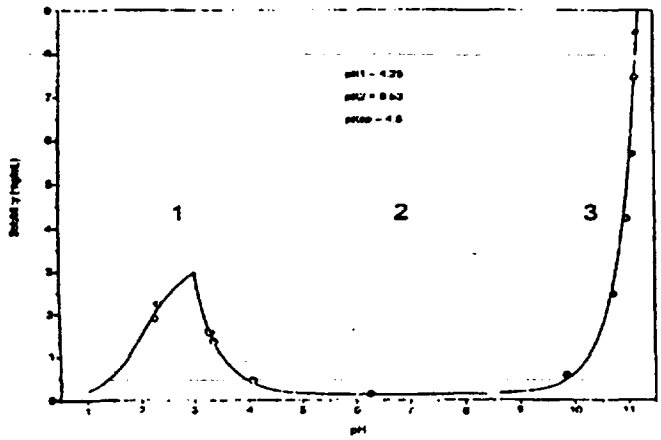


Figure: Solubility vs pH

Partition Coefficient: The n-octanol/water partition coefficient remains relatively constant over the pH range of 3 to 8, varying from 2.6 to 2.0.

9-2. DRUG PRODUCT

Following table shows that the proposed tablet formulations in different strengths are compositionally proportional:

	30 mg tablet	60 mg tablet	120 mg tablet	180 mg tablet
Component	Weight (mg/tablet)	Weight (mg/tablet)	Weight (mg/tablet)	Weight (mg/tablet)
Tabble core				
Fexofenadine HCl	30.00	60.0	120.0	180.0
Microcrystalline Cellulose (Avicel PH 101)				
Pregelatinized starch (Starch 1500)				
Croscarmellose sodium(ixtragranular)				
Microstalline cellulose (Avicel PH 102)				
Croscarmellose sodium(extragranular)				
Magnesium Stearate				
Water purified				
Total core weight				
Peach aqueous coating suspension				
Colloidal silicon dioxide (M-7)				
Hydroxymethylcellulose E-15				
Hydroxymethylcellulose E-5				
Povidone				
Titanium Dioxide				
Polyethylene glycol 400				
Pink iron oxide blend				
Yellow iron oxide blend				
Water, purified				
Total solids				
Fexofenadine HCl film-coated tablets				
Core tablet				
Coating suspension				
Total coated tablet weight				

Reviewer's comment:
The to-be-marketed tablet formulations are compositionally proportional.
All the clinical pharmacology studies have been conducted using appropriate formulations, i.e. to-be-marketed formulation (Please refer to the Appendix I for the quantitative composition of the investigational fexofenadine HCl tablet batches.)

10. ANALYTICAL METHOD

Reviewer's comment on the analytical method:
The analytical method employed in the present submission is appropriate and acceptable.
(For analytical performance in individual study, please refer to the individual study review.)

11. PHARMACOKINETICS (GENERAL INFORMATION)
The following information has been obtained after administration of capsule formulation (NDA 20-625).

11-1. Absorption
Fexofenadine is rapidly absorbed following oral administration of fexofenadine HCl with tmax occurring from 1 to 3 hours postdose. The intrasubject variability estimate of single and multiple dose AUCs range from 20.62% to 29.31 %. High-fat breakfast coadministration reduces AUCinf to 83.05% and Cmax values to 89.06% of the fasted values, respectively. This magnitude of interaction is not considered clinically important and dose adjustment has not been warranted.

11-2. Distribution
Fexofenadine is 69.4%, 62.3 %, and 66.3 % bound to plasma proteins (albumin and alpha-1 -acid glycoprotein) in healthy, renally, and hepatically impaired subjects, respectively. It distributes into plasma more extensively than whole blood and saliva.

11-3. Metabolism
A total of 80.04% and 11.48% of ingested dose is excreted in the feces and urine, respectively. Fexofenadine is the only major species identified in both matrices, indicating this drug undergoes minimal biotransformation. Biliary and renal excretion are considered the principal routes of elimination for fexofenadine.

11-4. Dose proportionality
The plasma concentration profile is characterized by a bi-exponential decline with an apparent elimination half-life ranging from 11 to 16 hours. Fexofenadine exhibits linear pharmacokinetics over the dosing range of 20 to 120 mg b.i.d. above which there is a small departure from dose proportionality. Single dose pharmacokinetics of fexofenadine are predictive of steady-state systemic drug exposure at a twice daily dosing regimen.

11-5. Stereoisomers
Fexofenadine HCl is a racemic mixture of two enantiomers which have similar potency in binding to histamine-H1 receptors. The plasma concentration ratio of the R(+) isomer versus the S(-) isomer is 62:38 which is independent of time or dose changes. The mean concentration ratio approximates 50:50 in the urine.

11-6. Population pharmacokinetics in patients with seasonal allergic rhinitis
The pharmacokinetics of fexofenadine in patients suffering from seasonal allergic rhinitis (SAR) are similar to those in healthy subjects after administration of allegra capsule.
Oral clearance in male patients is 14% to 17% higher than in female patients.
The apparent volume of distribution increases with body weight. Systemic exposure of fexofenadine appears to be dose proportional in SAR patients over the 40 to 240 mg b.i.d. range.
Peak fexofenadine concentration was similar between patients 12 to 16 years of age and adult patients.

11-7. Special populations pharmacokinetics
The pharmacokinetics are different between genders, as steady-state AUC and Cmax values in healthy female subjects are 33% and 46% higher than those of the healthy male subject values. Hepafic disease has little impact on the absorption and disposition of fexofenadine. Systemic drug exposure increases 62.5% in elderly and 88.5% in renally impaired patients.

11-8. Drug-drug interactions
Ketoconazole and erythromycin increase the systemic bioavailability of fexofenadine by 159.31% and 103.38%, respectively, possibly due to an alteration in the absorptive phase as the elimination phase of the process remains unchanged. There is no effect on safety parameters, including QTC, indicating dosage adjustment is not necessary. Fexofenadine has no effect on the pharmacokinetics of ketoconazole and erythromycin.

11-9. Pharmacodynamics
Fexofenadine HCl inhibits histamine mediated skin wheal and flare responses following histamine injection. The extent of inhibition is related to plasma drug concentrations according to a curvilinear relationship; percent inhibition in flare and wheal area reaches a maximum, despite continuing increase in concentration beyond 200 ng/mL. Following a single oral dose administration, peak inhibition occurs from 3 to 6 hours postdose, followed by a steady decline of drug effect. There is a positive dose-response relationship between the 10 and 130 mg dose, above which little increase in skin wheal and flare inhibition is apparent. The 40 mg dose is considered the minimum pharmacologically active dose.

12. REVIEW ON THE COMPARATIVE PHARMACOKINETICS OF FEXOFENADINE AFTER ADMINISTRATION OF TABLET FORMULATIONS AND THAT OF CAPSULES

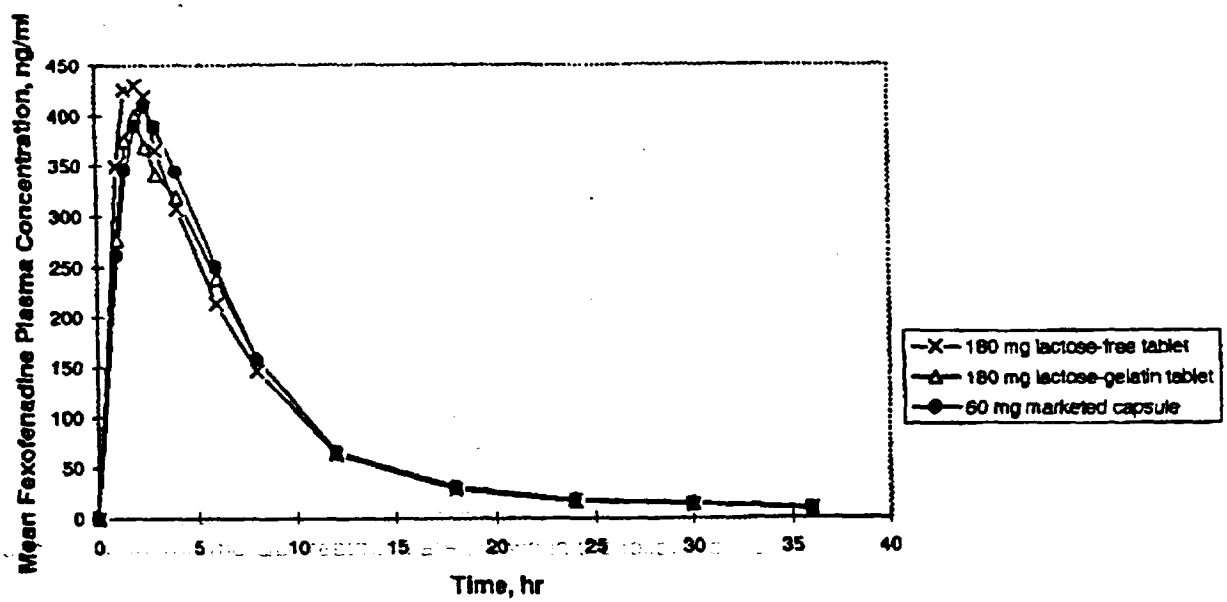
12-1. Bioequivalence:

The bioequivalence of fexofenadine lactose-free tablet in relation to the marketed capsule was evaluated at two tablet strengths, 60 mg and 180 mg.

12-1-1. 180 mg lactose-free tablet:

The bioequivalence of the 180 mg lactose-free tablet compared to the marketed capsules was evaluated in a pivotal trial following oral administration of a 180 mg single dose to healthy, male subjects (Protocol PJPR0045). The adjusted mean AUCinf for this tablet was 3091.31 ng·hr/mL, and the Cmax was 443.75 ng/mL.

The 90% confidence intervals for these parameters compared to the capsule were within 80% to 125%. Mean plasma concentration versus time profiles for the lactose-free tablet (treatment A), marketed capsule (treatment C), and the back-up formulation (lactose-gelatin tablet, treatment B) are illustrated in the following Figure. Mean pharmacokinetic parameters and statistical comparisons are given in *the following table.*



Plasma fexofenadine concentrations following administration of 180 mg lactose-free and lactose gelatin tablet and 60 mg marketed capsule to healthy male volunteers

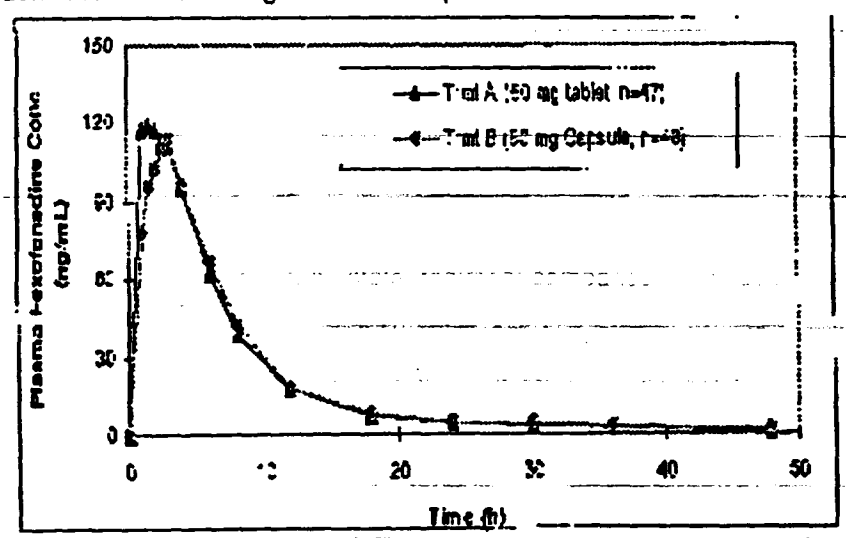
Treatment comparisons for key pharmacokinetic parameters calculated from plasma fexofenadine concentrations following 180 mg doses of fexofenadine HCl to healthy male volunteers

Parameter	*Trmt*	*Mean*	%CV	*pair*	Ratio (%)	90 % CI
AUC inf	A	3330.08	39.49	A/C	95.17	86.0,105.3
ng·h/ml	B	3192.02	36.84	B/C	97.08	87.7,107.5
	C	3396.65	32.60	-	-	-
Cmax	A	494.24	55.24	A/C	100.02	87.3,114.6
(ng/mL)	B	453.64	44.27	B/C	93.72	81.7,107.5
	C	476.32	40.98	-	-	-
Tmax	A	2.0	34.15	A/C	76.17	67.1,86.4
(h)	B	2.5	53.70	B/C	90.04	79.3,102.3
	C	2.6	38.77	-	-	-
Treatment A: Single dose oral administration of 1 x 180 mg fexofenadine hydrochloride lactose-free (with Ac-Di-Sol as disintegrant) tablet formulation.						
Treatment B: Single dose oral administration of 1 x 180 mg fexofenadine hydrochloride lactose-gelatin tablet formulation.						
Treatment C: Single dose oral administration of 3 x 60 mg fexofenadine hydrochloride hard-gelatin capsule formulation.						

12-1-2. 60 mg lactose-free tablet:

The bioequivalence of the 60 mg lactose-free tablet compared to marketed capsule was evaluated in a bioequivalence study following oral administration of a 60 mg single dose to healthy, male subjects. The adjusted mean AUCinf for the lactose-free tablet was 926.07 ng·hr/mL, and the Cmax was 134.41 ng/mL. The 90% confidence intervals for the ratio of these parameters compared to the capsule were within 80% to 125%. Mean plasma concentration versus time profiles for the lactose-free tablet and marketed capsule are illustrated in *Figure*. Mean pharmacokinetic parameters and statistical comparisons are given in *Table*.

Figure presents the mean plasma fexofenadine concentration versus time profiles following administration of 60 mg tablet and capsule.



Following table presents the key mean fexofenadine pharmacokinetic parameters for each treatment and pairwise treatment comparisons.

Table. Treatment comparisons for key pharmacokinetic parameters calculated from plasma fexofenadine concentrations following 60 mg doses of fexofenadine HCl to healthy male volunteers

Parameter	*Treatment*	*Mean*	%CV	*pair*	Ratio (%)	90 % CI
AUC inf ng·h/ml	A	973.77	33.36	A/B	100.29	(93.3,107.8)
	B	958.98	30.39			
Cmax (ng/mL)	A	141.80	34.84	A/B	109.57	(100.1,120.0)
	B	131.25	42.23			
Tmax (h)	A	1.7	49.07	A/B	66.48	(57.8,76.5)
	B	2.49	34.04			
A: Fexofenadine HCl (1 x 60 mg) tablets (Lot # RD9723) given as a single dose (n=47) B: Fexofenadine HCl (1 x 60 mg) ALLEGRA capsules (Lot # 98053501) given as a single dose (n=48)						
For Treatment A, the tmax median value was 1.5 h and ranged from 1 to 4 h. For Treatment B, the tmax, median value was 2.5 h and ranged from 1 to 4 h.						

