



SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: EXPEDIENTE 05-053-234

TÍTULO SOLICITADO: "USO DE LEVOCETIRICINA PARA EL TRATAMIENTO DE LA RINITIS ALÉRGICA PERSISTENTE."

PUBLICACIÓN: GACETA No. 575 de 30 de Abril de 2007, N° de publicación: 1430

SOLICITANTE: UCB FARCHIM S.A.

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APODERADO: HÉCTOR GÓMEZ MEJÍA

TRÁMITE: SUSTENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LAFRANCOL S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2° de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada el 28 de marzo de 2007, en los siguientes términos:

I. RATIFICACIÓN

Comendidamente me permito insistir en los argumentos planteados en la oposición referida, los cuales, como se dijo en su momento, demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los

artículos 14, 16, 18, 20-d y 21 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

- En primer término, es importante resaltar que es obvio que la formación de sales de los fármacos permite obtener cambios en la biodisponibilidad de los mismos, en especial en principios activos donde la previa disolución en fluidos acuosos (como en el caso del fluido gástrico) es un factor limitante en la posterior absorción de dicho fármaco, en consecuencia, la formación de una sal como el dihidrocloruro de un fármaco, en este caso de la levocetirizina, al igual que la formación de sales de cualquier fármaco se encuentra reconocida con bastante anterioridad en el estado de la técnica, se emplea extendidamente en la industria farmacéutica y por lo tanto, no supone nivel inventivo de ninguna índole.
- Es necesario anotar que el uso de antihistamínicos de segunda generación (grupo al que corresponde la levocetirizina) en el tratamiento de la sintomatología de la rinitis alérgica es conocido y ha sido ampliamente divulgado en la literatura científica, al igual que la característica distintiva del principio activo en cuestión, de no presentar los efectos adversos que en el sistema nervioso central pueden ocasionar los llamados fármacos de primera generación; lo anterior se encuentra revelado en varios artículos de tipo científico^{1,2,3}.
- La publicación internacional WO 94/006429 publicada el 31 de marzo de 1994 y titulada "COMPOSITIONS FOR TREATING ALLERGIC DISORDERS USING (-) CETIRIZINE" revela desde 1994 absolutamente toda la materia que se reivindica en la solicitud colombiana en trámite, específicamente en lo referido al tratamiento de la sintomatología de la rinitis ya sea estacionaria o perenne (permanente, duradera, continúa, persistente, etc), formas farmacéuticas que contienen levocetirizina o (-) cetirizina o sus sales farmacéuticamente

¹ Effect of cetirizine, levocetirizine, and dextrocetirizine on histamine-induced nasal response in healthy adult volunteers. (eng; includes abstract) By Wang DY, Allergy [Allergy], 2001 Apr; Vol. 56 (4), pp. 339-43; PMID: 11284803

² Management of rhinitis--the specialist's opinion. By: Cauwenberge, P. Van. Clinical & Experimental Allergy, Dec98 Supplement 6, Vol. 28, p29, 5p; (AN 6103107)

³ Diagnosis and Management of Rhinitis: Complete Guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology. Mark S Dykewicz, MD,† Stanley Fineman, MD, MBA,§ Editors David P Skoner, MD, Chair, Workgroup on Rhinitis Richard Nicklas, MD\; Rufus Lee, MD; Joann Blessing-Moore, MD; James T Li, MD, PhD*; I Leonard Bernstein, MD††; William Berger, MD, MBA‡‡; Sheldon Spector, MD§§; and Diane Schuller, MD,\ Associate Editors. Ann Allergy Asthma Immunol 1998;81:478-518.

Background: Cetirizine is a highly efficacious and long-acting second-generation H₁-receptor antagonist for the treatment of allergic diseases, such as allergic rhinitis and chronic idiopathic urticaria, in adults and children. Pharmacologic studies have demonstrated that cetirizine, a racemate mixture composed of equal amounts of two enantiomers, does not undergo hepatic metabolism to any significant level. The enantiomers are excreted mainly unchanged, predominantly in the urine and to a lesser extent in the faeces.

