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# Bioavailability assessment of fexofenadine and montelukast in a fixed-dose combination tablet *versus* the components administered simultaneously

Everardo Piñeyro-Garza<sup>a\*</sup>, Magdalena Gómez-Silva<sup>a</sup>, Maria Elena Gamino-Peña<sup>a</sup>,  
Vanessa Cohen-Muñoz<sup>b</sup>, Gabriela Sánchez-Casado<sup>b</sup>

<sup>a</sup>Ipharma, S.A. de C.V., Monterrey, Mexico

<sup>b</sup>Medical Department, Consumer Health Care, Sanofi, Ciudad de México, Mexico

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antihistamine-  
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fixed-dose  
combination

### Abstract

**Introduction and Objectives:** Allergic rhinitis is a condition with high global prevalence most effectively treated with antihistamines and antileukotrienes. This study aimed to evaluate the bioequivalence of fexofenadine and montelukast in a fixed-dose combination tablet versus the components administered simultaneously.

**Materials and Methods:** An open, randomized, 2x2 crossover study was performed in 78 healthy volunteers. Fexofenadine-montelukast tablets containing 120 mg and 10 mg, respectively, were used as the test treatment, and 120 mg fexofenadine tablets and 10 mg montelukast tablets were used as the reference treatment. Concentrations of fexofenadine and montelukast in plasma were determined by protein precipitation and analysis by liquid chromatography/mass spectrometry or liquid chromatography tandem mass spectrometry.

**Results:** The 90% confidence intervals (CIs) obtained for fexofenadine were 87.612-102.144 for area under the curve of the plasma concentration after administration to the last concentration ( $AUC_{0-t}$ ), 88.471-102.282 for the AUC of the plasma concentration extrapolated to infinity ( $AUC_{0-\infty}$ ), and 91.413-108.544 for the maximum plasma concentration ( $C_{max}$ ). For montelukast, they were 96.418-108.416 for  $AUC_{0-t}$ , 93.273-106.642 for  $AUC_{0-\infty}$  and 94.749-110.178 for  $C_{max}$ . The ratio and CIs of the values subjected to logarithmic transformation for each parameter were within the range of acceptability of 80%-125%, demonstrating the bioequivalence of the combined fixed-dose tablet to the components administered separately at the same doses. No adverse events were recorded during the study.

**Conclusions:** This study has shown the bioequivalence of the combined fixed-dose tablet, which may be considered a new alternative for the treatment of allergic rhinitis.

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\*Corresponding author: Everardo Piñeyro-Garza. Ipharma, S.A. de C.V., Celaya 322, Mitras Centro, 64460 Monterrey, N.L., Mexico. Email address: [epineyro@i-pharma.com.mx](mailto:epineyro@i-pharma.com.mx)

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## Introduction

Allergic rhinitis, whether seasonal or perennial, is a condition with a high global prevalence that can affect between 10% and 30% of adults and up to 40% of children,<sup>1</sup> thus generating an economic and social burden.

In the pathophysiology of allergic rhinitis, histamine and cysteinyl leukotrienes (CysLTs) increase vascular permeability and resistance to nasal flow, causing symptoms, such as rhinorrhea, nasal itching, and sneezing (among others), which are associated with an increased risk of nasal congestion and reductions in quality of life and productivity.<sup>2-4</sup>

The Allergic Rhinitis and its Impact on Asthma Guidelines (ARIA) recommend managing allergic rhinitis with various treatments, including second-generation antihistamines (histamine type 1, H<sub>1</sub>) and leukotriene receptor antagonists.<sup>3,4</sup>

Fexofenadine, the active metabolite of terfenadine, is a selective antagonist of the H<sub>1</sub> receptor that does not cross the blood-brain barrier and has anti-inflammatory properties. It is rapidly absorbed with a long-lasting effect and can therefore be administered once daily for the treatment of allergic rhinitis.<sup>5,6</sup>

Montelukast is an antagonist of the CysLT type 1 receptor, and its anti-inflammatory effect is exploited to treat seasonal and perennial allergic rhinitis.<sup>4</sup>