Reviewer's comment:
The data analyses of bioequivalency studies are appropriate and demonstrated the bioequivalence of the lactose-free tablets (60 and 180 mg) to the marketed capsule (60 mg). These two studies are sufficient to support to the other strengths (30 and 120 mg tablets), provided that the formulations are compositionally proportional, and show similar dissolution profiles across the different strengths.

12-2. Effect of food on fexofenadine bioavailability :

The effect of food on the bioavailability of the lactose-free tablets was evaluated in healthy, adult male subjects using two strengths of tablets (180 and 120 mg: Protocol PJPR 0062 and 0098).

Compared to administration under fasted conditions, high-fat breakfast co-administration reduces Cmax and AUCinf by 20% and 21 %, respectively, for the 180 mg tablet, and 14% and 15%, respectively, for the 120 mg tablet. This magnitude of interaction is similar to the marketed capsule 60 mg (21 % reduction of AUCinf and 14 % reduction of Cmax).
It should be noted that the dose adjustment due to the food effect was not considered in the case of capsule due to a wide therapeutic index for this product.

Results of 180 mg tablet study:
Results are summarized in the following figure and table.

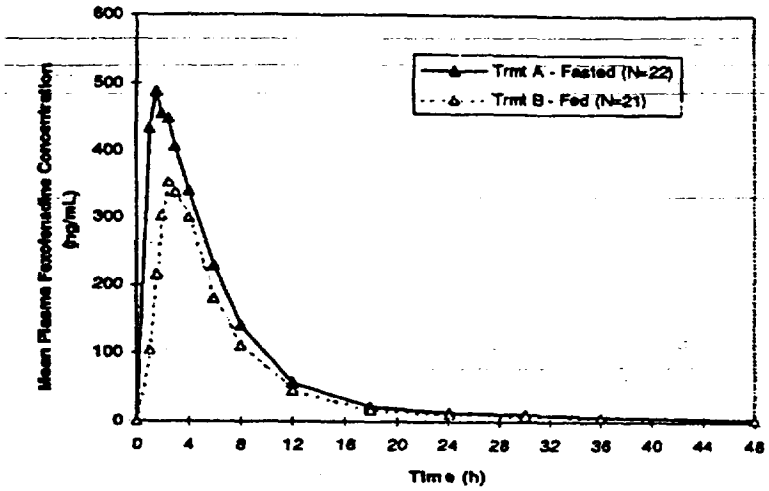


Figure. Mean fexofenadine plasma concentration versus time profile following oral administration of a single 180 mg dose of fexofenadine HCl lactose-free tablet to fasted or fed healthy male subjects

Table. Treatment comparisons for key plasma fexofenadine pharmacokinetic parameters

Parameter	*Treatment*	*Mean*	%CV	*pair*	Ratio (%)	90 % CI
AUC inf	A	3462.92	52.21			
ng·h/ml	B	2582.15	26.11	B/A	78.9	68.3, 91.1
Cmax	A	559.91	65.39			
(ng/mL)	B	399.62	32.07	B/A	80.1	64.0, 100.1
Tmax	A	2.18	54.57			
(h)	B	2.57	32.12	B/A	121.6	96.8, 152.9
Treatment A: One 180 mg fexofenadine HCl tablet (Lot RG9529) given as a single dose to fasted subjects Treatment B: One 180 mg fexofenadine HCl tablet (Lot RG9529) given as a single dose to subjects after a high fat breakfast.						

The ratio of the mean fexofenadine AUCinf value for fed subjects compared to fasted subjects was 79%. The 90% confidence interval (CI) for this ratio was 68% to 91 %.
The ratio of the mean fexofenadine Cmax value for fed subjects compared to fasted subjects was 80%, respectively. The 90% confidence intervals (CI) for the ratio was 64% to 100%.

Results of 120 mg tablet:

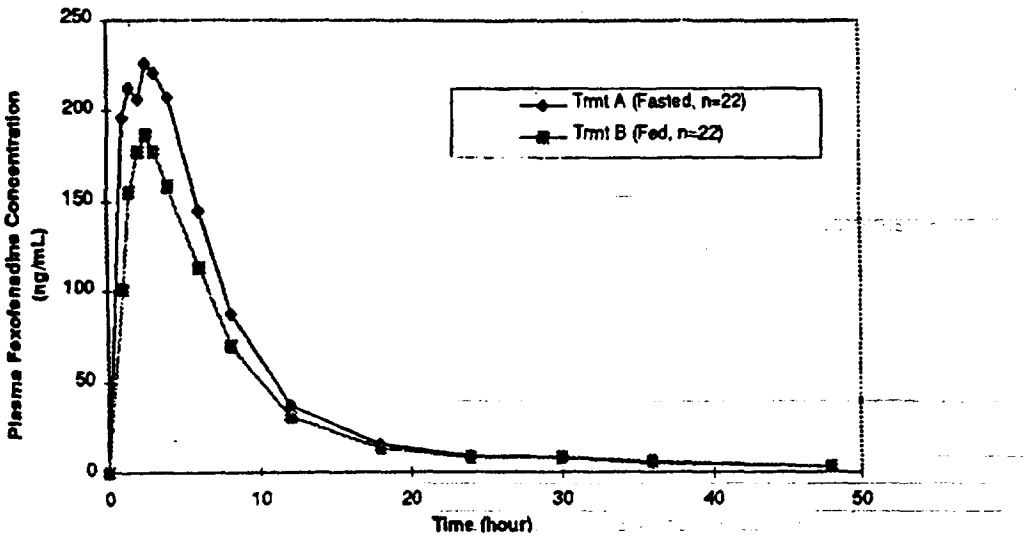


Figure. Mean fexofenadine plasma concentration versus time profile following oral administration of a single 120 mg dose of fexofenadine HCl lactose-free tablet to fasted or fed healthy male subjects

Table. Treatment comparisons for key plasma fexofenadine pharmacokinetic parameters

Parameter	*Treatment*	*Mean*	%CV	*pair*	Ratio (%)	90 % CI
AUC inf	A	2013.66	38.08			
ng·h/ml	B	1642.16	27.61	B/A	84.88	(75.3,95.7)
Cmax	A	289.31	47.86			
(ng/mL)	B	235.81	30.96	B/A	85.90	(72.7,101.5)
Tmax	A	2.48	48.04			
(h)	B	2.57	53.50	B/A	102.29	(86.2,121.4)

A: One 120 mg fexofenadine HCl tablet (Lot # RJ9729) given as a single dose to fasted subjects (n=22)
B: One 120 mg fexofenadine HCl tablet (Lot # RJ9729) given as a single dose to subjects after a high fat breakfast (n=22)

For both treatments A and B, the tmax median was 2.5 h with values ranging from 1 to 6 h.

12-3. Effect of surface area of drug substance on absorption

12-3-1. Bioavailability of fexofenadine HCl tablets made with raw material of different surface areas

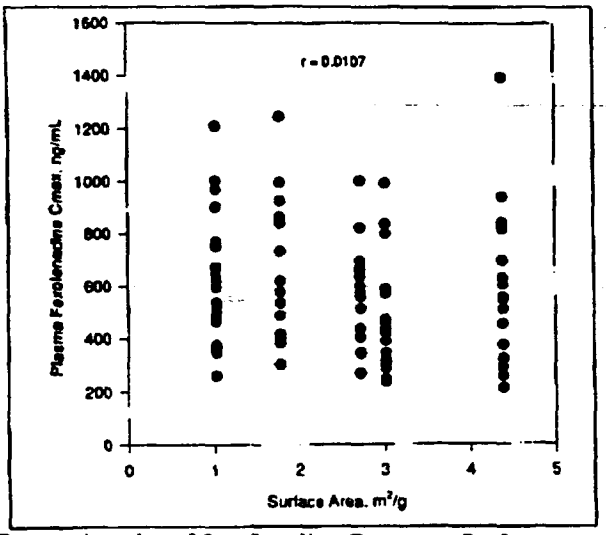
The bioavailability of the lactose-free tablet made with anhydrous fexofenadine HCl raw material of different surface areas was evaluated in healthy, adult male *subjects(Protocol PJPR0071).*

Cmax values are not in the regulatory range for bioequivalence (80-125 % of confidence interval). No relationship, however, can be observed between surface area and AUC within the surface area range of 1.03 m^2/g to 4.39 m^2/g. A similar lack of relationship was also observed between surface area and fexofenadine Cmax. These data indicates that there is no relationship between surface area and bioavailability.

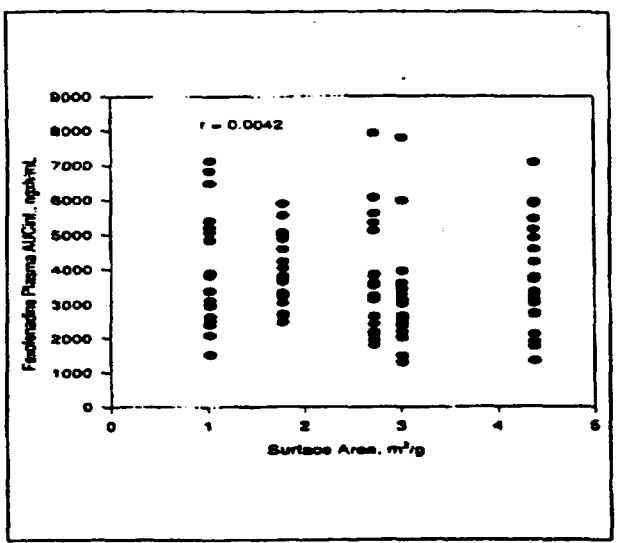
Results:

Bioavailability of fexofenadine tablets made with different surface area raw material

The relationship of fexofenadine AUC to surface area for all anhydrous treatments was evaluated by regression analysis. These data are illustrated in the following Figure,



Regression plot of fexofenadine C max vs. Surface area



Regression plot of fexofenadine AUCinf vs. Surface area

Surface area does not appear to have a relationship to AUC. The correlation coefficient was less than 0.01, indicating that these parameters are not correlated. A similar lack of relationship was also observed between surface area and Cmax (r=0.0107). Statistical comparisons of AUC_{∞}, Cmax and tmax are given in the following table.

Table. Treatment comparisons for pharmacokinetic parameters following administration of 180 mg tablets made with raw materials of different surface areas

Parameter	*Treatment*	*Mean*	%CV	*pair*	Ratio (%)	90 % CI
AUC inf	A	3805	41	A/D	99.94	88.3,113.1
ng·h/ml	B	3145	49	B/D	81.78	72.2, 92.6
	C	3919	26	C/D	104.68	92.4, 118.5
	D	3924	42			
	F	3791	44	F/D	94.24	83.1, 106.8
Cmax	A	571	51	A/D	88.94	71.8, 110.1
(ng/mL)	B	495	49	B/D	74.85	60.4, 92.8
	C	627	41	C/D	98.97	79.8, 122.8
	D	614	41			
	F	554	35	F/D	87.02	70.0, 108.1
Tmax	A	2.08	53	A/D	109.23	87.9, 135.8
(h)	B	1.79	43	B/D	88.73	71.2, 110.5
	C	1.74	35	C/D	92.12	73.9, 114.8
	D	2.00	56			
	F	2.08	52	F/D	94.65	75.9, 118.1

Treatment A: Anhydrous, 4,.39 m^2/g
Treatment B: Anhydrous, 3.02 m^2/g
Treatment C: Anhydrous, 1.79 m^2/g
Treatment D: Anhydrous, 1.03 m^2/g, Reference Treatment
Treatment F: Anhydrous, 2.73 m^2/g

12-3-2. Effect of hydration of drug substance on absorption:
The comparison of the relative bioavailability of a tablet containing anhydrous drug substance to a tablet containing the hydrated drug substance has been reviewed and the two fexofenadine tablets are shown to be bioequivalent (Please refer to the Biopharm review: N20-786; allegra-D, submission date 7/21/97, reviewed on 9/2/97).

12-4. Comparison of pharmacokinetics after QD and BID
At equal total daily doses, fexofenadine exhibits similar pharmacokinetics whether administered once- or twice daily. Steady state AUC_τ is about 2 and 21 % greater than single dose AUCinf at 120 and 180 mg q.d., respectively. (Please refer to the present individual study review on protocol PJPR0068 and 0098) . These data support the QD dosage regimen of 120 or 180 mg tablets provided this dose is shown to be safe and effective.

Mean plasma fexofenadine concentration-time profiles on day 8 for the 90 mg BID treatment compared to 180 mg QD treatment are shown in the following Figure.

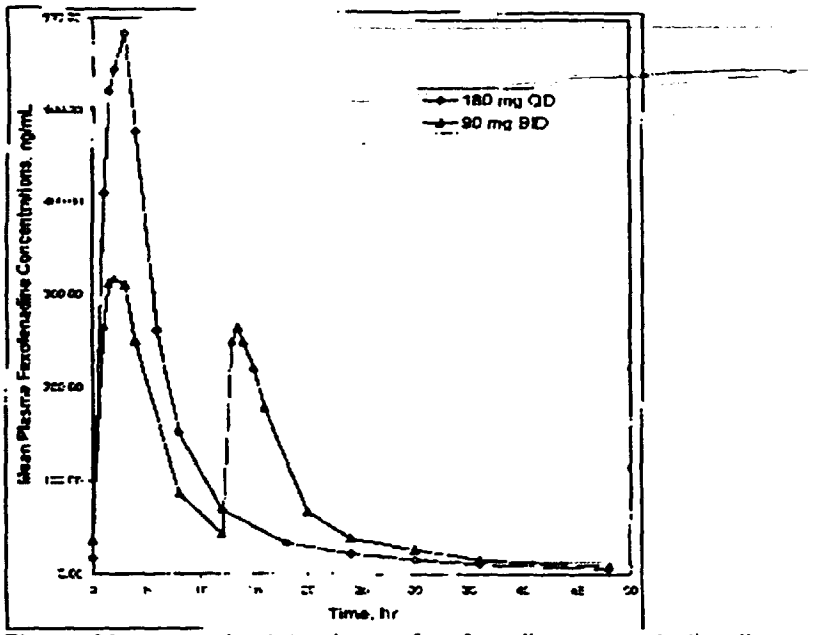


Figure. Mean steady state plasma fexofenadine concentration-time profiles following oral administration of 180mg QD or 90 mg BID fexofenadine HCl to normal healthy subject.