Methods: The pharmacologic activity and potency of the two enantiomers of cetirizine in the management of allergic skin conditions were investigated by studying the effect of treatment with 5.0 mg cetirizine; 2.5 mg levocetirizine, the (*R*)-enantiomer; and 2.5 mg ucb 28557, the (*S*)-enantiomer, on histamine-induced wheal and flare response in 18 healthy volunteers. Each treatment was administered as a single oral dose in randomized, double-blind, and crossover manner, and the efficacy of treatment was assessed over a period of 32 h, as per cent inhibition of the histamine-induced wheal and flare areas before treatment. Blood and urine samples were collected in a time-dependent manner and analyzed for the total amounts of each study drug, to elucidate their pharmacokinetic profiles.

Results: Both cetirizine and levocetirizine caused a marked inhibition of histamine-induced wheal and flare, whereas ucb 28557 was inactive in this model. Inhibition of the wheal response observed for cetirizine and levocetirizine was apparent by 1 h after dosage and lasted for mean durations of 24.4 and 28.4 h, respectively. In addition, the response for cetirizine and levocetirizine became maximal by 6 h after treatment, rising to 79.5% and 83.8%. Similarly, cetirizine and levocetirizine also markedly inhibited the histamine-induced flare response. This effect was evident for both drugs by 1 h after dosage and lasted over a mean period of 28.4 and 26.0 h, respectively, for cetirizine and levocetirizine. The inhibitory effect of these compounds on histamine-induced flare response was also maximal by approximately 6 h after dosage, peaking at 88.5% and 83.6%, respectively. Statistical evaluation showed that cetirizine and levocetirizine were equivalent for maximum inhibition of histamine-induced wheal and flare. However, levocetirizine was found to be superior to cetirizine when area under the curve was compared. In contrast, ucb 28557 was not found to inhibit histamine-induced wheal and flare responses at any time during the study period. Plasma concentrations of levocetirizine were found to be approximately double those of ucb 28557 at 4 and 8 h after dosing, and 50–60% of the drugs were excreted unchanged in urine over a period of 32 h.

Conclusions: The finding that, in this model, levocetirizine 2.5 mg has comparable antihistaminic activity to cetirizine 5 mg, whereas its other enantiomer ucb 28557 has no pharmacodynamic effect, suggests that the antihistaminic properties of cetirizine observed in the management of allergic skin conditions are likely to be attributable to levocetirizine.

➤ **Comparison of the effects of levocetirizine and loratadine on histamine-induced wheal, flare, and itch in human skin⁵.**

⁵ Comparison of the effects of levocetirizine and loratadine on histamine-induced wheal, flare, and itch in human skin. (eng; includes abstract) By Clough GF, Allergy [Allergy], 2001 Oct; Vol. 56 (10), pp. 985-8; PMID: 11576078

Background: This randomized, double-blind, crossover study compared the effects of the *R*-enantiomer of cetirizine, levocetirizine, with those of loratadine on the wheal, flare, and itch response to histamine in human skin.

Methods: Levocetirizine (5 mg), loratadine (10 mg), or placebo was taken orally 4 h before the intradermal injection of histamine (20 μ l, 100 μ M) or the control vehicle into the forearm skin of healthy volunteers. Flare areas were assessed by scanning laser Doppler imaging before and at 30-s intervals for a period of 9 min. Wheal areas were measured by planimetry at 10 min. Itch was scored every 30 s with a visual analogue scale.

Results: After placebo administration, the mean peak flare area was 23.01 ± 1.94 cm², the wheal area 248 ± 27 mm², and the cumulative itch score $28.8 \pm 4.6\%$ (mean $\pm$ SEM). Levocetirizine reduced the flare, wheal, and itch by 60%, 68%, and 91%, respectively (all $P < 0.001$, Student's *t*-test for paired data). The effects of loratadine were variable and not statistically significant.