Antihistamines and antileukotrienes are frequently used in combination for the treatment of allergic rhinitis because histamine and CysLTs have different roles in the pathophysiology of allergic rhinitis, and antihistamine-antileukotriene therapy has been shown to be more effective than monotherapy due to simultaneous blockade of two mediators with complementary effects, thereby effectively reducing symptoms.<sup>2,7,8</sup> In addition, therapeutic adherence is an important factor in the optimal management of allergic rhinitis, and administration of a fixed-dose combination of an antihistamine with an antileukotriene can improve this condition.<sup>3</sup>

The addition of montelukast to treatment with H<sub>1</sub> antihistamines has been assessed in multiple clinical trials, demonstrating additional advantages compared with monotherapies.<sup>2,9,10</sup> In particular, the fixed-dose combination of fexofenadine with montelukast has been used to treat allergic rhinitis and has demonstrated efficacy and safety.<sup>7,8,11</sup>

A fixed-dose combination tablet containing fexofenadine 120 mg and montelukast 10 mg was developed with the aim of offering a new therapeutic alternative to improve treatment adherence and convenience for patients with allergic rhinitis. The objective of this study was to evaluate the bioequivalence of the fixed-dose combination tablet and simultaneous administration of each compound at the same doses and at the same time in healthy volunteers under fasting conditions.

The study was carried out in the facilities of Ipharma S.A. de C.V. following the protocol A473-18 authorized by the research committee 16CI19039043 and by the Mexican Ministry of Health (COFEPRIS) 183301410B0368/2018.

## Materials and Methods

Healthy volunteers (men and women) between 18 and 55 years of age, with body mass index (BMI) between 18

and 27 kg/m<sup>2</sup>, were included in the study. The volunteers had negative results for pregnancy tests (women) and for exams assessing substance abuse during selection and at the beginning of each test period of study. Volunteers also had negative results for tests detecting anti-HIV antibodies (HIV Ag), Australia surface antigens for hepatitis B (HBsAg), anti-hepatitis C antibodies (HCV Ag), and the rapid plasma reagin (RPR) test.

The volunteers were required to have the following biochemical test results within the normal ranges: complete blood count, urinalysis, and biochemical profile. Additionally, their electrocardiograms could not show any abnormalities.

The exclusion criteria were drug allergies, intolerance to venipuncture, tobacco abuse (more than five cigarettes per day), currently receiving medical treatment, breastfeeding, swallowing or phagophobia problems, a history of asthma, drug addiction or alcohol abuse, having received a vaccine in the past 2 weeks, and consumption of more than five cigarettes, alcoholic beverages, xanthine-containing drinks, grapefruit juice, foods prepared on charcoal, food supplements, herbal remedies, or other drugs (phenytoin, magnesium hydroxide, or aluminum) in the past 48 hours.

## Sample size calculation

Assuming a true ratio of 95% and an intrasubject variability of 35.08%,<sup>12,13</sup> a sample size of 70 subjects was required to conclude comparative bioavailability between the two products with a power of 90%. After accounting for dropouts, it was decided to enroll 78 subjects, including 49 females and 29 males whose characteristics met the criteria to define a homogenous population according to the current norm, the protocol, and good clinical practices.

The number of subjects required for this comparative bioavailability study (sample size) was selected as established in the literature to determine the intrasubject variability (intrasubject CV) of the AUC and C<sub>max</sub> values from previous studies published for the same substances. The sample size was also selected according to the criteria established in the Mexican official standard NOM-177-SSA1-2013 for the administration of a single dose of a drug to healthy volunteers. Feeding variables were controlled to avoid effects from the consumption of food<sup>14</sup> or substances (alcohol or drugs).

## Study design

An open, randomized, 2×2 crossover study with two treatments applied over two periods at a single dose and two sequences under fasting conditions was conducted in January and February 2019. The analysts were blinded to the test (T) and reference (R) group assignments.

The study was conducted in accordance with applicable Mexican laws and regulations and adhered to good clinical practice (ICH 6), good documentation practices, and other regulatory provisions applicable in Mexico.