Table. Treatment comparisons for key steady-state fexofenadine pharmacokinetic parameters following 180 mg QD (Treatment A) compared to 90 mg BID (Treatment B)

Parameter	Trmt	Mean	%CV	Pair	Ratio (%)	90% CI
AUC ss 0-24 ng h/ml	A B	3874 3515	32 36	A/B	111.8	96.6, 129.5
CL po,ss l/h	A B	47.9 52.87	32 30	A/B	89.4	77.2, 103.6
t1/2 ss h	A B	11.68 11.28	40 32	A/B	102.4	90.0, 116.6
Cmax,ss ng/ml	A B	681.43 396.17	38 42	A/B	177.8	150.8, 209.8
Cmin,ss ng/ml	A B	21.67 36.28	31 31	A/B	60.04	53.1, 67.9
tmax,ss hr	A B	2.3 2.2	41 46	A/B	106.35	85.1, 132.9

Table. Single dose to steady-state treatment comparisons for key pharmacokinetic parameters for 180 mg QD regimen (Treatment A)

Parameter	Single dose/ Steady state	Mean	%CV	Pair	Ratio (%)	90% CI
AUC * ng h/ml	SD SS	3313 3874	47 32	SS/SD	120.93	106.6, 137.1
CL po l/h	SD SS	59.09 47.91	36 32	SS/SD	82.70	72.9, 93.8
t1/2 h	SD SS	12.52 11.68	24 40	SS/SD	90.82	80.7, 102.2
Cmax ng/ml	SD SS	568.44 681.43	59 38	SS/SD	128.14	109.2, 150.4
tmax hr	SD SS	2.0 2.3	49 41	SS/SD	116	91.3, 147.4

* For single dose AUC inf and for steady state AUC 0-24 hours were compared.

The mean plasma concentration versus time profiles after 120 mg single dose and 120 mg QD to steady state are illustrated in the following Figure and the pharmacokinetic parameters and treatment comparison are summarized in the following table.

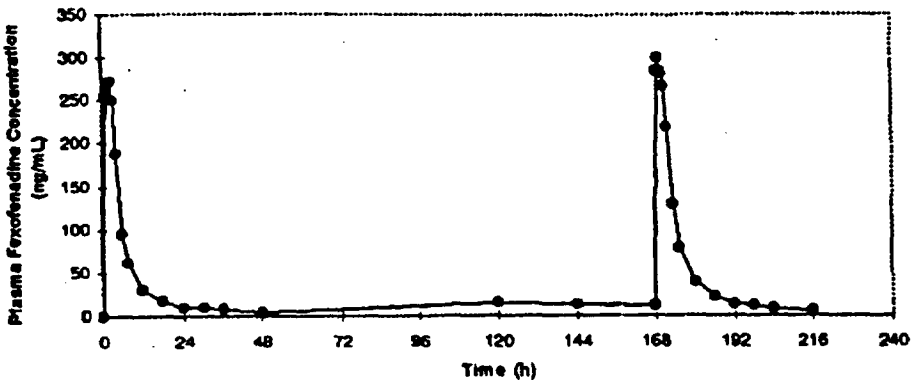


Figure: Mean single dose and steady state plasma fexofenadine concentration-time profile following oral administration of 120 mg QD fexofenadine HCl to healthy male subjects.

Table. Single dose to steady-state treatment comparisons for key pharmacokinetic parameters for 120 mg QD regimen

Parameter	Single dose/ Steady state	Mean	%CV	Pair	Ratio (%)	90% CI
AUC * ng h/ml	SD	1978	35.74			
	SS	2033	41.42	SS/SD	101.82	92.4, 112.2
CL po l/h	SD	64	37.8			
	SS	63	37.55	SS/SD	98.21	89.1, 108.2
t1/2 h	SD	16.63	36.52			
	SS	15.27	35.12	SS/SD	91.92	82.4, 102.5
Cmax ng/ml	SD	323.89	43.78			
	SS	348.91	49.60	SS/SD	107.08	93.0, 123.4
tmax hr	SD	2.02	42.80			
	SS	1.89	51.04	SS/SD	91.25	76.2, 109.3

* For single dose AUC inf and for steady state AUC 0-24 hours were compared.

12-5. Comparison of Pharmacokinetics in children to adult

Following oral administration of 30 mg and 60 mg dose to pediatric patients, fexofenadine exhibits dose-proportional pharmacokinetics. At equal doses, fexofenadine AUCinf in pediatric patients is estimated to be about 56 % greater than in healthy adult subjects. Based upon pharmacokinetic data in pediatric patients, a 30 mg bid dose will provide fexofenadine concentrations that are associated with efficacious doses (60 mg bid) in adult. (Please refer to the present individual study review on protocol PJPR0037).

Table. Summary of NONMEM Population Parameter Estimates

Parameter	*Population Model*	*Parameter Estimate for Adult Subjects Mean(±SD)*	*Parameter Estimate for Pediatric Patients*
AUC inf (ng hr/ml) *	AUC = 8260 / weight $^{0.354}$	1774(±433)	2773(±687)
CL po (L/h)	CLpo = 25.4 · BSA**	50.7 (± 16.0)	30.3 (± 8.3)
C max (ng/ml)	C max = 484 / BSA**	250(±52)	460 (± 118)

* Data for AUC(inf) and Cmax have been dose normalized to the 80 mg dose.
** Body Surface Area (BSA, m^2) = weight $^{0.51456}$ * height $^{0.42246}$ · 0.0235 (Gehan and George formula)

Reviewer's comment on the dose for 6-12 years old children:.
When the clearance values in children after oral administration of fexofenadine was compared to that of adult using all the available data including or excluding spare sample data from clinical trials, clearance in pediatric patients appeared to be 40 % less than that of adult. This result is comparable with the sponsor's report. All the results indicate that approximately half of the adult dose will result in similar systemic exposure in children.

Based on the linear pharmacokinetics of fexofenadine, the exposure in the children after 60 mg bid seems to be relatively high (comparable with 240 mg daily dose in adult). Although fexofenadine is a relatively wide therapeutic index drug, a dose of 60 mg bid seems to be not appropriate for children due to the following reasons:

(1) Pharmacokinetic data supports a dose in children equivalent to half the approved dose in adults.
(2) From the wheal and flare analysis, it should be noted that 60 mg dose showed only a slightly increased efficacy compare to 30 mg bid, indicating that 60 mg bid may not proved any greater benefit. This was also showed in clinical trials according to the Medical Officer. (Please refer to the following figures, table and individual study review on PJPR0037)

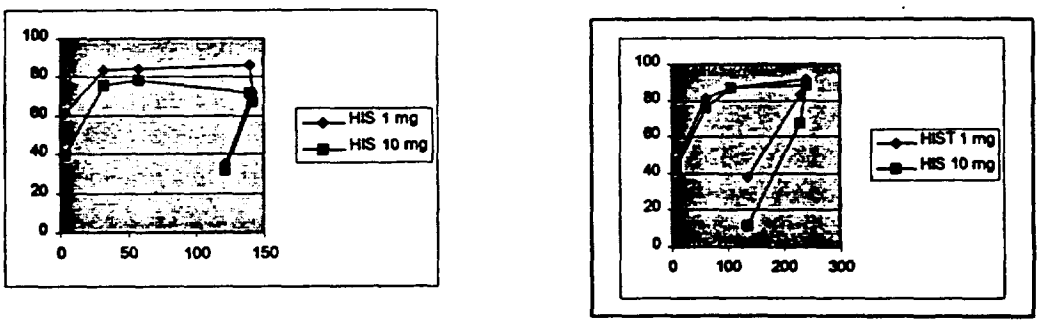


Figure. Concentration vs. inhibitory effect of fexofenadine 30 (left panel) or 60 mg (right panel) p.o. on flare induced by histamine 1 or 10 mg.

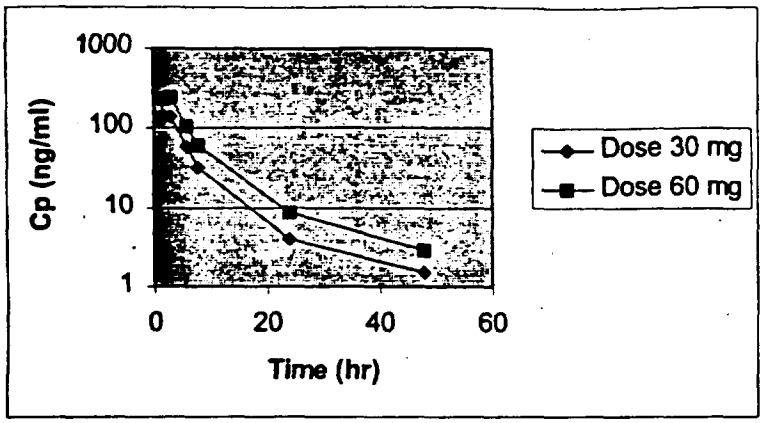


Figure: Comparison of the plasma concentration of fexofenadine after administration of 30 mg and 60 mg dose in 6-12 years of child SAR patients.

Table. Summary of wheal and flare area percentage inhibitions - mean (CV%)

	Wheal				Flare			
	Emax (%)		Eavg (%)		Emax (%)		Eavg (%)	
Histamine level	1 mg	10mg	1 mg	10mg	1 mg	10mg	1 mg	10mg
30mg fexofenadine	84.76 (11)	76.84(19)	44.55(44)	37.70(61)	92.26(7)	87.55(9)	72.16(22)	59.73(23)
60mg fexofenadine	88.78(10)	78.91(11)	54.72(39)	43.47(46)	93.29(6)	91.18(5)	67.62(26)	62.58(24)

Treatment A (60 mg) generally produced maximum observed effects that were only slightly greater than produced by treatment B (30 mg). Similar results were recorded when comparing the Average Effect (Eavg - Area Under Effect Curve over 24 hours divided by 24, AUEC[0-24h]/24). These results indicate that 30 mg dose is almost the maximum effective dose. For example, wheal inhibition effect on histamine 10 mg induced wheal appeared to be highly comparable between 30 and 60 mg of fexofenadine, even though the plasma concentration is almost 2 times higher with 60 mg of fexofenadine.
Therefore, knowing that the systemic exposure in children after 30 mg dose is similar with that in adult after 60 mg dose, the dose of 30 mg of fexofenadine is recommended for the children.

It is also recommended that the sponsor analyze the PK-PD modeling study to establish the fexofenadine concentration vs. effect relationship.

12-6. Drug-drug interaction
A drug-drug interaction study has been performed using omeprazole and Maalox.
Administration of a single 40 mg dose of omeprazole with 120 mg fexofenadine HCl (2 x 60 mg capsule) did not affect fexofenadine pharmacokinetics. However, administration of 120 mg fexofenadine HCl (2 x 60 mg capsule) within 15 minutes of an aluminum and magnesium containing antacid (MAALOX) decreased fexofenadine AUC by 41 % and Cmax by 43%.
This interaction is presumably due to binding of fexofenadine HCl to Maalox rather than due to the increased pH.
Dosage adjustment may not be warranted based on Maalox coadministration. However, it is recommended that a precautionary statement with respect to the decreased AUC that may result in upon concomitant administration of Maalox with fexofenadine may need to be included in the labeling.

Table. Treatment comparisons for key pharmacokinetic parameters calculated from plasma fexofenadine concentrations from the study 016455PR0022

Parameter	*Trmt*	*Mean*	%CV	*pair*	Ratio (%)	90 % CI
AUC inf	A	1967	50.4			
ng·h/ml	B	1894	47.5	B/A	101	86 – 119
	C	1101	34.4	C/A	59	51 – 70
Cmax	A	331	52.2			
(ng/mL)	B	329	65.7	B/A	98	80 – 119
	C	177.8	35.4	C/A	57	47 – 69
Tmax	A	2.84	56.1			
(h)	B	2.81	56.3	B/A	102	78 – 135
	C	2.33	63.8	C/A	81	62 - 107

A. Single 111.88 mg dose of MDL 16,455 (given as 120 mg of the hydrochloride salt, MDL 16,455A prepared as two capsules each containinfg 60 mg)

B. Single 20 mg dose of omeprazole approximately 1 0 hours prior to a single 40 mg dose of omeprazole ((2X20 mg), followed 1 hour later by a single 111.88 mg dose of MDL 16,455 as for treatment A.

C. Single 20 ml dose of MAALOX suspension followed 15 minutes later by a single 111.88 mg dose of MDL 16,455 for treatment A.

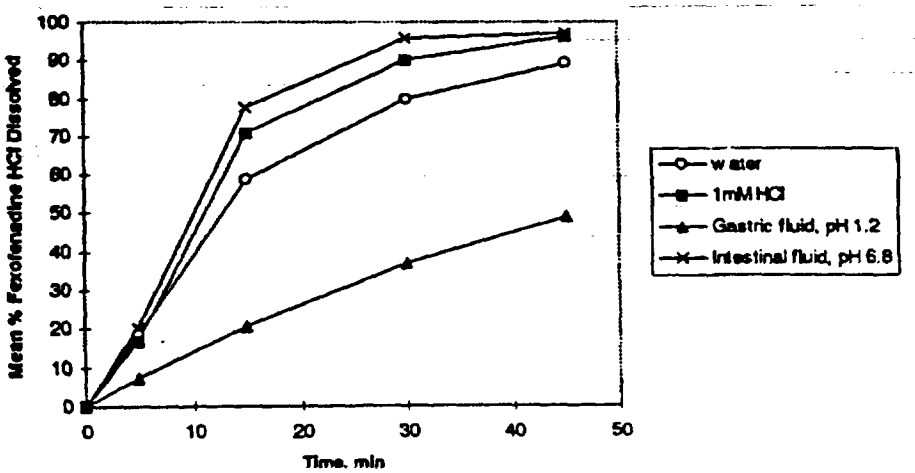
12-7. Population pharmacokinetics

The population analyses showed that the oral clearance values of SAR patients appeared to be comparable to that of CIU patients as well as healthy volunteers: 64.3 ± 12.3 l/h, 55.3 ± 14.7 l/h , and 47.9 – 59.1 l/h for SAR patients, CIU patients, and normal healthy volunteers.
None of the demographic factors, or concomitant medications, had a clinically significant effect on fexofenadine pharmacokinetics. Please refer to the individual study review (Appendix I).