Conclusions: Levocetirizine (5 mg) is a potent inhibitor of the effects of histamine in human skin with an efficacy that exceeded that of loratadine (10 mg) when single doses of the drugs were administered 4 h before the test.

➤ **Lack of effect of single and repeated doses of levocetirizine, a new antihistamine drug, on cognitive and psychomotor functions in healthy volunteers⁶.**

Aims Levocetirizine (*R*-cetirizine), is the active enantiomer of cetirizine, an antihistamine indicated in the treatment of allergic rhinitis and chronic idiopathic urticaria. The purpose of this trial was to analyse the effects of levocetirizine single and multiple doses on CNS using integrated measures of cognitive and psychometric performance.

Methods A battery of psychometric tests was used: critical flicker fusion (CFF), choice reaction time (CRT), body sway (BS), learning memory test (LMT) and subjective assessments of alertness compared with placebo. Nineteen (19) healthy male volunteers received either levocetirizine 5 mg (therapeutic dose), diphenhydramine 50 mg or placebo once daily for 5 consecutive days (3-way cross-over). Diphenhydramine was used as a positive control. CFF tests were performed on days 1 and 5 at baseline and up to 24 h following drug intake. Subjects used the Bond-Lader visual analogue scales (VAS) to assess their mood and vigilance.

Results In contrast to diphenhydramine, when compared with placebo, levocetirizine did not modify the CFF (primary endpoint), regardless of the dosing scheme (-1.62 Hz [-2.61 , -0.64] and -0.81 Hz [-1.80 , 0.19], respectively, 3 h after dosing on day 1). CRT was decreased with both levocetirizine and placebo up to 5 h after dosing on day 1 and up to 3 h after dosing on day 5. Body sway data were similar with levocetirizine and placebo but increased with diphenhydramine. LMT was similar in all three groups. No relevant difference between placebo and levocetirizine was recorded by the subjects on their assessment of alertness using the VAS, whilst decreased alertness was reported following diphenhydramine 50 mg.

Conclusions This study showed that levocetirizine does not produce any deleterious effect on cognitive and psychometric functions compared with placebo in healthy male volunteers.

⁶ Lack of effect of single and repeated doses of levocetirizine, a new antihistamine drug, on cognitive and psychomotor functions in healthy volunteers. By: Gandon, J. M.; Allain, H.. British Journal of Clinical Pharmacology, Jul2002, Vol. 54 Issue 1, p51-58, 8p; DOI: 10.1046/j.1365-2125.2002.01611.x; (AN 6902140)

Short communication

Comparison of the effects of levocetirizine and loratadine on histamine-induced wheal, flare, and itch in human skin

Background: This randomized, double-blind, crossover study compared the effects of the *R*-enantiomer of cetirizine, levocetirizine, with those of loratadine on the wheal, flare, and itch response to histamine in human skin.

Methods: Levocetirizine (5 mg), loratadine (10 mg), or placebo was taken orally 4 h before the intradermal injection of histamine (20 µl, 100 µM) or the control vehicle into the forearm skin of healthy volunteers. Flare areas were assessed by scanning laser Doppler imaging before and at 30-s intervals for a period of 9 min. Wheal areas were measured by planimetry at 10 min. Itch was scored every 30 s with a visual analogue scale.

Results: After placebo administration, the mean peak flare area was $23.01 \pm 1.94 \text{ cm}^2$, the wheal area $248 \pm 27 \text{ mm}^2$, and the cumulative itch score $28.8 \pm 4.6\%$ (mean $\pm$ SEM). Levocetirizine reduced the flare, wheal, and itch by 60%, 68%, and 91%, respectively (all $P < 0.001$, Student's *t*-test for paired data). The effects of loratadine were variable and not statistically significant.