Each medication was administered to each volunteer only once because the duration of action is sufficiently long to measure pharmacokinetic parameters. Each volunteer's commitment was approximately 21 days. The treatment was administered during two periods of hospitalization for 37 hours, and two samples were collected at 48 and 72 hours after discharge. A 7-day washout period was implemented to ensure compliance with the norm establishing a seven-half-life period for the drug.

### Administration of the drugs

Fexofenadine-montelukast tablets containing 120 mg and 10 mg, respectively (lot 8MXA001, expiration date: April 2, 2020, manufactured by Sanofi-Aventis de Mexico, S.A. de C.V.), were used as the test treatment (T). As the reference treatment (R), 120-mg fexofenadine tablets (Allegra®, lot 8MXA003, expiration date: December 29, 2019, manufactured by Sanofi-Aventis Farmacéutica Ltd. and distributed by Sanofi-Aventis de Mexico, S.A. de C.V.) and 10-mg montelukast tablets (Singulair®, lot R007030, expiration date: January 31, 2020, manufactured by Merck Sharp & Dohme Ltd. and distributed by Schering-Plough, S.A. de C.V.) were used. See Supplementary Material 1 for additives used in tablet formation.

After a fast of at least 10 hours, baseline samples were collected, and then a 120-mg/10-mg fixed-dose fexofenadine-montelukast tablet was administered or the two individual drugs (fexofenadine 120 mg and montelukast 10 mg) were administered simultaneously dependent on previous randomization (T or R). The drugs were taken orally with 250 mL of room-temperature water.

Random group assignment was performed in two blocks under a balanced design such that half of the subjects were assigned to the RT administration sequence and the remaining subjects were assigned to the TR sequence. Random assignment was performed using the software R<sup>15</sup> with its internal algorithm Mersenne Twister, which has been previously validated with the DIEHARD test set for the assessment of random number generators.

### Sampling

A venous catheter was placed in a vein selected by the phlebotomist to facilitate the collection of subsequent samples. In each period, 22 4-mL samples were collected from each volunteer, including a sample at time 0.00 (pre-dose) and samples at 0.33, 0.66, 1.00, 1.33, 1.66, 2.00, 2.33, 2.66, 3.00, 3.33, 3.66, 4.00, 4.5, 5.0, 6.0, 8.0, 10.00, 12.00, 24.00, 48.00, and 72.00 hours. EDTA was added to each sample as an anticoagulant.

Each test tube was marked with a unique key for each subject, the consecutive number of the subject from 1 to 78, the period of study (T1 or T2), and the number corresponding to the sample collection time (01 to 22). The medication (T or R) was not indicated.

The samples were sent to an analytical laboratory for centrifugation at 3000 RPM for 10 minutes at a temperature of 5°C. The samples were then fractioned and immediately frozen.

### Analytical methods

Analyses were performed via precipitation of proteins, with subsequent analyses by liquid chromatography/mass spectrometry (HPLC/MS) or liquid chromatography tandem mass spectrometry (HPLC/MS-MS). The FXF-esi-MRM.m method for fexofenadine-montelukast and the MTKS.M, developed by the company Ipharma and validated with the official Mexican standard NOM-177-SSA 1-2013, were used. The concentration ranged from 5 ng/mL to 1000 ng/mL for both drugs.

### Pharmacokinetic analysis

The pharmacokinetic parameters measured were the time to reach the maximum plasma concentration ( $T_{max}$ ), the maximum plasma concentration ( $C_{max}$ ), the area under the curve of the plasma concentration after administration to the last concentration observed ( $AUC_{0-t}$ ), the area under the curve of the plasma concentration extrapolated to infinity ( $AUC_{0-\infty}$ ), the elimination constant ( $K_e$ ), and the elimination half-life ( $t_{1/2}$ ). The parameters assessed to establish possible equivalence in bioavailability were the  $C_{max}$  and  $AUC_{0-t}$ .

The pharmacokinetic parameters were determined with Phoenix WinNonlin 8.1 software. The range for acceptance of bioequivalence for both substances is 80% to 125% (90% confidence intervals [CI] of the geometric means of the T/R ratios for the  $C_{max}$  and  $AUC_{0-t}$  after logarithmic transformation).

### Analysis of safety

During the study and the sampling periods, the volunteers underwent a general physical examination protocol to assess the following vital signs: respiratory rate, body temperature, blood pressure, and heart rate. They were also monitored for the occurrence of adverse events.