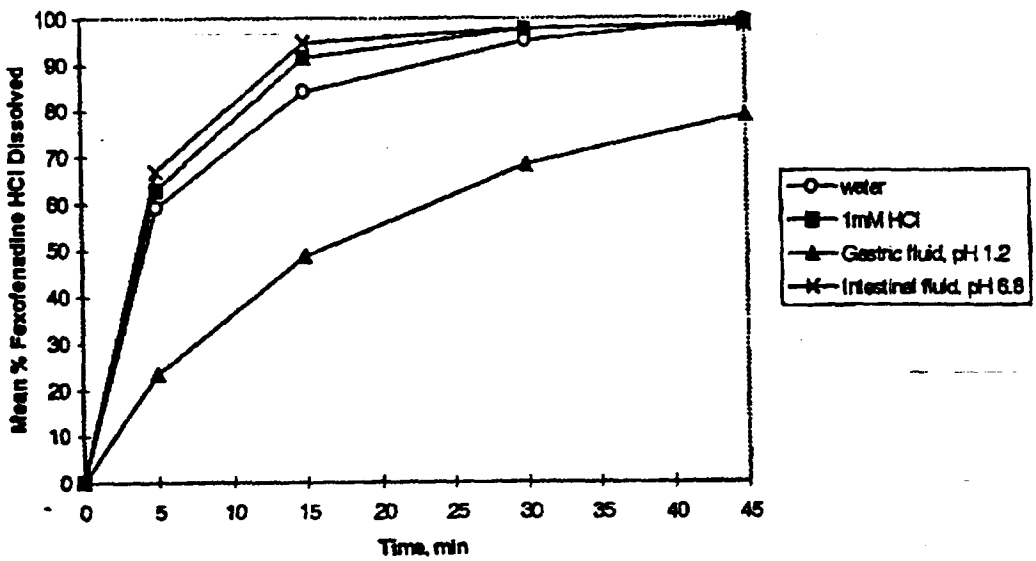
13. DISSOLUTION

In establishing dissolution conditions, the sponsor performed dissolution testing in selected media of pH 1.2, water, pH 3, and pH 6.8 buffer. Dissolution behavior was considerably slow and incomplete in pH 1 due to the salting out effect of chloride ion. The dissolution profile in media of pH 2 and 3 are comparable. The selection of dissolution medium of pH 3 appears to be acceptable.

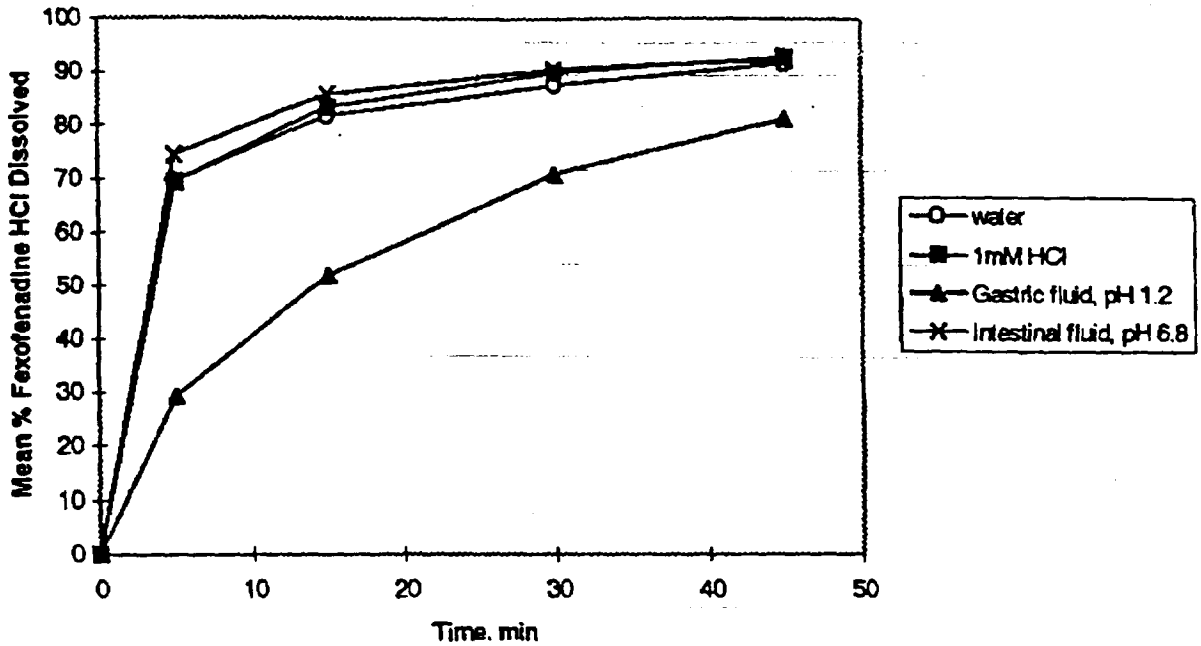
30 mg Tablet



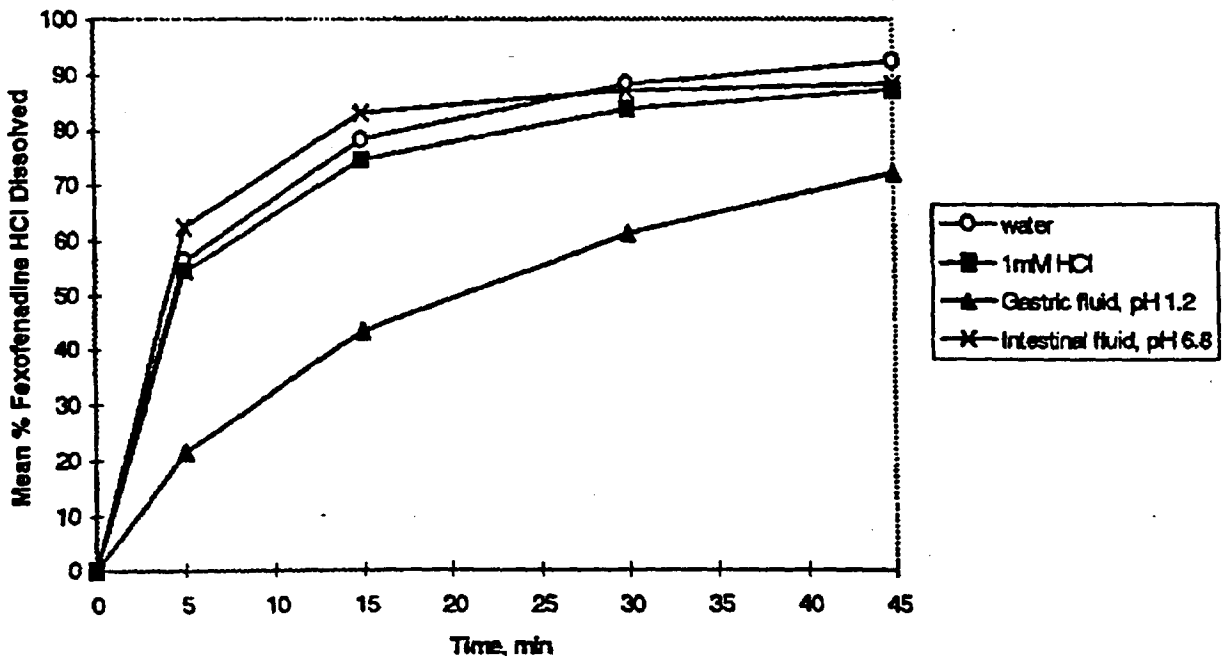
60 mg Tablet



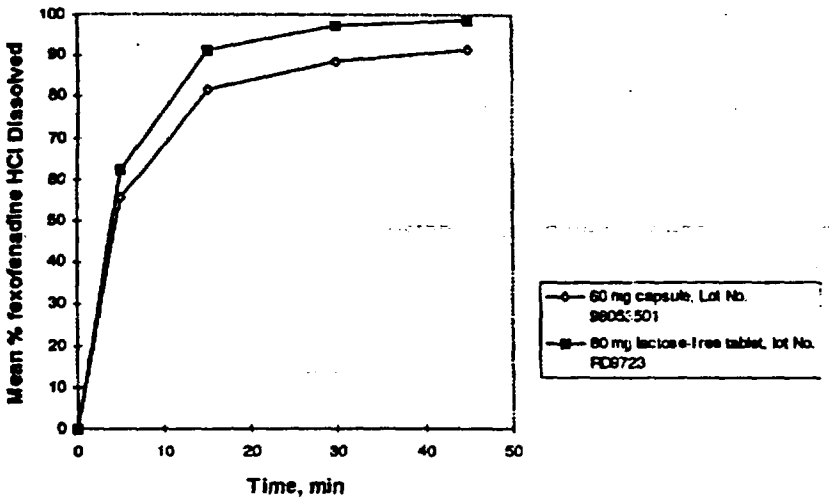
120 mg Tablet



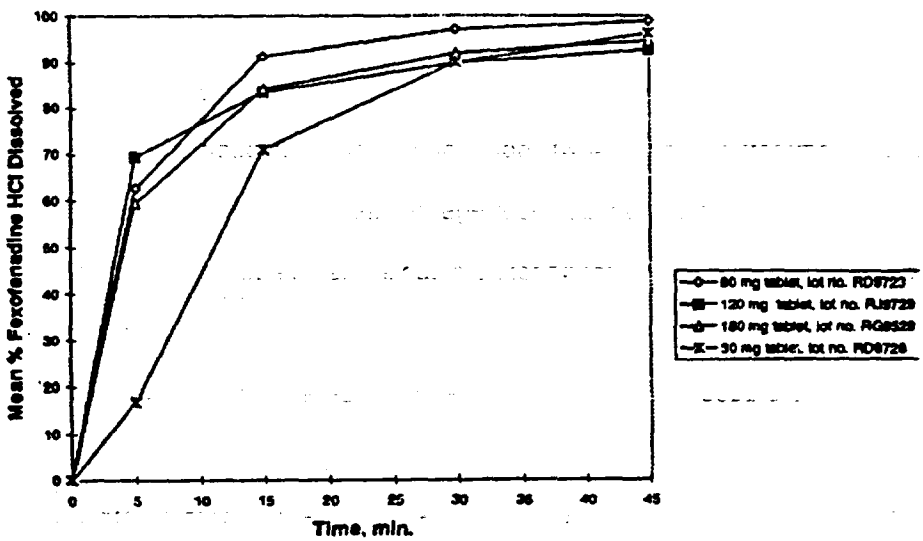
180 mg tablet



Following figure illustrates the typical fexofenadine dissolution profiles of the 60 mg ALLEGRA capsules (deionized water) and the 60 mg lactose-free tablets with AC-DI-SOL (I mM HCl) at 50 rpm. The data indicate that the two formulations have comparable dissolution profiles.



Following figure illustrates typical fexofenadine dissolution profiles for the 30 mg, 60 mg, 120 mg, and 180 mg lactose-free tablets with AC-DI-SOL used in clinical studies. The data show that all four strengths have greater than 85% dissolved at 45 minutes.



The fexofenadine released quickly from the tablets and the dissolution profile appeared to be similar for 60, 120, and 180 mg . The 30 mg tablet has a slower initial dissolution rate. The f2 values for 30 mg tablet in pH 3 medium were 30 compared to 60 mg tablet, 35 compared with 180 tablet, and 33 compared with 60 mg capsule and 38 compared to the 30 mg capsule. Similar values were observed in other media, e.g., distilled water and pH 6.8 as well. The low f2 values are mainly due to the initial slow dissolution rate of 30 mg tablet. However, it should be noted that the initial slow dissolution of

30 mg tablets of the biobatch appeared to have no impact on the pharmacokinetics. In the clinical study (Protocol PJPR0066/0077) in which the 30 and 60 mg tablet batches of the above dissolution profile were used, there was no impact of the dosage strength (30 or 60 mg tablet) on the pharmacokinetics of fexofenadine, indicating that the in vivo performance of the 30 and 60 mg tablet is similar. Also, the 30 mg tablet was evaluated in clinical studies.
The f2 values for 120 mg compared to 180 mg tablet were greater than 50.

Dissolution specification
The sponsor's proposed dissolution specifications are as follows:
Apparatus: USP apparatus II (Paddle)
Speed: 50 rpm
Temperature: 37 °C
Medium: 0.001 M HCl
Volume: 900 ml (30 and 60 mg tablets) or 1800 ml (120 and 180 mg tablets)
Q: Two time points at 30 min Q %, at 45 min Q: %.

Upon reviewing the dissolution data of bio-batches including full production scale batches, this reviewer recommends a dissolution specification of Q %at 30 min for all strengths of Allegra tablets. At this level, 35 of 36 tablets tested would meet the specification. (Please refer to the data attached in the appendix IV.)

APPENDIX I. INDIVIDUAL STUDY REVIEW

APPENDIX I-1. Protocol PJPR0045, Report K-96-0021-D

Title: Pivotal bioequivalence study of 180 mg fexofenadine hydrochloride tablet formulations

Protocol Number: PJPR0045

Project Report Number: K-96-0021-D

Investigator and Location:

Objectives:
The objective of the study as stated in the protocol was to establish the bioequivalence of 180 mg fexofenadine hydrochloride tablet formulations that were representative of full-scale, relative to the capsule formulation administered in pivotal clinical trials.

Formulations:
Following table summarizes the fexofenadine HCl formulations used in this study.

The fexofenadine HCl formulations

Trmt	*Lot Number*	*Formula Number*	*Release Date*	*Dosage Form*	*Strength*	*Batch Size*	*Comments*
A *	RG9529	PJXTX7-005	9/15/95	Lactose-Free Tablet with Ac-Di-Sol ® as disintegrant	180 mg	tablets	Granulation lot of 80 kg is representative of full-scale (275 kg)
B	RG9533	PJXTX7-004	9/15/95	Lactose-gelatin Tablet	180 mg	tablets	Granulation lot of 80 kg is representative of full-scale (275 kg)
C	RH9411	PJXCX5-001	9/20/94	White gelatin capsule	60 mg	capsules	Full-scale lot

* Formulation A is to-be-marketed formulation.

Study Design and Sampling:
The study was conducted as an open-label, randomized, six-period, complete crossover design in 27 healthy volunteers, between the ages of 20 and 37 years.
Each dosing period was separated by a washout period of 7 days. Three treatments, each repeated twice, were administered to subjects.
Fourteen serial blood samples were collected for 36 hours (at 0, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 30, and 36 hr) following the drug administration.

