Comparison of Systemic and Pulmonary Bioavailability of Fluticasone Propionate HFA pMDI 250 mcg per actuation with and without Spacer Device in Healthy Volunteers

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Introduction

•Fluticasone propionate given by inhalation offers prophylactic treatment for asthma of all severities. The recommended dose in adults and children over 16 years is 100 to 1,000 micrograms twice daily, usually as two twice daily inhalations

•FlixotideEvohaler may be used with a Volumatic spacer device by patients who find it difficult to synchronise aerosol actuation with inspiration of breath

Study Products

Innovator- Flixotide® 250 Evohaler® manufactured by GlaxoWellcome Production, France

Generic- Fluticasone propionate HFA pMDI 250 mcg/actuation manufactured by CiplaLtd., India

Objective

•The aim of these studies was to evaluate the rate and extent of absorption of test formulation of Fluticasone propionate HFA pMDI 250 mcg/actuationmanufactured by CiplaLtd., Indiaagainst the reference formulation Flixotide®250 Evohaler® (containing fluticasone propionate 250 mcg per actuation) manufactured by GlaxoWellcome Production, France, with and without volumatic spacer device under fasting conditions in order to assess bioequivalence

Methods

Study design

•Study-1 was a, randomized, single dose, laboratory-blinded, 2-sequence, 4-period, crossover replicate design without volumatic spacer in 32 healthy volunteers under fasting conditions with a washout period of 14 days

•Study-2 was a randomized, single dose, laboratory-blinded, 2-sequence, 2-period, crossover design with volumatic spacer in 28 healthy volunteers under fasting conditions with a washout period of 14 days

•In both the studies, a single dose of fluticasone propionate HFA pMDI 1000 µg (250 µg per actuation × 4 puffs) was used to compare test and the reference formulation

Study Protocols

•The study protocols were approved by Dakshata, an independent ethics committee prior to study initiation. The studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice Guideline.∴

•Both the studies were conducted at Sitec Labs. Pvt. Ltd., Navi Mumbai, India

Study volunteers and eligibility criteria

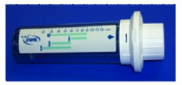
•Volunteers were screened within 21 days prior to dosing

•A total of 32, and 28 Indian adult male non-smoker volunteers, between 18 and 45 years of age (inclusive), having body mass index ≥ 18.5 kg/m2 and ≤ 25.00 kg/m2, in general good health were enrolled in study-1, and 2 respectively.

•Before inclusion into the study, the volunteers were judged to be healthy by physician based on physical examination, ECG, chest X-ray, pulmonary function test, pulse oximetry, and clinical laboratory test results

Training On the Inhalation Technique

•Volunteers were trained on the inhalation technique with the help of an in-check dial, aerosol inhalation monitor and a placebo (inactive) inhaler at least for 5 days continuously prior to dosing



Study procedures

On check in day-

•written informed consent was obtained from all willing volunteers

•Volunteers who fulfilled all the criteria for inclusion were admitted to the study center at least 12hrs prior to each dosing

•In the study-1, a total of 32 were recruited. In the study-2, a total of 28 were recruited

Drug administration

•After priming, investigational product was inhaled. In study-1, A single dose of 4 puffs (each puff releases 250 µg of fluticasone propionate) of the test or the reference product were inhaled by the volunteer as per the randomized sequence in the standing position on four separate treatment days

•In study-2, A single dose of 4 puffs (each puff releases 250 µg of fluticasone propionate) of the test or the reference product were inhaled by the volunteer with the aid of the volumatic spacer device as per the randomized sequence in the standing position on two separate treatment days

Study restrictions

•Volunteers remained seated at least for the first 2 hrs after dosing

•Water was not permitted from 1 hr before dosing until 1 hr following dosing, but it was allowed at all other times. Post dosing, food was withheld for at least 4 hrs. Standardized lunch, snack and dinner were served at 4, 9, and 13 hrs after dosing

•They were asked not to take any drugs at least two weeks before the first dosing, to avoid taking food or drinks that contain xanthine: chocolate, tea, coffee and cola drinks, not to drink alcoholic products 48 hours before dose administration and during the study

Blood sampling

•In both the studies, venous blood samples (1 x 5 mL) were collected at -0.00 hours (pre-dose) and at 0.08, 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 18.00, 24.00 and 36.00 hr post dose

•Blood samples for fluticasone propionate analysis were collected via an indwelling catheter (intra-venous) with respect to start time offirst puff in vacutainers containing K_2EDTA anticoagulant

•The blood sample tubes were centrifuged to separate plasma and plasma samples were stored at –70°C or below until sample analysis

Bioanalysis

•Fluticasone propionateplasma concentrations were determined using validated LC-MS/MS method. The lowest limit of quantitation of method was 3.0 pg/ml for both the studies

Results

Safety

•In study-1, 4 volunteers (12.50%) experienced an adverse event. In study-2, 8 volunteers (28.57%) experienced an adverse event. No serious adverse events (SAE)/death occurred during conduct of study-1 and 2.

Pharmacokinetics and statistics

•In study 1, 32 volunteers were randomised of which 28 volunteers completed the study. 3 volunteers discontinued from the study due to personal reasons and 1 volunteer was discontinued due to unacceptable inhaler technique. In study 2, 28 volunteers were randomised of which 25 volunteers completed the study. There were 3 volunteers who discontinued from study 2 due to personal reasons

•Mean plasma concentration profiles of fluticasone propionate are presented in Figure 1 (for without spacer study-1), and Figure 2 (for with spacer study-2). The statistical results of primary pharmacokinetic parameters for fluticasone propionate of Study-1 and Study-2 are presented in Table 1. The Geometric mean ratios, 90% CIs, power and intra subject coefficient of variation of test and reference for Ln transformed pharmacokinetic parameters C_{max}, and AUC_{0-t} for fluticasone propionate of Study-1 and Study-2 are presented.

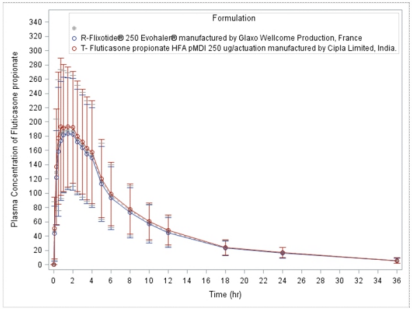


Figure 1

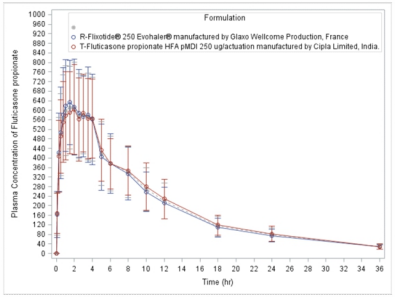


Figure 2

Pharmacokinetic Parameters	Study-1		Study-2	
	Test (T) (Mean ± SD)	Reference (R) (Mean ± SD)	Test (T) (Mean ± SD)	Reference (R) (Mean ± SD)
N	56	56	25	25
C_{max} (ng/mL)	222.97 ± 96.55	208.34 ± 86.73	656.50±180.37	687.25±199.70
AUC_{0-t} (hr.ng /mL)	1798.83 ± 772.15	1683.67 ± 744.36	7127.75±2139.82	6898.32±2111.43
$AUC_{0-\infty}$ (hr.ng /mL)	1890.35 ± 798.98	1769.58± 765.67	7529.96±2299.02	7252.67±2194.47
*T_{max} (hr)	1.00 (0.50-3.50)	1.00 (0.25-4.00)	2.00 (0.50 – 4.00)	1.50 (0.75 – 10.00)
K_{el} (1/hr)	0.087 ± 0.018	0.085 ± 0.018	0.082±0.009	0.083±0.013
$T_{1/2}$ (hr)	8.40 ± 2.06	8.54 ± 1.73	8.58±1.07	8.58±1.35

*Median (range)

Table 1

Pharmacokinetic Parameters	Geometric Mean		*(%)T/R	90% Confidence Interval	Power (%)	Intra subject CV%
	Test	Ref				
Study-1						
N	56	56	-	-	-	-
C_{max} (pg/mL)	199.41	190.57	104.64	97.46-112.34	99.97	22.61**
AUC_{0-t} (hr.pg/mL)	1610.36	1525.58	105.56	98.55-113.06	99.98	22.61**
Study-2						
N	25	25	-	-		
C_{max} (pg/mL)	631.5617	656.8985	96.14	88.13 - 104.88	99.33	18.08
AUC_{0-t} (hr.pg/mL)	6832.3683	6604.9426	103.44	96.21 - 111.22	99.92	15.02

*(%) T/R is ratio of Test Geometric Mean / RefGeometric Mean
**intra-subject variability for reference product

Table 2

Conclusion

Overall it is concluded that the test formulation fluticasone propionate HFA pMDI (CIPLA LTD., INDIA) is therapeutically equivalent to the reference formulation of Flixotide® Evohaler® manufactured by GLAXO WELLCOME PRODUCTION, FRANCE