### Analysis of tablet stability

Stability tests including for weight, uniformity, disintegration, and identification were performed. See Supplementary Material 2 for full list of tests and parameters.

### Statistical analysis

The  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $C_{max}$ ,  $K_e$ ,  $t_{1/2}$ , and  $T_{max}$  were estimated using a noncompartmental model; the  $AUC_{0-t}$  and  $AUC_{0-\infty}$  were estimated using the linear-logarithmic trapezoidal method, while the  $C_{max}$  and  $T_{max}$  were obtained directly from the decoded data. Descriptive statistics were calculated from the pharmacokinetic parameter values. Subsequently, the logarithmically transformed  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ , and  $C_{max}$  values were subjected to analysis of variance (ANOVA) to assess the possible effects of factors that could influence the response variables. The fixed factors included in this model were the sequence, the treatment

(formulation), the period, and the subject nested within sequence as random effect. The sequence, period, and treatment effects were assessed at the 5% two-sided significance level. Furthermore, the CI, test power, and unilateral double Schuirmann *t*-test results were assessed.<sup>16-19</sup> Statistical analysis was performed without subjects with extreme values. The statistics used to evaluate comparative bioavailability were calculated using Phoenix WinNonlin 8.1 software.

This comparative bioavailability study was conducted following the guidelines outlined in the Mexican Official Standard NOM-177-SSA1-2013, which establishes tests and procedures used to demonstrate that a drug is interchangeable, requirements to which authorized third parties who carry out interchangeability tests must adhere, requirements for carrying out biocompatibility studies, and requirements to be considered by authorized third parties, research centers, or hospital institutions that conduct biocompatibility tests.

## Results

### Population

A total of 78 healthy volunteers were included in the study. Only one volunteer did not show up for the second period of hospitalization and was excluded according to the elimination criteria. The demographic characteristics of the 77 volunteers assessed in the study are presented in Table 1.

Data from the 77 volunteers who completed the study according to the protocol were used to calculate the pharmacokinetic parameters  $T_{max}$ ,  $C_{max}$ ,  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $K_e$ , and  $t_{1/2}$ , with the concentrations measured in relation to the time profiles for fexofenadine and montelukast. The results are presented in Table 2.

In Tables 3 and 4, 90% CIs are presented for the  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ , and  $C_{max}$  of fexofenadine and montelukast. For both drugs, the CIs of the three parameters are within the bioequivalence range of 80% to 125% established in the protocol.

The ANOVA results revealed no statistically significant effect on the administration sequence, the administration period, or the formulation. For the sequence factor, for fexofenadine, the p-values were 0.2423 for  $\ln(AUC_{0-t})$ , 0.2549 for  $\ln(AUC_{0-\infty})$ , and 0.4728 for  $\ln(C_{max})$ , and for montelukast, the p-values were 0.6679 for  $\ln(AUC_{0-t})$ ,

**Table 1** Demographic characteristics.

Parameter (n = 77)	Mean	SD
Age (years)	25.68	6.24
Height (m)	1.65	0.08
Weight (kg)	64.55	8.92
BMI (kg/m <sup>2</sup> )	23.5	2.16

n, number; SD, standard deviation; m, meters; kg, kilograms.

**Table 2** Pharmacokinetic parameters of fexofenadine and montelukast from test and reference products.

Parameter (Unit)	Fexofenadine (n = 77)				Montelukast (n = 77)			
	Reference		Test		Reference		Test	
	Mean	(±SD)	Mean	(±SD)	Mean	(±SD)	Mean	(±SD)
$AUC_{0-t}$ (ng/mL*h)	2145.799	(±1077.646)	1989.35	(±977.377)	1619.151	(±676.638)	1672.533	(±712.287)
$AUC_{0-\infty}$ (ng/mL*h)	2228.951	(±1094.014)	2080.045	(±988.172)	1849.535	(±1459.149)	1761.885	(±733.498)
$C_{max}$ (ng/mL)	376.441	(±202.552)	368.247	(±190.075)	270.472	(±124.419)	273.8	(±113.817)
Parameter (Unit)	Median (range)		Median (range)		Median (range)		Median (range)	
$K_e$ (1/h)	0.13	(0.022, 0.322)	0.137	(0.022, 0.355)	0.129	(0.002, 0.341)	0.129	(0.049, 0.432)
$t_{1/2}$ (h)	5.326	(2.148, 30.885)	5.044	(1.951, 30.911)	5.356	(2.036, 272.054)	5.366	(1.602, 14.071)
$t_{max}$ (h)	2.66	(1, 5.066)	3	(1, 6)	3.66	(1, 8)	3.66	(1.33, 6)