Number of Subjects:
A total of 27 subjects were enrolled in the study, and all 27 subjects received study medication. Due to personal reasons, two subjects dropped out of the study; one subject prior to period II and another subject prior to period III. A total of 25 subjects received all three repeated treatments in accordance with the randomization. The total number of subjects exposed to each treatment was: Treatment A, n=26; Treatment B, n=25; Treatment C, n=27. There were a total of 51

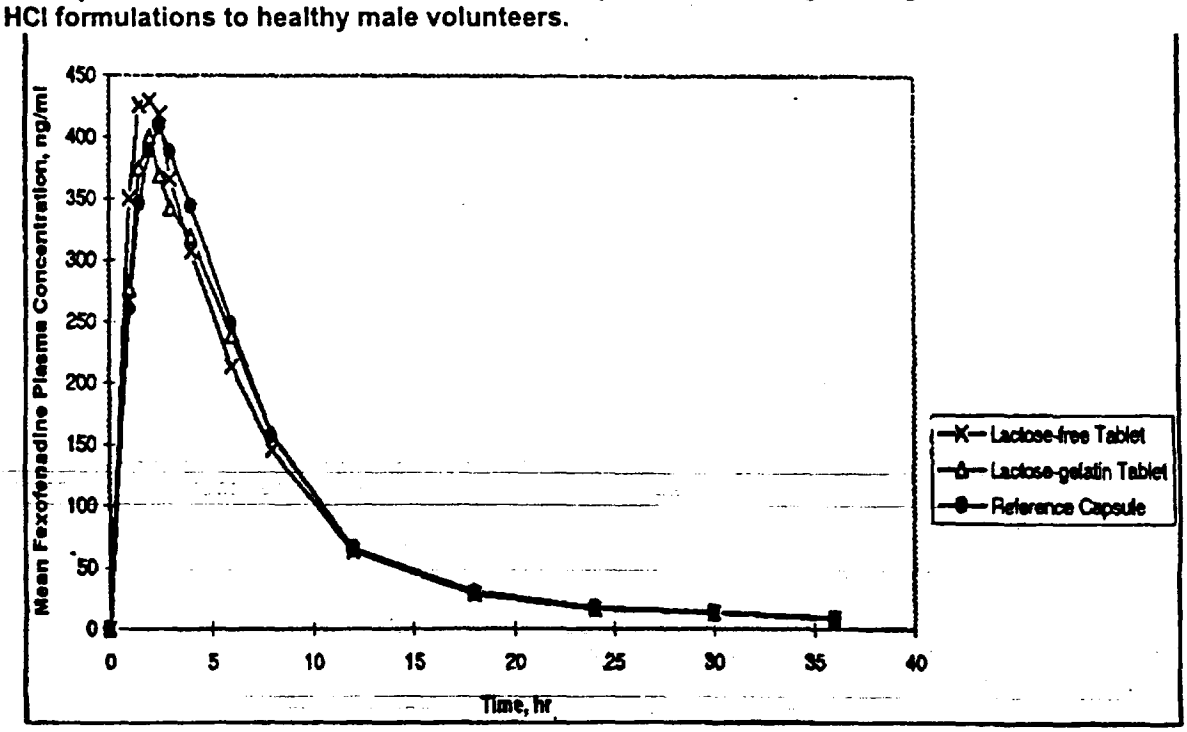
observations for Treatment A, 50 observations for Treatment B, and 52 observations for Treatment C.

Assay:

Data Analysis:
Pharmacokinetic parameters for fexofenadine in plasma were calculated from concentration-time data using model-independent methods. Treatment comparisons were evaluated with an analysis of the natural log-transformed data, as recommended in the *1992 FDA Guidance, Statistical Procedures for Bioequivalence Studies Using a Standard Two-treatment Crossover Design.* A three-way analysis of variance with terms for subject, treatment and period was done for each parameter, from which 90% confidence interval for the ratio of treatment means was obtained. Treatment C (capsule) was used as the reference treatment.

Results:

Mean plasma fexofenadine concentration-time profiles following 180 mg doses of various fexofenadine HCl formulations to healthy male volunteers.



Treatment comparisons for key pharmacokinetic parameters calculated from plasma fexofenadine concentrations following 180 mg doses of fexofenadine HCl to healthy male volunteers

Parameter	*Trmt*	*Mean*	%CV	*pair*	Ratio (%)	90 % CI
AUC inf	A	3330.08	39.49	A/C	95.17	86.0,105.3
ng·h/ml	B	3192.02	36.84	B/C	97.08	87.7,107.5
	C	3396.65	32.60	-	-	-
Cmax	A	494.24	55.24	A/C	100.02	87.3,114.6
(ng/mL)	B	453.64	44.27	B/C	93.72	81.7,107.5
	C	476.32	40.98	-	-	-
Tmax	A	2.0	34.15	A/C	76.17	67.1,86.4
(h)	B	2.5	53.70	B/C	90.04	79.3,102.3
	C	2.6	38.77	-	-	-
Treatment A: Single dose oral administration of 1 x 180 mg fexofenadine hydrochloride lactose-free (with Ac-Di-Sol as disintegrant) tablet formulation.						
Treatment B: Single dose oral administration of 1 x 180 mg fexofenadine hydrochloride lactose-gelatin tablet formulation.						
Treatment C: Single dose oral administration of 3 x 60 mg fexofenadine hydrochloride hard-gelatin capsule formulation.						

Sponsor's Conclusion:
The results of the study showed that both tablet formulations were bioequivalent to the capsule formulation.

Reviewer's comment:
It appeared that the analysis of variance with terms of sequence was not done for each pharmacokinetic parameter in PJPR0045. The sponsor is advised to re-analyze the data including sequence and submit the result for the study.

APPENDIX I-2. Protocol PJPR0094, Report K-98-0063-D:

Title: Pivotal bioequivalence study of 60 mg fexofenadine hydrochloride tablet formulation

Protocol Number: PJPR0094

Project Report Number: K-98-0063-D

Investigator and Location:

Objectives:

The objective of the study was to establish the bioequivalence of 60 mg fexofenadine hydrochloride production-scale tablet formulations relative to the 60 mg marketed ALLEGRA capsule.

Formulation:
The fexofenadine HCl formulations

Trmt	*Lot Number*	*Formula Number*	*Release Date*	*Dosage Form*	*Strength*	*Batch Size*	*Comments*
A *	RD9723	PJO96-01	7/28/97	tablet	60 mg		Pivotal size lot, peach, modified, oval-shaped, film-coated tablet
B	98053501	PJO82-01	3/24/97	capsule	60 mg		US commercially available capsule

* Formulation A is to-be-marketed formulation.
A: Fexofenadine HCl (1 x 60 mg) tablets (Lot # RD9723) given as a single dose (n=47)
B: Fexofenadine HCl (1 x 60 mg) ALLEGRA capsules (Lot # 98053501) given as a single dose (n=48).
** The critical step in manufacturing process, ie, granulation, was made at greater than % full-scale, sufficient to yield greater than tablets.

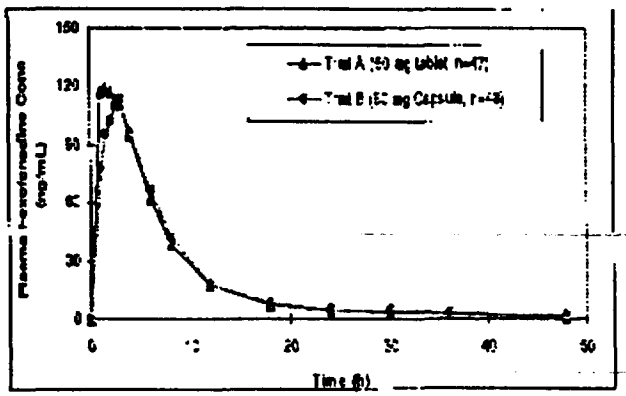
Study Design and Sampling:
The study was conducted using an open-label, two-period, two-treatment, randomized, complete crossover, single dose design.
Subjects between 18 and 45 years of age received the treatments A and B.
Prestudy and poststudy laboratory tests, 12-lead ECGs, and physical examinations were conducted on each subject, as well as monitoring for general well-being, vital signs, and adverse events throughout the study.
Serial blood (plasma) samples were collected for fexofenadine analysis during a 48-hour period after each treatment (at 0, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 30, 36, and 48 hr).
Treatments were administered to subjects over two periods separated by a washout period of 6 days.

Number of Subjects:
Fifty volunteers entered the study. A total of three volunteers dropped during the study, two for personal reasons and one due to a protocol violation. There were a total of 47 observations for Treatment A and 48 observations for Treatment B.

Assay:

Data analysis:
Pharmacokinetic analyses of fexofenadine plasma concentrations were conducted by noncompartmental methods. Comparisons between treatments A and B were evaluated with an analysis of the natural log transformed data. An analysis of variance, with terms for sequence, subject, period, and treatment, was done for each parameter from which 90% confidence intervals for the ratio of treatment means were obtained. Treatment A was compared to treatment B, with treatment B as the reference treatment. The primary statistical comparison was based on Cmax and AUCinf.

Results:
Figure presents the mean plasma fexofenadine concentration versus time profiles for all treatments.



Following Table presents the key mean fexofenadine pharmacokinetic parameters for each treatment and pairwise treatment comparisons.

Table. Treatment comparisons for key pharmacokinetic parameters calculated from plasma fexofenadine concentrations following 60 mg doses of fexofenadine HCl to healthy male volunteers

Parameter	*Treatment*	*Mean*	%CV	*pair*	Ratio (%)	90 % CI
AUC inf ng·h/ml	A	973.77	33.36	A/B	100.29	(93.3,107.8)
	B	958.98	30.39			
Cmax (ng/mL)	A	141.80	34.84	A/B	109.57	(100.1,120.0)
	B	131.25	42.23			
Tmax (h)	A	1.7	49.07	A/B	66.48	(57.8,76.5)
	B	2.49	34.04			
A: Fexofenadine HCl (1 x 60 mg) tablets (Lot # RD9723) given as a single dose (n=47) B: Fexofenadine HCl (1 x 60 mg) ALLEGRA capsules (Lot # 98053501) given as a single dose (n=48)						
For Treatment A, the tmax, median value was 1.5 h and ranged from 1 to 4 h. For Treatment B, the tmax, median value was 2.5 h and ranged from 1 to 4 h.						

The time to maximum exposure for the tablets was faster than the capsules.

Sponsor's conclusions:

The tablet formulation, given as a single dose of 1 x 60 mg, was bioequivalent to the marketed Allegra capsule formulation given as a single dose of 1x 60 mg.

APPENDIX I-3. Protocol PJPR0062, Report K-96-0891-D

Title: The effect of food on the bioavailability of fexofenadine hydrochloride 180 mg lactose-free tablets

Protocol Number: PJPR0062

Project Report Number: K-96-0891-D

Investigator and Location:

Objectives:
The objective of the study was to characterize the effect of food on the rate and extent of fexofenadine absorption from the lactose-free tablet.

Formulation:
Table summarizes the manufacturing history of the fexofenadine HCl formulations used in this study.

Table 2-22. Manufacturing history of the fexofenadine HCl formulations

Trmt	*Lot Number*	*Formula Number*	*Release Date*	*Dosage Form*	*Strength*	*Batch Size*	*Comments*
A	RG9529	PJXTX7-005	9/15/95	Lactose-Free Tablet with Ac-Di-Sol ® as disintegrant	180 mg	tablets	Granulation lot of 80 kg is representative of full-scale (275 kg)

Study Design and Sampling:
The study was conducted using an open-label, two-period, two-treatment (Treatment A: One 180 mg fexofenadine HCl tablet (Lot RG9529) given as a single dose to fasted subjects; Treatment B: One 180 mg fexofenadine HCl tablet (Lot RG9529) given as a single dose to subjects after a high fat breakfast) crossover single-dose design. Subjects between 18 and 43 years of age received the treatments.
Treatments A and B were administered to subjects over two periods separated by a washout period of 6 days. Serial blood (plasma) samples were obtained for 48 hours following drug administration. Blood pressure and heart rate measurements were obtained prior to and 3 hours after dosing.

Number of Subjects:
A total of 22 healthy volunteers entered the study. All 22 subjects received study drug during period 1. Subject PJST0532-0020 was discontinued from the study because of adverse events (bronchitis and tooth pain) during the washout period prior to dosing in period 2, treatment B. Pharmacokinetic data of all subjects receiving study drug were included in the pharmacokinetic and statistical analyses. The total number of subjects exposed to each treatment was : Treatment A, n=22; Treatment B, n=21.

Assay:

Data Analysis:
All subjects dosed with study drug were included in the safety and pharmacokinetic analyses. Pharmacokinetic analyses of fexofenadine plasma concentrations were conducted by noncompartmental methods. Treatment comparisons were evaluated with an analysis of the natural log transformed data, as recommended in the *1992 FDA Guidance, Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design.* A three-way analysis of variance with terms for subject, treatment and period was performed for each parameter from which 90% confidence intervals for the ratio of treatment means were obtained.

Results:
Results are summarized in the following figure and table.

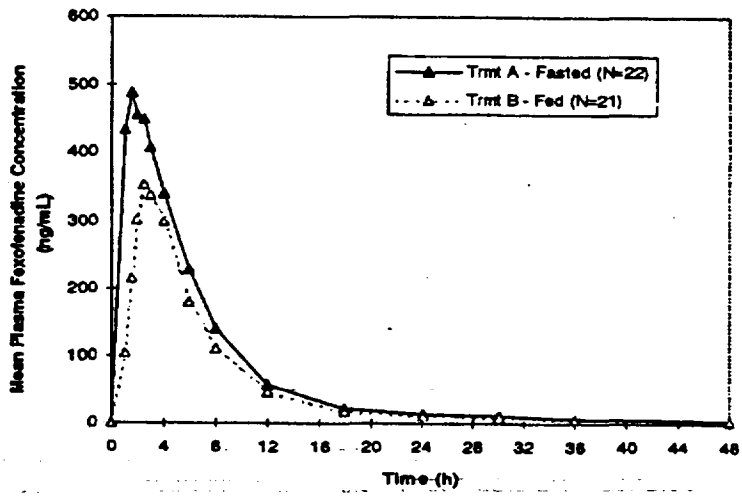


Figure. Mean fexofenadine plasma concentration versus time profile following oral administration of a single 180 mg dose of fexofenadine HCl lactose-free tablet to fasted or fed healthy male subjects

Table. Treatment comparisons for keyplasmafexofenadinepharmacokineticparameters

Parameter	*Treatment*	*Mean*	%CV	*pair*	Ratio (%)	90 % CI
AUC inf	A	3462.92	52.21			
ng·h/ml	B	2582.15	26.11	B/A	78.9	68.3, 91.1
Cmax	A	559.91	65.39			
(ng/mL)	B	399.62	32.07	B/A	80.1	64.0, 100.1
Tmax	A	2.18	54.57			
(h)	B	2.57	32.12	B/A	121.6	96.8, 152.9
Treatment A: One 180 mg fexofenadine HCl tablet (Lot RG9529) given as a single dose to fasted subjects Treatment B: One 180 mg fexofenadine HCl tablet (Lot RG9529) given as a single dose to subjects after a high fat breakfast.						