Conclusions: Levocetirizine (5 mg) is a potent inhibitor of the effects of histamine in human skin with an efficacy that exceeded that of loratadine (10 mg) when single doses of the drugs were administered 4 h before the test.

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Key words: antihistamines; flare; itch; levocetirizine;
loratadine; skin; wheal.

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Cetirizine and loratadine, both inverse agonists at the histamine H_1 -receptor (1), are widely used to prevent the symptoms of allergic reactions, particularly in the nose, eye, and skin. Early studies using the histamine-induced skin wheal reaction showed both drugs to be effective antihistamines (2, 3), and numerous clinical trials have confirmed this (4, 5).

Cetirizine is a racemic mixture of equal quantities of *S*- and *R*-enantiomers, and the *R*-enantiomer, levocetirizine, carries the majority of the histamine H_1 -receptor-blocking activity (6). To confirm this, we have assessed the effectiveness of a single dose of 5 mg levocetirizine, the amount of this isomer in the standard 10 mg dose of the racemic mixture, in inhibiting the wheal and flare response to histamine in human skin. A standard 10-mg dose of loratadine was used as positive control and matching placebo as negative control.

Material and methods

The study was performed as a randomized, double-blind, placebo-controlled, crossover trial on 11 healthy volunteers with no history of allergy. The study was approved by the Southampton (UK) and South West Local Research Ethics Committee (study number 191/00), and all volunteers gave signed informed consent. Matching capsules of levo-

cetirizine (5 mg), loratadine (10 mg), or placebo were taken orally 4 h before the start of each visit, and subjects were asked to refrain from eating, drinking caffeine-containing liquids, or taking excessive exercise for 2 h before attending the laboratory. As previous studies have shown that basal skin blood flow and vasoreactivity vary during the day (7-9), subjects were studied at the same time of day (between 1100 and 1300) in order to minimize intraindividual variation. All subjects were studied lying horizontally with their arms at heart level. Twenty microlitres of histamine (100 µM, UCB Pharma SA) or control vehicle (phosphate-buffered saline, PBS) was injected intradermally into the volar surface of the forearm, one injection per arm. Before and at intervals of 30 s for a period of 9 min after injection, changes in skin blood flow were assessed by scanning laser Doppler imaging (Moor Instruments Ltd, UK). Flare areas were calculated from the calibrated images with the manufacturer's software (10). The perimeter of the wheal at 10 min was traced onto an acetate sheet, and the area was calculated by planimetry. Itch sensation was scored every 30 s for a period of 10 min after histamine injection on a 10-cm visual analogue scale. All data are expressed as mean $\pm$ SEM, and statistical analysis was performed with Student's *t*-test for paired data. A probability value of $P < 0.05$ was taken as statistically significant.

Results

Intradermal injection of histamine caused a wheal and flare response in all volunteers, which was accompanied by the sensation of itch.

Analysis of the time course of the development of the

Lack of effect of single and repeated doses of levocetirizine, a new antihistamine drug, on cognitive and psychomotor functions in healthy volunteers

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Aims Levocetirizine (R-cetirizine), is the active enantiomer of cetirizine, an antihistamine indicated in the treatment of allergic rhinitis and chronic idiopathic urticaria. The purpose of this trial was to analyse the effects of levocetirizine single and multiple doses on CNS using integrated measures of cognitive and psychometric performance.

Methods A battery of psychometric tests was used: critical flicker fusion (CFF), choice reaction time (CRT), body sway (BS), learning memory test (LMT) and subjective assessments of alertness compared with placebo. Nineteen (19) healthy male volunteers received either levocetirizine 5 mg (therapeutic dose), diphenhydramine 50 mg or placebo once daily for 5 consecutive days (3-way cross-over). Diphenhydramine was used as a positive control. CFF tests were performed on days 1 and 5 at baseline and up to 24 h following drug intake. Subjects used the Bond-Lader visual analogue scales (VAS) to assess their mood and vigilance.

Results In contrast to diphenhydramine, when compared with placebo, levocetirizine did not modify the CFF (primary endpoint), regardless of the dosing scheme (-1.62 Hz [-2.61 , -0.64] and -0.81 Hz [-1.80 , 0.19], respectively, 3 h after dosing on day 1). CRT was decreased with both levocetirizine and placebo up to 5 h after dosing on day 1 and up to 3 h after dosing on day 5. Body sway data were similar with levocetirizine and placebo but increased with diphenhydramine. LMT was similar in all three groups. No relevant difference between placebo and levocetirizine was recorded by the subjects on their assessment of alertness using the VAS, whilst decreased alertness was reported following diphenhydramine 50 mg.

Conclusions This study showed that levocetirizine does not produce any deleterious effect on cognitive and psychometric functions compared with placebo in healthy male volunteers.

Keywords: antihistamine, critical flicker fusion, levocetirizine, psychomotor performance, reaction time

Introduction

Recently developed antihistamine drugs have an increased benefit-risk ratio compared with first generation antihistamines. As a matter of fact, the efficacy of new antihistamines is not correlated with sedation, which has been demonstrated to be minimal [1]. However, it remains

that the effect of a given drug on the CNS has to be explored specifically, especially when this drug could be administered to people involved in potentially dangerous activities. Methodological aspects are central to this exploration, and some study designs were sometimes controversial in appreciating CNS effects of a given drug [2, 3]. Therefore, a battery of psychometric tests is essential to characterize the level of CNS impact of a new drug.

Cetirizine is a chiral molecule with potent antiallergic effects and clinically insignificant sedative effects with minimal impact on routine daily activities [2–5].

Levocetirizine (R-cetirizine) is the active enantiomer of cetirizine. This molecule has been shown to have both

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Original article

A randomized, double-blind, crossover comparison among cetirizine, levocetirizine, and ucb 28557 on histamine-induced cutaneous responses in healthy adult volunteers

Background: Cetirizine is a highly efficacious and long-acting second-generation H₁-receptor antagonist for the treatment of allergic diseases, such as allergic rhinitis and chronic idiopathic urticaria, in adults and children. Pharmacologic studies have demonstrated that cetirizine, a racemate mixture composed of equal amounts of two enantiomers, does not undergo hepatic metabolism to any significant level. The enantiomers are excreted mainly unchanged, predominantly in the urine and to a lesser extent in the faeces.

Methods: The pharmacologic activity and potency of the two enantiomers of cetirizine in the management of allergic skin conditions were investigated by studying the effect of treatment with 5.0 mg cetirizine; 2.5 mg levocetirizine, the (R)-enantiomer; and 2.5 mg ucb 28557, the (S)-enantiomer, on histamine-induced wheal and flare response in 18 healthy volunteers. Each treatment was administered as a single oral dose in randomized, double-blind, and crossover manner, and the efficacy of treatment was assessed over a period of 32 h, as per cent inhibition of the histamine-induced wheal and flare areas before treatment. Blood and urine samples were collected in a time-dependent manner and analyzed for the total amounts of each study drug, to elucidate their pharmacokinetic profiles.

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Conclusions: The finding that, in this model, levocetirizine 2.5 mg has comparable antihistaminic activity to cetirizine 5 mg, whereas its other enantiomer ucb 28557 has no pharmacodynamic effect, suggests that the antihistaminic properties of cetirizine observed in the management of allergic skin conditions are likely to be attributable to levocetirizine.

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Key words: antihistamines; cetirizine; equivalence; levocetirizine; ucb 28557; urinary excretion; urticaria.

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Several studies have suggested that histamine plays a central role in the pathologic effects of urticaria (1, 2). Comparative studies of patients with chronic

urticaria and healthy subjects have demonstrated that the urticaria patients release greater amounts of histamine than the healthy subjects, both sponta-