Note: Arithmetic mean, SD, Standard deviation.

**Table 3** Geometric least square means of test and reference products of fexofenadine.

Parameter (Unit)	Geometric least squares means (n = 77)		Intrasubject CV%	Test/Reference %	90% CI	
	Reference	Test				
$AUC_{0-t}$ (ng/ml*h)	1867.7948	1766.9247	29.1788	94.59	87.612	102.144
$AUC_{0-\infty}$ (ng/ml*h)	1957.0566	1861.6752	27.5198	95.12	88.471	102.282
$C_{max}$ (ng/ml)	325.6306	324.3628	32.8305	99.61	91.413	108.544

The geometric least square means are presented as antilog means.

**Table 4** Geometric least square means of test and reference products of montelukast.

Parameter (unit)	Geometric least squares means (n = 77)		Intrasubject CV%	Test/Reference %	90% CI	
	Reference	Test				
AUC <sub>0-t</sub> (ng/ml*h)	1488.1401	1521.495	22.1086	102.2	96.418	108.416
AUC <sub>0-∞</sub> (ng/ml*h)	1616.1098	1611.803	25.3442	99.73	93.273	106.642
C <sub>max</sub> (ng/ml)	243.58963	248.8821	28.6665	102.2	94.749	110.178

The geometric least square means are presented as antilog means.

0.4705 for  $\ln(AUC_{0-\infty})$ , and 0.1319 for  $\ln(C_{max})$ . Regarding the period factor, the p-values were 0.3254 for  $\ln(AUC_{0-t})$ , 0.2697 for  $\ln(AUC_{0-\infty})$ , and 0.1319 for  $\ln(C_{max})$  for fexofenadine, and for montelukast, the p-values were 0.4758 for  $\ln(AUC_{0-t})$ , 0.8670 for  $\ln(AUC_{0-\infty})$ , and 0.3045 for  $\ln(C_{max})$ , and the factor formulation p-values were 0.2270 for  $\ln(AUC_{0-t})$ , 0.2489 for  $\ln(AUC_{0-\infty})$ , and 0.9242 for  $\ln(C_{max})$  for fexofenadine, and for montelukast, the p-values were 0.5248 for  $\ln(AUC_{0-t})$ , 0.9455 for  $\ln(AUC_{0-\infty})$ , and 0.6269 for  $\ln(C_{max})$ .

The mean plasma concentrations after administration of the fexofenadine and montelukast reference and test products are reported in [Figure 1](#) and [Figure 2](#), respectively.

### Tolerability

During the development of the study, the research subjects were constantly monitored, and the aforementioned safety measures, good clinical practices, and pharmacovigilance were applied. Vital signs and/or the studied parameters were recorded according to the frequencies established in the protocol.

Changes in vital signs recorded at the times established in the protocol were not clinically significant. Some