The ratio of the mean fexofenadine AUCinf value for fed subjects compared to fasted subjects was 79%. The 90% confidence interval (CI) for this ratio was 68% to 91 %.

The ratio of the mean fexofenadine Cmax value for fed subjects compared to fasted subjects was 80%. The 90% confidence intervals (CI) for the ratio of Cmax was 64% to 100 %.

Sponsor's conclusions:
Administration of the lactose-free fexofenadine tablet with a high-fat breakfast resulted in a 21 % decrease in the extent of drug absorption. Cmax was reduced by about 20 % This difference is similar to that observed with the marketed fexofenadine capsule (21 % reduction of AUCinf and 14 % reduction of Cmax).

Reviewer's comment:
It should be noted that a dose adjustment due to the food effect was not considered necessary in the case of capsule due to a wide therapeutic index for this product. Therefore, the fexofenadine tablet can be safely administered without regard to food.

APPENDIX I-4. Protocol PJPR0098, Report K-98-0065-D

Title: The effect of food on the bioavailability of fexofenadine hydrochloride 120 mg lactose-free tablets in healthy male subjects

Protocol Number: PJPR0098

Project Report Number: K-98-0065-D

Investigator and Location:

Objectives:
There were two study objectives in Protocol PJPR0098. This study report (K-98-0065-D) addresses the effect of food on the rate and extent of fexofenadine absorption from the 120 mg tablet. The second study objective which deals with single and multiple dose pharmacokinetics of the 120 mg fexofenadine HCl tablet can be found in *Protocol PJPROO98, Report K-98-0071-D, S6-VI.40-PI.*

Formulation:

Following Table summarizes the manufacturing history of the fexofenadine HCl formulations used in this study.

Table . Manufacturing history of the fexofenadine HCl formulations

Trmt	*Lot Number*	*Formula Number*	*Release Date*	*Dosage Form*	*Strength*	*Batch Size*	*Comments*
A,B	RJ9729	PJO61-02	11/24/97	tablet	120 mg		Pivotal size lot, peach, capsule-shaped, film-coated, tablet plain on both sides

A: One 120 mg fexofenadine HCl tablet (Lot # RJ9729) given as a single dose to fasted subjects (n=22)

B: One 120 mg fexofenadine HCl tablet (Lot # RJ9729) given as a single dose to subjects after a high fat breakfast (n=22)

** The critical step in manufacturing process, was made at greater than % of full-scale, sufficient to yield greater than tablets.

Study Design and Sampling:
The study was conducted using an open-label, two-period, two-treatment, randomized, complete crossover, single dose design. Subjects between 18 and 27 years of age received the treatments. Prestudy and poststudy laboratory tests, 12-lead ECGS, and physical examinations were conducted on each subject, as well as monitoring for general well-being, vital signs, and adverse events throughout the study. Serial blood (plasma) samples were collected for fexofenadine analyses during a 48-hour period after each treatment. Treatments were administered to subjects over two periods separated by a washout period of 6 days.

Number of Subjects:
Twenty-two volunteers entered the study and all of them successfully completed both periods of the study. Pharmacokinetic data for all subjects were included in the pharmacokinetic and statistical analyses. The total number of subjects exposed to each treatment was: TRMT A: 22; and TRMT B: 22.

Assay:

Data Analysis:

Pharmacokinetic analyses of fexofenadine plasma concentrations were conducted by noncompartmental methods. Comparisons between treatments A and B were conducted with an analysis of the natural log transformed data. An analysis of variance, with terms for sequence, subject, period, and treatment, was done for each parameter from which 90% confidence intervals for the ratio of treatment means were obtained. Treatment B was compared to treatment A with treatment A as the reference treatment. The primary statistical comparison was based on Cmax and AUCinf.

Results:

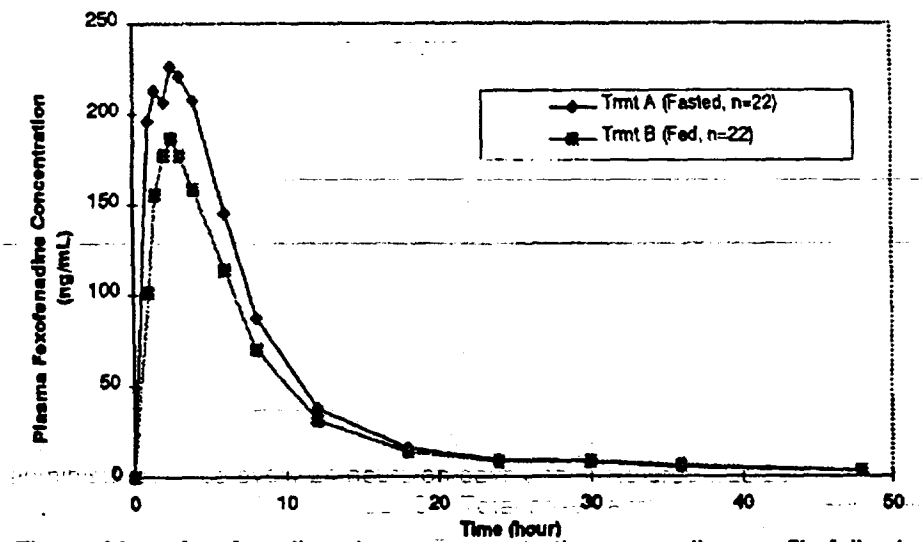


Figure. Mean fexofenadine plasma concentration versus time profile following oral administration of a single 120 mg dose of fexofenadine HCl lactose-free tablet to fasted or fed healthy male subjects

Table. Treatment comparisons for key plasma fexofenadine pharmacokinetic parameters

Parameter	*Treatment*	*Mean*	%CV	*pair*	Ratio (%)	90 % CI
AUC inf	A	2013.66	38.08			
ng·h/ml	B	1642.16	27.61	B/A	84.88	(75.3, 95.7)
Cmax	A	289.31	47.86			
(ng/mL)	B	235.81	30.96	B/A	85.90	(72.7,101.5)
Tmax	A	2.48	48.04			
(h)	B	2.57	53.50	B/A	102.29	(86.2,121.4)

A: One 120 mg fexofenadine HCl tablet (Lot # RJ9729) given as a single dose to fasted subjects (n=22)

B: One 120 mg fexofenadine HCl tablet (Lot # RJ9729) given as a single dose to subjects after a high fat breakfast (n=22)

For both treatments A and B, the tmax median was 2.5 h with values ranging from 1 to 6 h.

Under fed conditions, fexofenadine mean AUCinf values decreased by 15% and Cmax values decreased by 14%. The time to maximum concentration was similar with and without food. Mean differences of this magnitude do not represent a significant effect on the extent or rate of absorption of the fexofenadine HCl 120 mg tablet. This difference is similar to that observed with the marketed fexofenadine capsule and is not expected to be clinically important.

Sponsor's conclusions:
Administration of the lactose-free fexofenadine tablet (120 mg) with a high-fat breakfast resulted in a 15 % decrease in the extent of drug absorption. Cmax was reduced about 14 % This difference is similar to that observed with the marketed fexofenadine capsule (21 % reduction of AUCinf and 14 % reduction of Cmax).

Reviewer's comment:
It should be noted that a dose adjustment due to the food effect was not considered necessary in the case of capsule due to a wide therapeutic index for this product. Since there is minimal food effect, fexofenadine tablet can be safely administered without regard to food.

APPENDIX I-5. Protocol PJPR0071, Report K-97-0145-D

Title: Relative bioavailability of prototype fexofenadine hydrochloride tablets in normal healthy male subjects

Protocol Number: PJPR0071

Project Report Number: K-97-0145-D

Investigator and Location:

Objectives:
The objectives of the study were to examine the bioavailability of formulations made with drug substance with different surface areas, relative to the bioavailability of a formulation made with unmilled drug, and to compare the relative bioavailability of a tablet containing anhydrous drug substance to a tablet containing the hydrated drug substance.

Reviewer's Comment:
The comparison of the relative bioavailability of a fexofenadine tablet containing anhydrous drug substance to a tablet containing the hydrated drug substance has been reviewed and concluded to be bioequivalent (Please refer to the Biopharm review: N20-786; allegra-D, submission date 7/21/97, reviewed on 9/2/97). The present review is only on the effect of surface area.

Formulation:

The following table summarizes the manufacturing history of the fexofenadine HCl formulations used in this study.

Table. Manufacturing history of the 180 mg fexofenadine HCl tablets

Trmt	Lot #	*Formula*	*Release date*	*Surface area*	Miilled/ Unmilled	Batch size	Comment
A	RG9610	PJXTX7-007	10/l/96	4.39 m2/g	Milled		Anhydrous, Lab scale
B	RG9636	PJXTX7-007	10/l/96	3.02 m2/g	Milled		Anhydrous, Lab scale
C	RG9612	PJXTX7-009	10/l/96	1.79 m2/g	Milled		Anhydrous, Lab scale
D	RG9611	PJXTX7-009	10/l/96	1.03 m2/g	Milled		Anhydrous, Lab scale
E	RG9638	PJXTX7-007	10/l/96	3.02 m2/g	Unmilled		Hydrate, Lab scale
F	RG9529	PJXTX7-005	9/15/95	2.73 m2/g	Milled		Anhydrous, Full scale

Study Design and Sampling:
The study was conducted in 30 healthy, adult, male volunteers in a four-period, six-treatment, open-label, randomized, incomplete block crossover design. Each subject received four of the six treatments. There was a washout period of at least 6 days between each treatment.

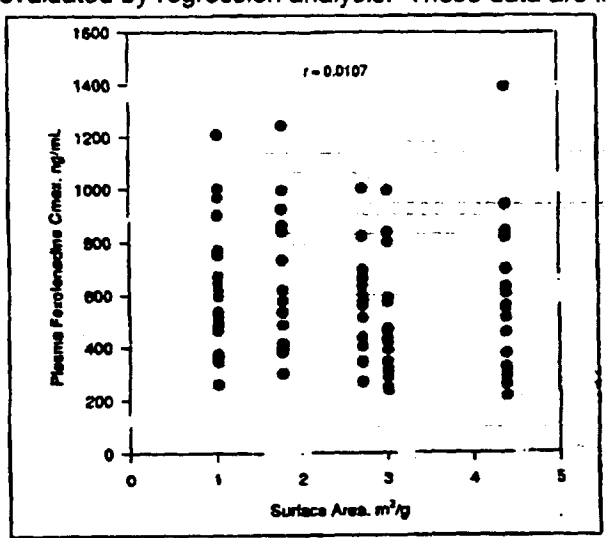
Number of Subjects:
A total of 30 subjects were enrolled in the study, and all 30 subjects received study medication. Two subjects withdrew from the study for personal reasons. A total of 28 subjects completed all four periods of the study. The total number of subjects exposed to each treatment was: Treatment A, n=20; Treatment B, n= 19; Treatment C, n= 19; Treatment D, n=20; Treatment E, n=20; Treatment F, n=18.

Assay:

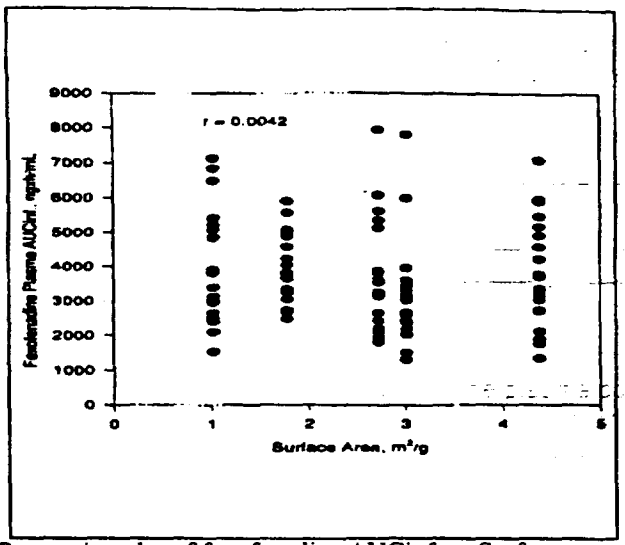
Data Analysis:
Pharmacokinetic parameters for fexofenadine in plasma were calculated from concentration-time data using model-independent methods. Treatment comparisons were evaluated with an analysis of the natural log-transformed data. A three-way analysis of variance with terms for subjects, treatment and period was done for each parameter, from which 90% confidence intervals for the ratio of the treatment means were calculated. To test for surface area effects, Treatments A, B, C and F were compared to Treatment D, with Treatment D as the reference treatment. To test anhydrous versus hydrate, Treatment E was compared to Treatment B, with Treatment B as reference. Comparisons between treatments for fexofenadine concentrations were based on Cmax, tmax, and AUCinf.

Results:
Bioavailability of fexofenadine tablets made with different surface area raw material

The relationship of fexofenadine AUC to surface area for all anhydrous treatments was evaluated by regression analysis. These data are illustrated in the following Figure.



Regression plot of fexofenadine C max vs. Surface area



Regression plot of fexofenadine AUCinf vs. Surface area

Surface area does not appear to have a relationship to AUC. The correlation coefficient was less than 0.01, indicating that these parameters are not correlated. A similar lack of relationship was also observed between surface area and Cmax (r=0.0107). Statistical comparisons of AUC, Cmax and tmax are given in the following table.

