Original Article

การศึกษาชีวสมมูลของยาเลโวเซทิริซีนไดไฮโดรคลอไรด์ 5 มิลลิกรัม ในอาสาสมัครชายไทยสุขภาพดี

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บทคัดย่อ

บทนำ: เลโวเซทิริซีนเป็นอาร์ไอโซเมอร์ของเซทิริซีนซึ่งเป็นยาต้านฮิสตามีนรุ่นที่สอง เนื่องจากมีการใช้ยานี้ในการรักษาโรคภูมิแพ้ทางจมูก และโรคลมพิษเรื้อรังอย่างกว้างขวาง องค์การเภสัชกรรมจึงได้พัฒนายาสามัญของเลโวเซทิริซีนด้วยต้นทุนที่ต่ำกว่าขึ้น ซึ่งจะเป็นประโยชน์ต่อคนไข้ที่เป็นโรคภูมิแพ้ทางจมูก และโรคลมพิษเรื้อรัง **วิธีดำเนินการวิจัย** การศึกษาสุ่มไขว้สลับแบบไม่ปกปิดตัวยาที่ได้รับ โดยให้ยาทางปากครั้งเดียวเว้นระยะห่างการให้ยา 7 วัน ภายใต้สภาวะอดอาหารในอาสาสมัครชายสุขภาพดีจำนวน 26 คน ตัวอย่างเลือดที่เวลาต่างๆ ถูกเก็บจากอาสาสมัครจนครบ 48 ชั่วโมง นำพลาสมาไปตรวจวัดระดับยาในเลือดด้วยเทคนิควิเคราะห์แบบอะไครัลโดยใช้ LC-MS/MS และวิเคราะห์พารามิเตอร์ทางเภสัชจลนศาสตร์โดยใช้แบบจำลองแบบไม่ใช้ห้อง **ผลการวิจัย:** พารามิเตอร์ทางเภสัชจลนศาสตร์ระหว่างยาตำรับที่องค์การเภสัชกรรมผลิตกับยาต้นแบบ (ค่าเฉลี่ย ± ส่วนเบี่ยงเบนมาตรฐาน) พบว่า พื้นที่ใต้กราฟระหว่างระดับยาในพลาสมากับเวลาที่ 0 ชั่วโมงถึงเวลาที่ 48 ชั่วโมงมีค่า 1708.294 ± 372.005 และ 1739.707 ± 356.047 ชั่วโมง•นาโนกรัมต่อมิลลิลิตร พื้นที่ใต้กราฟระหว่างระดับยาในพลาสมากับเวลาที่ 0 ชั่วโมงถึงเวลาอนันต์มีค่า 1830.174 ± 360.107 และ 1847.587 ± 344.015 ชั่วโมง•นาโนกรัมต่อมิลลิลิตร ค่าระดับยาสูงสุดในพลาสมาเป็น 222.414 ± 37.189 และ 220.950 ± 36.342 นาโนกรัมต่อมิลลิลิตร อัตราส่วนค่าเฉลี่ยของพื้นที่ใต้กราฟระหว่างระดับยาในพลาสมากับเวลาที่ 0 ชั่วโมงถึงเวลาที่ 48 ชั่วโมง, พื้นที่ใต้กราฟระหว่างระดับยาในพลาสมากับเวลาที่ 0 ชั่วโมงถึงเวลาอนันต์และค่าระดับยาสูงสุดในพลาสมาระหว่างยาทดสอบและยาต้นแบบที่ช่วงความเชื่อมั่น 90 เปอร์เซนต์มีค่า 98.1 (94.60-101.72), 99.0 (95.81-102.31) และ100.6 (95.56-105.89) ตามลำดับ ค่าทั้งสามนี้ต่างอยู่ในช่วงการยอมรับ 80.00-125.00 อยู่ในเกณฑ์มาตรฐานที่ถือว่ามีชีวสมมูลกันตามที่สำนักงานคณะกรรมการอาหารและยากำหนดไว้ **สรุปผลการวิจัย:** ตำรับยาที่องค์การเภสัชกรรมผลิตกับตำรับยาต้นแบบชีวสมมูลกัน และสามารถใช้แทนกันได้