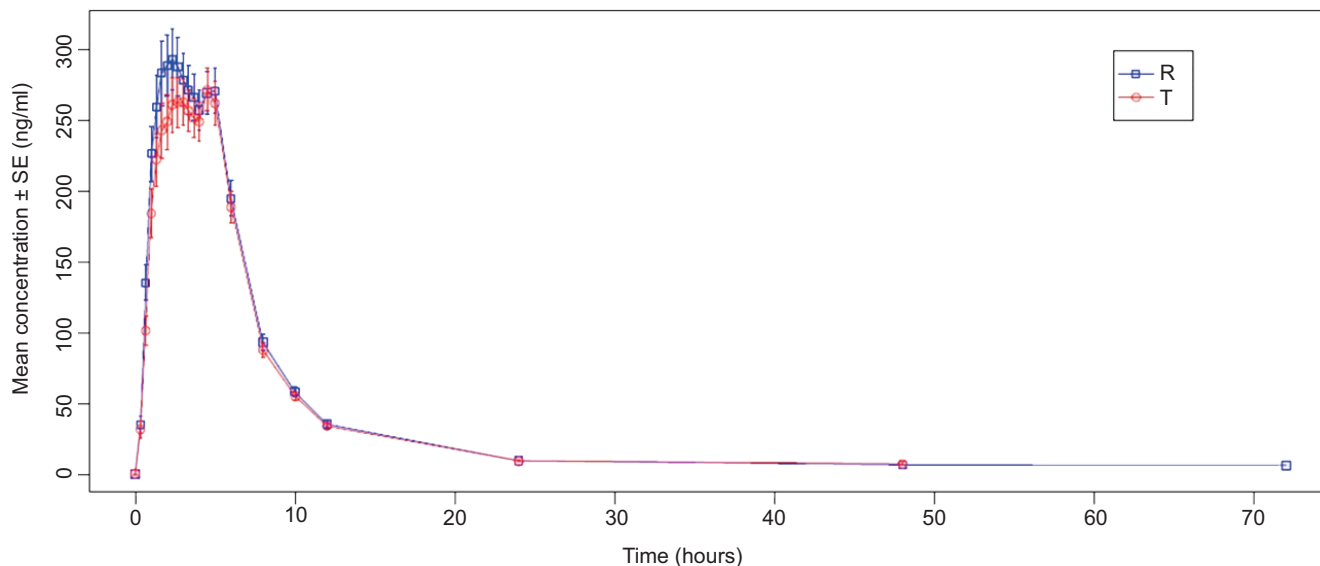
extreme values and fluctuations over time were noted but were not relevant.

No adverse events occurred from the time of signing the informed consent to the time of discharge from the research facilities.

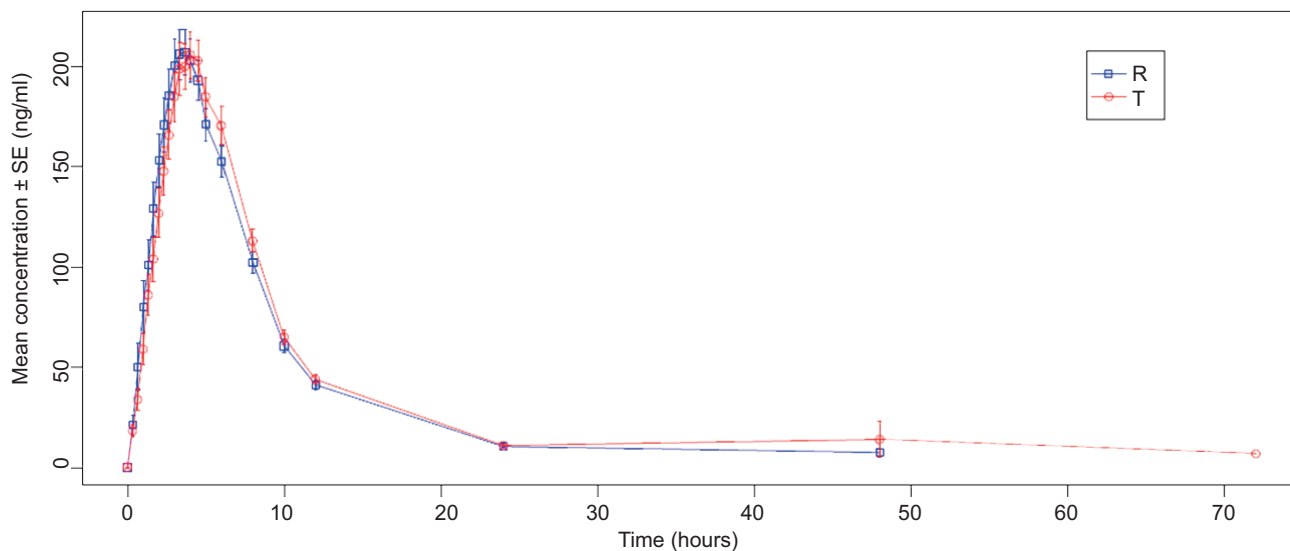
The additives used in the preparation of the tablets are presented in Supplementary Material 1. The additive profiles differed slightly; however, no considerable biological effects were reported in the study, or in the stability tests performed, presented in Supplementary Material 2.