Table. Treatment comparisons for pharmacokinetic parameters following administration of 180 mg tablets made with raw materials of different surface areas

Parameter	*Treatment*	*Mean*	%CV	*pair*	Ratio (%)	90 % CI
AUC inf	A	3805	41	A/D	99.94	88.3,113.1
ng·h/ml	B	3145	49	B/D	81.78	72.2, 92.6
	C	3919	26	C/D	104.68	92.4, 118.5
	D	3924	42			
	F	3791	44	F/D	94.24	83.1, 106.8
Cmax	A	571	51	A/D	88.94	71.8, 110.1
(ng/mL)	B	495	49	B/D	74.85	60.4, 92.8
	C	627	41	C/D	98.97	79.8, 122.8
	D	614	41			
	F	554	35	F/D	87.02	70.0, 108.1
Tmax	A	2.08	53	A/D	109.23	87.9, 135.8
(h)	B	1.79	43	B/D	88.73	71.2, 110.5
	C	1.74	35	C/D	92.12	73.9, 114.8
	D	2.00	56			
	F	2.08	52	F/D	94.65	75.9, 118.1

Treatment A: Anhydrous, 4,.39 m^2/g
Treatment B: Anhydrous, 3.02 m^2/g
Treatment C: Anhydrous, 1.79 m^2/g
Treatment D: Anhydrous, 1.03 m^2/g, Reference Treatment
Treatment F: Anhydrous, 2.73 m^2/g

Treatment B, with a medium surface area, had 18% lower AUC and 25% lower Cmax, than Treatment D. However, this does not appear to be related to surface area since AUC difference for Treatment A (4.39 m2/g) and Treatment D (unmilled drug, 1.03 m^2/g) was less than 1 %, whereas Treatment A had approximately 18-fold greater surface area than Treatment D. Also,

Treatments B, C, and F differed little from the unmilled drug, Treatment D; differences in AUC, Cmax and tmax were less than 13%.

Reviewer's comment:
Although all the confidence intervals were out of the regulatory limit of 80-125 %, the regression results strongly indicate that fexofenadine bioavailability is not related to particle surface area within the m^2/g range.

APPEARS THIS WAY
ON ORIGINAL

APPENDIX I-6. Protocol PJPR0068, Report K-97-0066-D

Title: Multiple dose pharmacokinetics of fexofenadine administered once every twenty-four hours compared to once every twelve hours

Protocol Number: PJPR0068

Project Report Number: K-97-0066-D

Investigator and Location:

Objectives:
The primary objective of the study was to compare the steady-state pharmacokinetics of 180 mg fexofenadine HCl administered once-daily with the pharmacokinetics of a 90 mg twice-daily regimen.

The secondary objectives of the study were to characterize the steady-state fexofenadine pharmacokinetics administered at a 40 mg BID regimen, and to characterize the single dose and steady-state pharmacokinetics of 180 mg fexofenadine HCl administered once-daily.

Formulations:
Table . Manufacturing history of the fexofenadine HCl formulations

Trmt	*Lot Number*	*Formula Number*	*Release Date*	*Dosage Form*	*Strength*	*Batch Size*	*Comments*
A,B	RF9633	PJXTXL 0-002	8/2/96	Tablet	90 mg		Pilot-Scale
C	RC9624	PJXTX4-005	8/2/96	Tablet	40 mg		Pilot-Scale

Study Design and Sampling:
The study was conducted as an open-label, randomized, three-period, multiple dose, crossover design in 24 healthy, male volunteers. Each of three treatments were administered to all subjects.

Treatment A: A 180 mg single dose (2 x 90 mg tablets) of fexofenadine hydrochloride was administered on day 1, followed by 180 mg (2 x 90 mg tablets) fexofenadine hydrochloride administered once every 24 hours on days 3 to 8. No drug was administered on day 2. (Last dose was administered at 7 AM on day 8). Total doses administered = 7. Serial blood sampling: Day 1 at 0, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 18, 24, 30, 36 and 48 hr; Serial blood sampling: Day 8 at 0, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 18, 24, 30, 36 and 48 hr.

Treatment B: A 90 mg (1 x 90 mg tablet) fexofenadine hydrochloride dose was administered once every 12 hours on days 3 to 8. No drug was administered on days 1 and 2. (Last dose was administered at 7 PM on day 8). Total doses administered = 12. Serial blood sampling: Day 8 at 0, 1, 1.5, 2, 3, 4, 8, 12, 13, 13.5, 14, 15, 16, 20, 24, 30, 36 and 48 hr.

Treatment C: A 40 mg (I x 40 mg tablet) fexofenadine hydrochloride dose was administered once every 12 hours on days 3 to 8. No drug was administered on days I and 2. (Last dose was administered at 7 PM on day 8). Total doses administered = 12. Serial blood sampling: Day 8 at 0, 1, 1.5, 2, 3, 4, 8, 12, 13, 13.5, 14, 15, 16, 20, 24, 30, 36 and 48 hr.

There was a drug-free washout period of 14 days between each treatment. Serial blood samples were collected after steady state for all three treatments. Serial blood samples were also collected after a single dose for treatment A only. Trough blood samples were collected on days 6, 7 and 8 for all treatments.

Number of subjects:
A total of 24 subjects were enrolled in the study, and all 24 subjects received study medication. One subject did not report to the clinic for period 2 check-in and was discontinued from the study. A total of 23 subjects completed all three treatment periods. The total number of subjects exposed to each treatment was: Treatment A, n=23; Treatment B, n=24; Treatment C, n=23.

Assay:

Data analysis:
Pharmacokinetic parameters for fexofenadine in plasma were calculated from concentration-time data using model-independent methods. Treatment comparisons were evaluated with an analysis of the natural log-transformed data. An analysis of variance with terms for sequence, subject, treatment and period was done for each parameter, from which 90% confidence intervals for the ratio of the treatment means were determined. Comparisons between single- and multiple-dose parameters for treatment A, and comparisons between the trough concentrations at days 6, 7 and 8 for each treatment were evaluated with an analysis of variance with terms for subject and day. Only descriptive statistics were used to characterize fexofenadine pharmacokinetics for the 40 mg BID regimen (treatment C).

Results:

Mean plasma fexofenadine concentration-time profiles on day 8 for the 90 mg BID treatment compared to 180 mg QD treatment are shown in Figure.

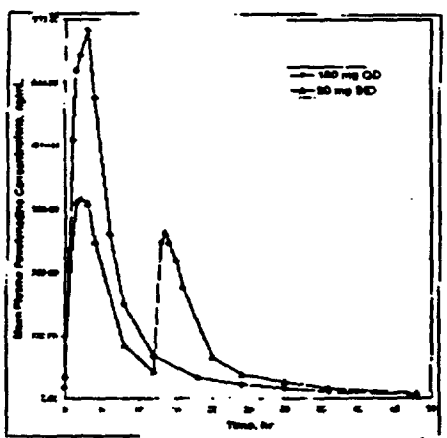


Figure. Mean steady state plasma fexofenadine concentration-time profiles following oral administration of 180mg QD or 90 mg BID fexofenadine HCl to normal healthy subjects.

The treatment comparisons for key pharmacokinetic parameters resulting from both regimens are summarized in the following table.

Treatment comparisons for key steady-state fexofenadine pharmacokinetic parameters following 180 mg QD (Treatment A) compared to 90 mg BID (Treatment B)

Parameter	Trmt	Mean	%CV	Pair	Ratio (%)	90% CI
AUC ss 0-24 ng h/ml	A B	3874 3515	32 36	A/B	111.8	96.6, 129.5
CL po,ss l/h	A B	47.9 52.87	32 30	A/B	89.4	77.2, 103.6
t1/2 ss h	A B	11.68 11.28	40 32	A/B	102.4	90.0, 116.6
Cmax,ss ng/ml	A B	681.43 396.17	38 42	A/B	177.8	150.8, 209.8
Cmin,ss ng/ml	A B	21.67 36.28	31 31	A/B	60.04	53.1, 67.9
tmax,ss hr	A B	2.3 2.2	41 46	A/B	106.35	85.1, 132.9

The adjusted mean differences in AUCss and CLpo for the once-daily regimen compared to twice-daily regimen were less than 12%. Apparent elimination half-life was equivalent for the two regimens. These data indicate the similarity in fexofenadine pharmacokinetics when dosed once daily compared to twice daily dosing.

Single dose to steady-state treatment comparisons for key pharmacokinetic parameters for 180 mg QD regimen (Treatment A)

Parameter	Single dose/ Steady state	Mean	%CV	Pair	Ratio (%)	90% CI
AUC * ng h/ml	SD SS	3313 3874	47 32	SS/SD	120.93	106.6, 137.1
CL po l/h	SD SS	59.09 47.91	36 32	SS/SD	82.70	72.9, 93.8
t1/2 h	SD SS	12.52 11.68	24 40	SS/SD	90.82	80.7, 102.2
Cmax ng/ml	SD SS	568.44 681.43	59 38	SS/SD	128.14	109.2, 150.4
tmax hr	SD SS	2.0 2.3	49 41	SS/SD	116	91.3, 147.4

* For single dose AUC inf and for steady state AUC 0-24 hours were compared.

At the 40 mg BID regimen, t1/2 was 11.06 hours and CL po was 55.71 l/hr. Tmax averaged about 1.8 hr.
Steady state was reached within 6 days.

Comments:
The differences between steady state and single dose AUC, CLpo, t1/2 and tmax were approximately 21 %. These data indicate that single dose pharmacokinetics underpredicts steady-state exposure by about 21 %. These differences are similar to what have been observed at the 20 mg, 60 mg, 120 mg and 240 mg BID regimens in the earlier study (NDA 20-625; Allegra capsule). In view of the large safety margin , these differences are unlikely to be of clinical significance.
At the 40 mg BID regimen, elimination half life and clearance appeared comparable to the other regimens, indicating linear pharmacokinetics.

APPENDIX I-7. Protocol PJPR0098, Report K-98-0071-D

Title: Single and multiple dose pharmacokinetics of fexofenadine hydrochloride 120 mg tablets in healthy male subjects

Protocol Number: PJPR0098 (Part Two)

Project Report Number: K-98-0071-D

Investigator and Location:

Objectives:
There were two study objectives. This study report (K-98-0071-D) addresses the single and multiple dose pharmacokinetics of the 120 mg fexofenadine HCl tablet. The second study objective which deals with the effect of food on the rate and extent of fexofenadine absorption from the 120 mg tablet can be found in *Protocol PJPROO98, Report K-98-0065-D, S6-VI.35-Pl.*

Formulation:
Table . Manufacturing history of the fexofenadine HCl formulations

Trmt	*Lot Number*	*Formula Number*	*Release Date*	*Dosage Form*	*Strength*	*Batch Size*	*Comments*
A,B	RJ9729	PJO61-02	11/24/97	tablet	120 mg		Pivotal size lot, peach, capsule-shaped, film-coated, tablet plain on both sides

Treatment C: Multiple daily oral doses of 120 mg fexofenadine HCl (Lot # RJ9729) to fasted subjects for 7 doses (n=22)

**: The critical step in manufacturing process, ie, granulation, was made at greater than % full-scale, sufficient to yield greater than tablets.

Study Design and Sampling:
The study was conducted as an open-label, single and multiple dose design using a single period and a single treatment. The treatment was:

Treatment C: A single 120 mg oral dose (l x 120 mg tablet) of fexofenadine HCl administered on day 1, followed by a 120 mg dose (1 x 120 mg tablet) of fexofenadine HCl administered once every 24 hours on days 3 to 8 with the last dose administered at 7 AM on day 8. No drug was to be administered on day 2. Total doses administered = 7.

Subjects between 19 and 45 years of age received the treatment. Pre- and poststudy laboratory tests, 12-lead ECGs, and physical examinations were conducted on each subject, as well as monitoring for general well-being, vital signs, and adverse events throughout the study. Blood samples (7 mL) were collected at predose, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 30, 36 and 48 hours postdose on both days I and 8. The 48 hour sample after the dose on day 1 was collected immediately prior to dose administration on day 3. Trough samples were collected on days 6 and 7 immediately prior to the morning dose.

Number of Subjects:
Twenty-two volunteers entered the study and all of them successfully completed the study. Pharmacokinetic data for all subjects were included in the pharmacokinetic and statistical analyses. The total number of subjects exposed to Treatment C was 22.

Assay:

Data Analysis:
Pharmacokinetic analyses of fexofenadine plasma concentrations were conducted by noncompartmental methods. Comparisons between single dose to multiple dose parameters were evaluated with an analysis of the natural log transformed data. An analysis of variance, with terms for subject and type of dose (single or multiple), was done for each parameter from which 90% confidence intervals for the ratio of dose types were obtained. Single dose was compared to multiple dose with single dose as the reference.

Trough concentrations of fexofenadine for days 6, 7, and 8 were evaluated with an analysis of the natural log transformed data. An analysis of variance, with terms for subject and day, was done for each treatment from which 90% confidence intervals for the ratio of days were obtained. Earlier days were compared to later days with the earlier day as the reference.

Results:

Following figure presents the mean single dose and steady-state plasma fexofenadine concentration versus time profile.

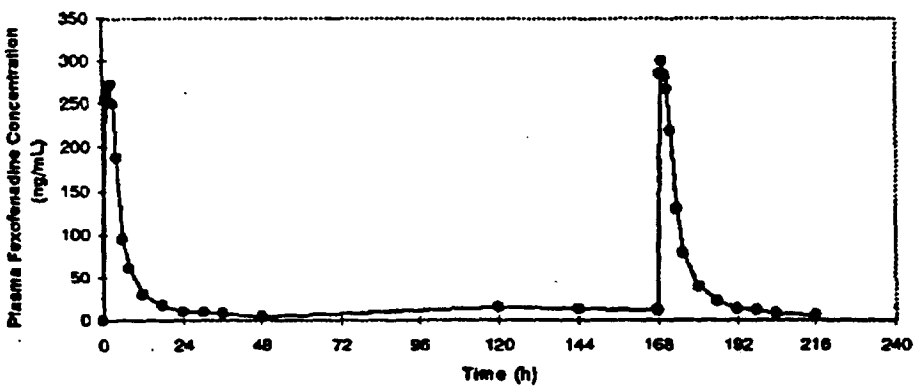


Figure: Mean single dose and steady state plasma fexofenadine concentration-time profile following oral administration of 120 mg QD fexofenadine HCl to healthy male subjects.

Following table summarizes key single dose and steady-state treatment comparisons for plasma fexofenadine pharmacokinetic parameters.