คำสำคัญ: เลโวเซทิริซีน เลโวเซทิริซีน ไดไฮโดรคลอไรด์ เภสัชจลนศาสตร์ ชีวสมมูล โครมาโทกราฟฟี่ของเหลว-แทนเดมแมสสเปคโทรเมทรี

วารสารเภสัชศาสตร์อีสาน 2558; 11(1): 79-88

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Bioequivalence Study of Levocetirizine Dihydrochloride 5 mg Tablets in Healthy Thai Male Volunteers

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Abstract

Introduction: Levocetirizine, a second generation H_1-receptor antagonist, is an (*R*)-isomer of cetirizine. Due to an extensive use of levocetirizine dihydrochloride for the relief of symptoms associated with seasonal and perennial allergic rhinitis (AR) and the treatment of the uncomplicated skin manifestations of chronic idiopathic urticarial (CIU), a generic product of levocetirizine dihydrochloride of the Government Pharmaceutical Organization (GPO) has been developed with a more affordable price. **Methods:** A randomized, open-label, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study was conducted using the generic levocetirizine dihydrochloride 5 mg tablets of GPO, Thailand and the reference product (Xyzal®) on 26 healthy male subjects, who under fasted for 7 day washout period. Blood samples were collected at predefined time up tp 48 hours. Plasma concentrations of levocetirizine were analyzed using an achiral assay by liquid chromatography tandem mass spectrometry. A Non-compartmental model was used for pharmacokinetic analysis. **Results:** The mean values (±SD) of pharmacokinetic parameters (test vs. reference) were $AUC_{0\text{-tlast}}$ (1708.294 ± 372.005 vs 1739.707 ± 356.047 hr.ng/mL), $AUC0\text{-}_{\infty}$ (1830.174 ± 360.107 vs 1847.587 ± 344.015 hr.ng/mL) and C_{max} (222.414 ± 37.189 vs 220.950 ± 36.342 ng/mL). The 90% Confidence Intervals for the ratios of mean $AUC_{0\text{-tlast}}$, $AUC0\text{-}_{\infty}$ and C_{max} for the test/reference were 98.1 (94.60-101.72), 99.0 (95.81-102.31) and 100.6 (95.56-105.89), respectively. These values were within the acceptable range of 80.00-125.00. Both the formulations were well tolerated. No clinically significant or serious ADRs were observed. **Conclusion:** Two formulations of levoceterizine dihydrochloride, GPO and Xyzal®, are bioequivalent and can be used interchangeably.

Keywords: Levocetirizine, Levocetirizine dihydrochloride, Pharmacokinetics, Bioequivalence, Liquid chromatography-tandem mass spectrometry

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Introduction

Levocetirizine, a second generation H_1-receptor antagonist, is an (*R*)-isomer of cetirizine It is chemically described as (R)-[2-[4-[(4-chlorophenyl) phenylmethyl]-1-piperazinyl] ethoxy] acetic acid as shown in figure 1 (UCB Inc, 2009). Levocetirizine is indicated for the relief of symptoms associated with seasonal and perennial allergic rhinitis (AR) and the treatment of the uncomplicated skin manifestations of chronic idiopathic urticarial (CIU) (UCB Inc, 2009). An *in vitro* study has demonstrated that levocetirizine exhibited higher affinity to human H1-receptor than cetirizine (2-fold) and its distomer, (S)-dextrocetirizine (30-fold) (Gillard et al, 2002). Levocetirizine is absorbed rapidly after oral administration with a time to maximum plasma concentration (t_{max}) of less than 1 hour in healthy adults (Hair et al, 2006). It has a smaller volume of distribution (V_d) compared to dextrocetirizine (0.41 L/Kg versus 0.60 L/Kg). Mean AUC and C_{max} of levocetirizine are 4136.4 ± 737.6 hr.ng/mL and 512.25 ± 104.98 ng/mL, respectively and they are higher than its distomer (Baltesa et al, 2001). Levocetirizine is mainly eliminated as unchanged form through renal excretion with limited metabolism (Hair et al, 2006). It has a longer half-life ($t_{1/2}$) about 7.76 ± 1.59 hr and a lower total plasma clearance (27.65 ± 6.98 L) (Baltesa et al, 2001). The most common adverse reactions were somnolence, nasopharyngitis, fatigue, dry mouth, and pharyngitis in adults, and pyrexia, cough, epistaxis, diarrhea, vomiting, and constipation in children (UCB Inc, 2009). In a randomized, double-blind, crossover comparison among cetirizine, levocetirizine, and dextrocetirizine on histamine-induced cutaneous responses, levocetirizine and cetirizine were able to inhibit histamine-induced wheal and flare while dextrotcetirizine was not (Devalia et al, 2001). Another randomized, double-blind, placebo-controlled, four-way, crossover study on inhibition of histamine-induced nasal response by among cetirizine, levocetirizine, and dextrocetirizine showed that cetirizine and levocetirizine able to attenuate nasal airway resistance induced by histamine but dextrocetirizine did not exert these antihistamine activities (Wang et al, 2001). Those two clinical trials suggested that antihistaminic effects of cetirizine might come from levocetirizine.

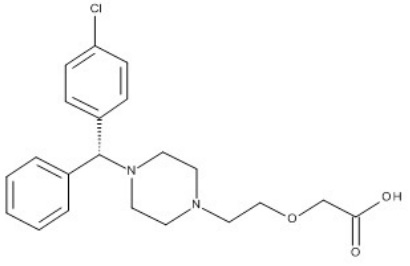

Figure 1 Chemical Structure of levocetirizine

Due to an extensive use of levocetirizine dihydrochloride in the relief of symptoms associated with seasonal and perennial allergic rhinitis and the treatment of the uncomplicated skin manifestations of chronic idiopathic urticarial, a generic product of levocetirizine dihydrochloride of The Government Pharmaceutical Organization (GPO) has been developed with lower price and would be benefit for patients with AR and CIU. Consequently, the bioequivalence study is conducted to

demonstrate the interchangeability between the generic levocetirizine dihydrochloride and the reference product.

Methods

Drugs and Chemicals: The test product (Levocetirizine GPO tablets) was manufactured from GPO (Batch number S540451, Manufactured on January 23, 2012, Expiry date January 23, 2014). The reference product (Xyzal®tablets) was manufactured by UCB FarchimSA, Bulle-Switzerland (Lot number 29281, Manufactured on November 30, 2010, Expiry date October 28, 2014).

Study Design: A randomized, open-label, two-treatment, two-period, two-sequence, single dose, crossover, bioequivalence study of the generic levocetirizine dihydrochloride 5 mg tablets of GPO, Thailand and the reference product (Xyzal®) of UCB Farchim SA, Bulle-Switzerland in healthy human male adult subjects, under fasting conditions was conducted. Washout period was at least 7 days between treatments. The study protocol was approved by the Ethics Committee of Institute for the Development of Human Research Protections (IHRP), Department of Medical Sciences, Ministry of Public Health.

Study Subjects: Twenty six subjects, randomly selected from healthy adult Thai male volunteers were participated in this study. Subject inclusion criteria included age between 18-55 years and Body Mass Index (BMI) between 18-25 kg/m^2. All subjects were determined healthy judged from medical history, physical examination and laboratory examination (complete blood count, hematocrit, hemoglobin, fasting blood sugar, blood urea nitrogen (BUN), serum creatinine, alkaline phosphatase, ALT, AST, total bilirubin, total protein, albumin, hepatitis B test, urine analysis and ECG). The exclusion criteria included history of hypersensitivity to levocetirizine or related substances, history of medical illness (like gastrointestinal, hepatic, renal, cardiovascular, diabetes mellitus, and gallstone disease), clinically significant illness within 4 weeks before the start of the study, asthma, urticaria or other allergic type reactions, alcohol abuse, participation in any other clinical trial involving drug administration and collection of blood samples or donation blood in the preceding 1 month prior to the start of the study. The subjects were informed about risks and benefits of the study and signed informed consent before participating into the study. The subjects were not received any medication and alcohol during 14 days prior to the beginning of the study and during the study. They were restricted from tea, coffee or xanthine products at least 24 hours prior to the first dose of study medicine or during the study.

Blood sampling: Blood samples were collected using the indwelling catheter for 22 sampling times (0, 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 hours). The blood samples were centrifuged at 3000 ± 100 RCF (Relative Centrifugal Force) for 5 minutes below 10 °C. All plasma samples were transferred to pre-labeled polypropylene tubes and stored frozen at -65 ± 10 °C until analysis.

Subject safety monitoring: Subjects will be informed for the side effects and questioned

for well being at the times of clinical examinations and during vital signs examination. Subjects will be monitored throughout the study period for adverse events. Seated blood pressure, pulse rate, body temperature will be measured after check-in, prior to study administration, at every 4 hours post-dosing and before check-out of each period. All adverse events will be treated by the attending physician and will be followed up. Laboratory assessment and urine analysis will be done before check-out for post-study safety assessment. All adverse events and results of examination will be recorded on Case Report Form.

Analytical Procedure: The plasma concentrations of levocetirizine in study samples were determined by a validated LC-MS/MS method using sertraline as an internal standard. The summary of validation results are shown in Table 1. The US FDA guidance for industry, bioanalytical method validation (FDA, 2001) and the European Medicines Agency guideline on bioanalytical method validation (EMA, 2011) were followed. The analyte and internal standard were extracted from plasma using protein precipitation technique and monitored in the positive ion mode using ESI; Electro Spray Ionization probe. MRM; Multiple Reaction Monitoring transitions of m/z 389.130$\rightarrow$201.000 and m/z 306.040$\rightarrow$159.000 were carried out for analyte and internal standard, respectively. The chromatographic system consisted of ACE 3 C18 150 x 4.6 mm column. The mobile phase was a mixture of 0.1% formic acid solution (v/v) and methanol (20:80 %v/v) with a flow rate of 1.1 mL/min at 40°C.

Pharmacokinetic Analysis: The pharmacokinetic parameters ($AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, λ_z and $t_{1/2}$) were determined by non-compartmental model using Phoenix WinNonlin Software Version 6.3. Values below lower limit of quantification (5.090ng/mL) were set as zero for calculation purposes.

Statistical Analysis: The statistical analysis was conducted using PROC GLM of SAS® Version 9.3. The primary pharmacokinetic parameters ($AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$ and C_{max}) were transformed to natural logarithm scale (ln) before statistical analysis. Bioequivalence of Test Product-T vs. Reference Product-R was concluded, if the 90% confidence interval of ratio of geometric least square mean fell within the acceptance range of 80.00-125.00% for ln-transformed pharmacokinetic parameters $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$ and C_{max} of levocetirizine (EMA, 2010).

Table 1 The summary of validation results

Information requested		Data
Linearity (Range)		5.090 to 516.585 ng/mL
Selectivity		No interference at the retention time and transition of drug and internal standard.
Selectivity in presence of co-administered drugs		No interference at the retention time and transition of drug and internal standard.
Verification of interfering potential by co-administered drugs		No interference with acceptable precision and accuracy.
Coefficient of determination (r^2)		Greater than 0.98
Lower limit of quantification		5.090 ng/mL
Limit of detection		0.509 ng/mL
Precision	Within-batch (Intra-day precision)	0.7% to 5.3%
	Between-batch (Inter-day precision)	2.7% to 6.8%
Accuracy	Within-batch (Intra-day accuracy)	95.8% to 115.4%
	Between-batch (Inter-day accuracy)	102.2% to 108.1%
Robustness and Ruggedness		Method is rugged and robust (up to 150 injections)
Recovery of drug (%) (HQC, MQC, LQC)		108.4%, 117.0%, 120.1%
Recovery of internal standard (%)		72.2%
Dilution integrity		774.877 ng/mL diluted 2 and 10 fold
Partial volume verification		400.080 ng/mL diluted 2 and 4 fold
Matrix effect		No ion suppression or enhancement
Reinjection reproducibility		Up to 3rd reinjection
Auto sampler/ Wet extract stability		107.0 hours (within 2 to 8°C)
Freeze and thaw stability		3 cycles
Bench top stability		7.0 hours (at room temperature)
Wet extract bench top stability		2.0 hours (at room temperature)

Results

Twenty six healthy, adult, male human subjects with a mean age (± SD) of 30.19 ± 8.02 years, a mean weight of 66.81 ± 7.95 kg, a mean height of 172.42 ± 7.37 cm and a mean BMI of 22.44 ± 1.95 were enrolled in the study. Twenty six subjects were used for pharmacokinetic and statistical analysis. Both the test and the reference

products were well tolerated. No clinically significant or serious ADRs were observed.

The mean plasma concentrations-time profiles of levocetirizine and their semi-log scale plots are shown in figure 2. The pharmacokinetic parameters including $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, λ_z and $t_{1/2}$ of both the test and the reference products are shown in Table 2. The extent of absorption reported as $AUC_{0\text{-tlast}}$ was 1708.294 ± 372.005 and 1739.707 ± 356.047 hr.ng/mL for the test and the reference products, respectively. $AUC_{0\text{-}\infty}$ was 1830.174 ± 360.107 and 1847.587 ± 344.015 hr.ng/mL for the test and the reference products, respectively. The rate of absorption reported as C_{max} was 222.414 ± 37.189 and 220.950 ± 36.342 ng/mL for the test and the reference products, respectively. The ANOVA model included Sequence, Formulation, Period as fixed effects and Subject (Sequence) as a random effect. Sequence effect was tested using Subject (Sequence) as error term.

From the standard of bioequivalence, bioequivalence of test product and reference product was concluded, if the 90% confidence interval of ratio of geometric least square mean fell within the acceptance range of 80.00-125.00% for ln-transformed pharmacokinetic parameters $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and C_{max}, the 90% confidence intervals for the ratios of mean for the Test/Reference were 98.1 (94.60-101.72), 99.0 (95.81-102.31) and 100.6 (95.56-105.89), respectively as shown in Table 3. These indicated that the test product and the reference product were bioequivalent. The $AUC_{0\text{-tlast}}/AUC_{0\text{-}\infty}$ ratio was 0.930 ± 0.033 and 0.939 ± 0.031 for the test and the reference products, respectively which was more than 80%. Then adequate sampling time points were obtained. The power for all primary pharmacokinetics parameters reported as $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and C_{max} was 100.0, 100.0 and 100.0, respectively. All reported power were greater than 80% indicating that the number of subjects was enough to confirm the bioequivalence of two formulations (Rani S et al, 2004).

Table 2 Mean pharmacokinetic parameters with %CV of levocetirizine of the test and the reference product

Parameters	Mean ± SD (%CV) of Test product	Mean ± SD (%CV) of Reference product
$AUC_{0\text{-tlast}}$ (hr.ng/mL)	1708.294 ± 372.005 (21.8%)	1739.707 ± 356.047 (20.5%)
$AUC_{0\text{-}\infty}$ (hr.ng/mL)	1830.174 ± 360.107 (19.7%)	1847.587 ± 344.015 (18.6%)
C_{max} (ng/mL)	222.414 ± 37.189 (16.7%)	220.950 ± 36.342 (16.4%)
t_{max} (hr)	0.763 ± 0.366 (48.0%)	0.683 ± 0.197 (28.9%)
λ_z (1/hr)	0.083 ± 0.011 (13.5%)	0.085 ± 0.011 (12.9%)
$t_{1/2}$ (hr)	8.451 ± 1.092 (12.9%)	8.276 ± 1.028 (12.4%)
$AUC_{0\text{-tlast}}/AUC_{0\text{-}\infty}$	0.930 ± 0.033 (3.5%)	0.939 ± 0.031 (3.3%)

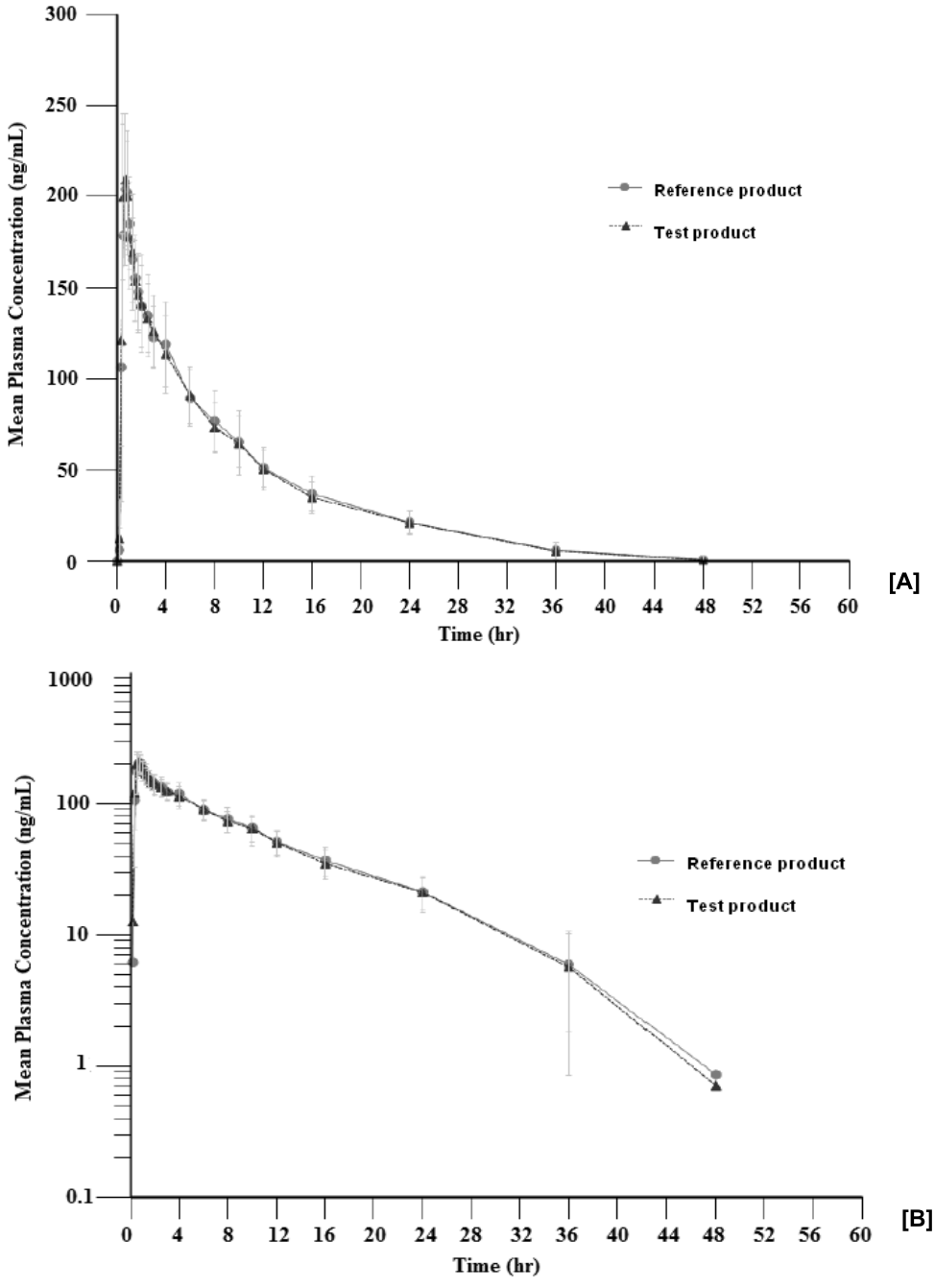

Figure 2 The linear plot of mean plasma concentrations-time profiles of levocetirizine [A] and their semi-log scale plots [B] of test product (T) and reference product (R)

Table 3 90% Confidence Interval for the ratios of mean $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and C_{max}

Parameters	Ratio of Geometric Least Square Mean	90% Confidence Interval
$AUC_{0\text{-tlast}}$	98.1	94.60-101.72
$AUC_{0\text{-}\infty}$	99.0	95.81-102.31
C_{max}	100.6	95.56-105.89

Discussion and Conclusion:

In summary, this study has demonstrated the bioequivalence of the generic levocetirizine dihydrochloride of GPO and the reference product (Xyzal®) in term of both extent and rate of absorption. Both the test and the reference products were well tolerated. Thus, interchangeability between the generic levocetirizine dihydrochloride and the reference product is confirmed.

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