### Discussion

The results of this study demonstrate the comparative bioavailability of the fixed-dose combination tablet containing fexofenadine 120 mg and montelukast 10 mg, with the components administered separately at the same dose, in healthy patients. The 90% CIs of the logarithmically transformed AUC<sub>0-t</sub>, AUC<sub>0-∞</sub>, and C<sub>max</sub> values were within the range of acceptability of 80% to 125% according to the requirements of the *Guideline on The Investigation of Bioequivalence of the European Medicines Agency*<sup>20</sup> and the norm NOM-177-SSA1-2013.<sup>21</sup>



**Figure 1** Mean concentrations of fexofenadine after administration of the test and reference products. R, reference; T, test.



**Figure 2** Mean concentrations of montelukast after administration of the test and reference products. R, reference; T, test.

The safety of fexofenadine<sup>5</sup> and montelukast<sup>4</sup> has been previously assessed, with both drugs showing safety profiles similar to placebo. Studies have been conducted to evaluate the efficacy of the fixed-dose combination of 120 mg of fexofenadine and 10 mg of montelukast administered once a day for 14 days, and a significant reduction in allergic rhinitis symptoms has been demonstrated.<sup>7</sup> In the study by Cingi et al., fexofenadine and montelukast were administered concomitantly for 21 days during the spring season when pollen levels are high for comparison with fexofenadine alone and fexofenadine plus placebo. The results showed that the combined treatment was significantly more effective in nasal congestion reduction compared to the other treatments.

The results are consistent with those obtained in the study by Walekar et al.<sup>11</sup> in which the bioequivalence of the fixed-dose combination and the medications administered concomitantly was established based on the 90% CIs of the geometric means of the logarithms of the parameters  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ , and  $C_{max}$ , which were within the range of 80% to 125%.

## Conclusion

In this study, the fixed-dose combination of fexofenadine 120 mg and montelukast 10 mg, and these medications administered concomitantly met the regulatory criteria for bioequivalence in healthy volunteers assessed under fasting conditions. The fixed-dose combination tablet may be considered a new alternative for the treatment of allergic rhinitis and may help patients to control their symptoms and improve therapeutic adherence.

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## Author contributions

EPG was involved in conceptualization and design of the study, data acquisition and analysis, manuscript revision, and final approval; MG-S and MEGP were responsible for data analysis, manuscript drafting, revision, and final approval; VCM and GSC contributed to the design of the study, manuscript revision, and final approval.

## Ethics approval and consent to participate

This study was approved by the Ethics Review Committee of 19-CEI-009-20160729.

The informed consent was obtained from all participants, as we sought permission from the patients before data collection. The procedures followed were in accordance with the ethical standards of Helsinki Declaration.

## Consent for publication

Not applicable.

## Competing interests

The authors VC-M and GS-C are employees of Sanofi Aventis de Mexico S.A. de C.V.

No conflict of interest from iPharma members.

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## Supplementary Materials

**Supplementary Material 1.** Additives used in tablet formation

### Drug

Fexofenadine hydrochloride 120 mg (amount is adjusted according to titration/2% excess added)

### Additives

Pregelatinized starch 120 mg  
Microcrystalline cellulose 81 mg PH101  
Microcrystalline cellulose 52 mg PH102  
Croscarmellose 24 mg  
Magnesium stearate 3 mg  
Purified water cs (evaporates during processing)

## Second layer

### Drug

Montelukast sodium equivalent to Montelukast 10 mg (the amount is adjusted according to the titration/an excess of 2% is added).

### Additives

Lactose monohydrate 150.600 mg  
Microcrystalline cellulose 15 mg PH112  
Microcrystalline cellulose 15 mg PH 101  
Croscarmellose 6 mg  
Hydroxypropylcellulose 2 mg  
Magnesium Stearate 0.500 mg  
Iron oxide yellow 0.500 mg E172  
Purified water cs (evaporates during processing)

## Supplementary Material 2 Final tablet product specifications

Test	Specification	Reference	Release	Stability	Justification
Description	Oblong, biconvex tablet, with yellow to dark yellow coating, engraved '120' on one side and '10' on the other side.	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X	X	Characteristics that must be fulfilled according to the formulation design.
Average weight	615.0 mg $\pm$ 5 % (584.25-645.75 mg)	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X		Failure to comply with these specifications would consequently have an impact on drug trial compliance.
Weight uniformity	No more than two individual weights deviate more than 5% from the average and none deviate more than 10%.	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X		
Disintegration	Maximum 30 minutes	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X		Test indirectly related to drug dissolution. Both the formulation process variables and storage conditions can have an effect on the test.
Identification					
a. Fexofenadine HCl by HPLC	The retention time of the Fexofenadine HCl peak in the chromatogram of the test solution corresponds to the Fexofenadine HCl peak in the chromatogram of the standard solution	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X		Drug identification is critical for safety and efficacy.
b. Montelukast by HPLC	The retention time of the Montelukast peak in the chromatogram of the test solution corresponds to the Montelukast peak in the chromatogram of the standard solution.	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X		Drug identification is critical for safety and efficacy.



Test	Specification	Reference	Release	Stability	Justification
Uniformity of Dose					
a. Fexofenadine HCl	Maximum 15	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X		Variability in content uniformity can affect safety and efficacy. Both formulation and process variables can affect content uniformity.
Stage I (L1 = 15.0) Acceptance Value (AV) of 10 units					
Acceptance value (AV) of 30 units					
0 Units < [1-(0.01)(L2)]M					
0 Units < [1 + (0.01)(L2)]M					
b. Montelukast	Maximum 15	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X		
Water content by Karl Fischer	Informative (%)	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X	X	Generally, water content can affect degradation and promote microbial growth.
Dissolution					
a. Fexofenadine HCl	Minimum 80%	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X	X	Failure to meet the dissolution specification may affect the bioavailability of the drug. Both the formulation and process variables can affect the dissolution profile.
Q = 80%, 30 minutes					
b. Montelukast	Mínimum 70%	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X	X	
Q = 70%, 30 minutes					
Assay					
a. Fexofenadine HCl	114.0-126.0 mg/tablet 95.0%-105.0%	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X	X	Variability in the trial can affect safety and efficacy.
b. Montelukast	10.0-11.0 mg/tablet 90.0%-110.0%				
		Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X	X	

Test	Specification	Reference	Release	Stability	Justification
<b>Fexofenadine HCl-Related Substances</b>					
a. Impurity A	≤ 0.40 %	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X	X	Degradation products can have an impact on safety and must be quantified and monitored.
b. Decarboxylated degradation	≤ 0.15 %	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X	X	
c. Any individual impurity	≤ 0.20 %	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X	X	
d. Impurity Sum	≤ 0.50 %	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X	X	
<b>Montelukast-Related Substances</b>					
a. Sulfoxide impurity	≤ 2.0	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X	X	Degradation products can have an impact on safety and must be quantified and monitored.
b. Hydroxy Impurity	≤ 0.2	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X	X	
c. Cis-isomer impurity	≤ 0.2	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X	X	
d. F impurity	≤ 0.2	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X	X	
e. Any other impurity	≤ 0.2	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X	X	

Test	Specification	Reference	Release	Stability	Justification
f. Total impurity	≤ 3.0	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X	X	
Identification test for ferric oxide	Positive	Finished product specification and analytical test procedure, T-069AMF120, EDITION No. 005.	X		<b>Test performed to verify the presence of ferric oxide as a coloring lacquer.</b>
<b>Microbiology</b>					
Aerobic mesophilic organisms	Maximum 10 <sup>3</sup>	FEUM 11ed	X	X	<b>Failure to comply with microbial limits would have an impact on patient health.</b>
Filamentous fungi and yeast counts	Maximum 10 <sup>2</sup>	FEUM 11ed	X	X	
<i>Escherichia coli</i>	Absence	FEUM 11ed	X	X	