Table . Single dose to steady-state treatment comparisons for key pharmacokinetic parameters for 120 mg QD regimen

Parameter	Single dose/ Steady state	Mean	%CV	Pair	Ratio (%)	90% CI
AUC * ng h/ml	SD	1978	35.74			
	SS	2033	41.42	SS/SD	101.82	92.4, 112.2
CL po l/h	SD	64	37.8			
	SS	63	37.55	SS/SD	98.21	89.1, 108.2
t1/2 h	SD	16.63	36.52			
	SS	15.27	35.12	SS/SD	91.92	82.4, 102.5
Cmax ng/ml	SD	323.89	43.78			
	SS	348.91	49.60	SS/SD	107.08	93.0, 123.4
tmax hr	SD	2.02	42.80			
	SS	1.89	51.04	SS/SD	91.25	76.2, 109.3

* For single dose AUC inf and for steady state AUC 0-24 hours were compared.

The differences in trough between consecutive days were less than 18%, indicating that steady-state was reached by day 6 of the study.

The plasma concentration profile was characterized by a bi-exponential decline with the apparent elimination tl/2 adjusted mean values of 15.8 h after single dose and 14.5 h at steady-state. The CLpo adjusted mean estimates were 60.1 and 59.0 L/h, respectively, after single dose and at steady-state.

The differences between steady-state and single dose in AUC, CLpo, tl/2, Cmax, and tmax were less than 9%. These data indicate that single and multiple dose pharmacokinetics of 120 mg fexofenadine HCl tablets were similar. The result of this study is consistent with previous findings at the 20 mg, 60 mg, 120 mg, and 240 mg BID regimens, and the 180 QD regimen.

Conclusion/comment:
Single and multiple dose pharmacokinetics of 120 mg fexofenadine HCl tablets were similar.

APPENDIX I-8. Protocol PJPR0037, Report K-96-0929-D

Title: Pharmacokinetics and pharmacodynamics of fexofenadine hydrochloride in 6 to 12 year old pediatric patients with allergic rhinitis (PJPR0037)

Protocol Number: PJPR0037

Project Report Number: K-96-0929-D

Investigator And Location:

Objectives:
The objective was to characterize the pharmacokinetics of fexofenadine hydrochloride and its inhibitory effects on skin wheal and flare induced by histamine in 6- to 12-year-old pediatric patients with allergic rhinitis.

Formulation
Table . Manufacturing history of the fexofenadine HCl formulations

Trmt	*Lot Number*	*Formula Number*	*Release Date*	*Dosage Form*	*Strength*	*Batch Size*	*Comments*
A & B	RE9501	PJXCXL - 004	05/11/95	Capsule	30 mg	capsules	Small scale
B only	RE9502	PJXCXO-006	05/17/95	Capsule	placebo	capsules	Small scale

Treatment A. Single oral dose of 60 mg (2x30mg) fexofenadine HCl capsule
Treatment B. Single oral dose of 30 mg (lx30mg) fexofenadine HCl capsule and placebo (1x0mg)

Study Design And Sampling:
This study was conducted as a double-blind, single oral dose, randomized, two-period complete crossover design. Treatments were to be administered to 6- to 12-year-old male and female pediatric patients, with allergic rhinitis. Each patient received for treatment A two 30 mg fexofenadine capsules, and for treatment B one 30 mg fexofenadine and one placebo capsule. Patients received each of the treatments shown on separate occasions. All treatments were separated by at least a 7-day washout period.

Patients fasted overnight prior to dose administration. Serial plasma samples were collected up to 48 hours after dosing. Inhibition of skin wheal and flare responses induced by epicutaneous histamine injection were measured up to 24 hours after dosing. Electrocardiogram (lead ii) measurements were obtained prior to and 2.5 hours after dosing.

Number of patients:

A total of 15 patients 7 to 12 years old with allergic rhinitis were enrolled in the study. Thirteen patients completed the study. A total of 15 patients were exposed to study medication. Fourteen patients were exposed to treatments A and B, respectively.

Assay:

Data analysis:

Pharmacokinetic parameters were calculated from plasma concentration-time data by model independent methods using WinNonlin, version 1.2. Estimated pharmacokinetic parameters included maximum plasma concentration (Cmax), time to maximum plasma concentration (tmax), area under plasma concentration-time curve (AUCinf), half-life (tl/2), and oral clearance (CLpo). Dose normalized values for pharmacokinetic parameters AUCinf, and Cmax were computed. These parameters were normalized to the 30 mg dose level. Data for these parameters from the 60 mg dose level were divided by two for the dose normalized parameter comparison.

Pharmacokinetic parameters were calculated from wheal and flare inhibition data by model independent method using Winnonlin, version 1.2. Estimated pharmacodynamic parameters included maximum percent wheal/flare inhibition (Emax), time to maximum wheal/flare inhibition (tmax), area under the wheal/flare percent inhibition-time curve (AUEC), and average percent inhibition, (Eavg).

Results:

Pharmcokinetic:

The mean AUCinf for treatments A (60 mg oral dose) and B (30 mg oral dose) were 1899.87 and 1090.67 ng/mLxh, respectively. The mean apparent oral clearance (CLpo) for treatments A and B were 31.57and 29.05 L/h, respectively. The mean maximum plasma concentration (Cmax) for treatments A (60 mg oral dose) and B (30 mg oral dose) were 280.12 and 183.52 ng/mL, respectively. The mean time to maximum plasma concentration (tmax,) for treatments A and B were 2.54 and 2.24 h, respectively. A summary of the pharmacokinetic parameters for treatments A and B are provided in the following table.

Table . Pharmacokinetic parameters – PJPR0037

Variable	*Treatment*	*Mean*	CV%	*Dose Normalized Mean**
Clpo (L/h)	A B	31.57 29.05	29.0 36.3	N/A*** N/A
AUC inf (ng*h/ml)	A B	1899.87 1090.67	26.1 36.7	949.94 1090.67
Cmax (ng/ml)	A B	280.12 183.52	43.3 48.1	140.06 183.52
t1/2 (h)**	A B	9.05 8.78	38.8 34.5	N/A N/A
tmax (h)	A B	2.54 2.24	26.3 38.3	N/A N/A

* Dose normalized means are based on parameters normalized to the 30 mg dose
** Due to the nature of population, 6-12 years old, a smaller number of plasma samples were collected during the terminal elimination phase of concentration time profile than were collected in studies with adult volunteers. The elimination t1/2 may not be applicable.
*** N/A not applicable
A : 60 mg Oral (2x 30 mg capsule)
B : 30 mg Oral (1x 30 mg capsule)

Pharmacodynamic:

Baseline wheal and flare were determined by measurement of skin wheal and flare areas 10 min after subcutaneous injections of histamine solution prior to receiving fexofenadine HCl. Wheal and flare inhibition was determined by comparing the baseline wheal and flare areas to the wheal and flare areas produced following oral fexofenadine HCl administration. The mean maximum observed inhibition of wheal and flare areas ranged from 84.76 to 93.29 %, and 76.84 to 91.18 % following the 1 mg and 10 mg histamine injections, respectively.

Table. Summary of wheal and flare area percentage inhibitions - mean (CV%)

	Wheal				Flare			
	Emax (%)		Eavg (%)		Emax (%)		Eavg (%)	
Histamine level	1 mg	10mg	1 mg	10mg	1 mg	10mg	1 mg	10mg
30mg fexofenadine	84.76 (11)	76.84(19)	44.55(44)	37.70(61)	92.26(7)	87.55(9)	72.16(22)	59.73(23)
60mg fexofenadine	88.78(10)	78.91(11)	54.72(39)	43.47(46)	93.29(6)	91.18(5)	67.62(26)	62.58(24)

Treatment A (60 mg) generally produced maximum observed effects that were slightly greater than produced by treatment B (30 mg). Likewise, the Emax, obtained from the 1 mg histamine challenge were from 2% to 13% greater than obtained from the 10 mg histamine challenge. Similar results were recorded when comparing the Average Effect (Eavg - Area Under Effect Curve over 24 hours divided by 24, AUEC[0-24h]/24).

The level of wheal and flare inhibition did not decline as rapidly as plasma fexofenadine concentrations as illustrated in the following Figures.

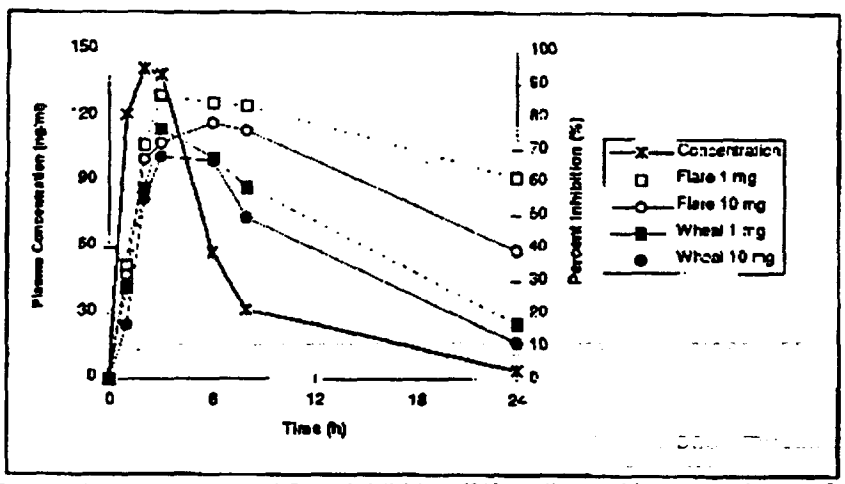


Figure. Mean wheal and flare inhibition (%) vs time with mean plasma fexofenadine concentrations (ng/ml) vs time - 30 mg oral fexofenadine HCl dose.

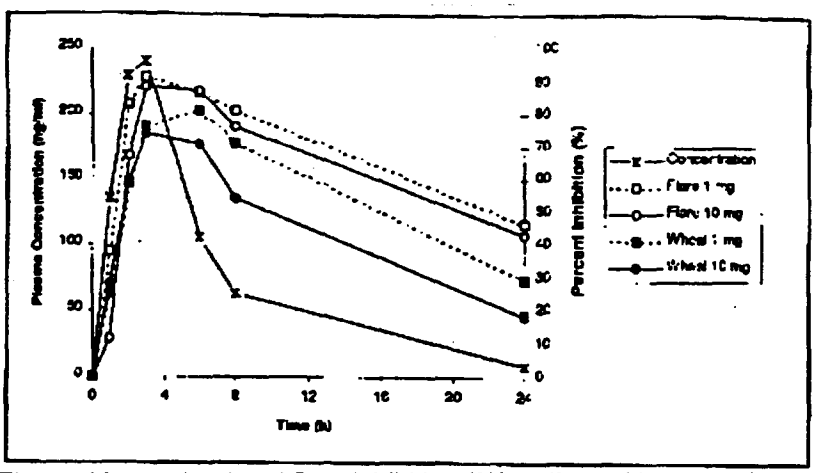


Figure. Mean wheal and flare inhibition (%) vs time with mean plasma fexofenadine concentrations (ng/ml) vs time - 60 mg oral fexofenadine HCl dose.

For the 30 mg dose the maximum mean wheal and flare inhibition levels occurred after the peak plasma fexofenadine concentration levels. The decline in plasma fexofenadine concentrations were visually more rapid than the decline in wheal and flare inhibition.

Sponsor's conclusions:

- Dose proportional increase in AUCinf and Cmax, were observed in pediatric patients when 30 mg and 60 mg single oral doses of fexofenadine hydrochloride were administered.
- Inhibition in histamine-induced wheal and flare areas was observed in pediatric patients following both the 30 mg and 60 mg oral fexofenadine hydrochloride doses.
- Following Cmax (maximum observed plasma fexofenadine concentration) the level of wheal and flare inhibition did not decline as rapidly as plasma fexofenadine concentrations indicating that continued wheal and flare inhibitory effect of fexofenadine is observed after plasma fexofenadine concentrations have started to decline.
- The 30 mg and 60 mg oral doses of fexofenadine hydrochloride were well tolerated in 7- to 12-year-old pediatric allergic rhinitis patients.

Reviewer's comments:
Treatment with 60 mg generally produced maximum observed effects that were only slightly greater than produced by treatment with 30 mg.. Inhibition effect of skin wheal and flare responses induced by epicutaneous histamine injection after 30 mg dose of fexpfenadine was almost identical with that after 60 mg dose, even though the plasma concentration is almost 2 times higher with 60 mg of fexofenadine.
Knowing that the systemic exposure in children after 30 mg dose is similar to that in adults after 60 mg dose, the dose of 30 mg of fexofenadine is recommended for the children.

It is recommended that the sponsor analyze the PK-PD modeling study to establish the fexofenadine concentration vs. effect relationship.

APPENDIX I-9. Report K-96-0978-D

Title: Fexofenadine population pharmacokinetic parameters in normal adult volunteers and pediatric patients

Protocol Numbers: PJPR0015; PJPR0025; PJPR0026; PJPR0029; PJPR0037

Project Report Number: K-96-0978-D

Objectives:
To compare the population mean estimates of fexofenadine pharmacokinetic parameters (AUC, oral clearance, Cmax, and half-life) and their corresponding variability between healthy normal adult volunteers and pediatric allergic rhinitis patients

Formulation:
Data included in this analysis is from phase I studies where fexofenadine hydrochloride was administered in capsule form.

Study Design And Sampling:
The fexofenadine pharmacokinetic parameters CLpo, AUCinf, Cmax, and t1/2 obtained from normal healthy adult volunteers and pediatric patients who had participated in five separate trials were analyzed using the nonlinear mixed effects modeling program NONMEM.
The 8-hour postdose time point was used in the determination of terminal half-life in the pediatric study (PJPR0037) because of inadequate plasma sampling points (i.e., 1, 2, 3, 6, 8, 24, and 48 hr; Based on previous pharmacokinetic studies it has been determined that the terminal portion of fexofenadine plasma profile begins 18 to 24 hours postdose). Due to this study design difference it is not appropriate to compare tl/2 across the populations.

All included studies were single-dose studies which used a capsule formulation. Data for normal healthy adult volunteers were obtained from bioavailability, bioequivalence, and food effect studies. Data for pediatric patients were obtained from a pharmacokinetic/pharmacodynamic study. Population parameter estimates and parameter variability estimates were computed for normal healthy volunteers and for pediatric patients.

Number of Subjects:
The pharmacokinetic parameter database included data from 174 treatment exposures to fexofenadine hydrochloride from 88 adult subjects, and 27 treatment exposures from 14 pediatric patients. Adult subjects may have been exposed to more than one dose of fexofenadine hydrochloride depending on the design of the individual studies (crossover or repeated treatment designs). Normal healthy adult volunteers were allowed to participate in more than one study. A total of 201 observations for CLpo, AUCinf and Cmax from 102 volunteers were included in this analysis.

Assay: