



No. 05-067473- -00006-0000

Fecha: 2007-10-26 16:10:51 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379.FASENACIONALI
Act. 329 CTOINFORMACION Folios: 15

SEÑOR

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: EXPEDIENTE 05-067-473

TÍTULO SOLICITADO: "BROMHIDRATO DE ESCITALOPRAM Y UN MÉTODO PARA SU PREPARACIÓN."

PUBLICACIÓN: GACETA No. 575 de 30 de Abril de 2007, N° de publicación: 1425

SOLICITANTE: H LUNDBECK A/S.

PRIORIDAD: PA 2002/02005 de Diciembre 23 de 2002.

APODERADO: EMILIO FERRERO

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 **LABORATORIO FRANCO-COLOMBIANO, 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

181 2 #10
~~46~~

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

- En primer término, para cualquier persona medianamente versada en la materia, 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. Así las cosas, no se puede pretender proteger mediante patente la formación de una sal como el bromhidrato de Citalopram, pues como se mencionó anteriormente, la formación de sales de fármacos 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.
- De la misma forma, y ya que el solicitante menciona que dicha sal se obtiene en forma sólida y cristalina, cabe resaltar que la obtención de cristales de sólidos a través de la solubilización y posterior cristalización con solventes donde dicha sustancia sea insoluble, como se expone en el capítulo descriptivo de la solicitud colombiana en trámite, es una práctica igualmente reconocida y ampliamente utilizada en el estado de la arte, por tanto no tiene fundamento pretender reclamar novedad y/o nivel inventivo en la manera de obtención de cristales de la mencionada sal de escitalopram.
- De otro lado, la solicitud internacional WO 01/03694 publicada el 18 de enero del 2001 y titulada "TREATMENT OF NEUROTIC DISORDERS" y la solicitud internacional WO 02/087566 publicada el 7 de Noviembre de 2002 y titulada "THE USE OF ENANTIOMERIC PURE ESCITALOPRAM" se refieren al uso del compuesto Escitalopram (nombre INN), el cual es el enantiómero S del conocido fármaco antidepresivo Citalopram, (S)-1-[3-(diethyl-amino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, o una sal farmacéuticamente aceptable del mismo para la preparación de medicamentos para el tratamiento de desórdenes neuróticos y depresión, respectivamente.

Como vemos, la sustancia (S)-Citalopram puede encontrarse como base o en forma de sal farmacéuticamente aceptable (afirmación amplia y que cubre

cualquier tipo de sal posible, incluso podría entenderse que la sal bromhidrato está incluida) y el uso de todas estas en el tratamiento de trastornos neuróticos como los mencionados en la solicitud colombiana en trámite, y en especial en las reivindicación 5 del respectivo capítulo reivindicatorio.

- Por su parte, la patente europea EP 0347066 publicada el 20 de diciembre de 1989 y titulada "NEW ENANTIOMERS AND THEIR INSOLATION" se refiere a los dos nuevos enantiómeros del fármaco antidepresivo 1-(3-dimethylamino propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (citalopram), en donde se incluye obviamente el (S)-citalopram (escitalopram) y se hace mención específica de la obtención de la sal bromhidrato del mismo. Con esta anterioridad se demuestra que desde 1989 ya se revelaba a (S)-(+)-Citalopram y así mismo su sal bromhidrato -entre otras- quedando demostrado la ausencia de nivel inventivo de la solicitud colombiana en trámite.
- La patente europea EP 1 152 000 publicada el 7 de Noviembre de 2001 y titulada "CITALOPRAM HYDROBROMIDE CRYSTAL AND METHOD FOR CRYSTALLIZATION THEREOF" revela la sal Bromhidrato en este caso de Citalopram además del el método de obtención de dicha sal en forma cristalina, y el empleo de algunos de los solventes utilizados en la recrystalización ya sea de Bromhidato de Citalopram (EP 1152000) o del bromhidrato de escitalopram (solicitud colombiana en trámite), por ejemplo el isopropanol, tolueno, THF, entre otros.
- Por último, me permito resaltar que el capítulo reivindicatorio de la solicitud colombiana en curso, dirigida al uso de una composición, es inaceptable a la luz de la Decisión 486 y a la luz de la normativa subregional resulta inaceptable pretender atribuirse exclusiva sobre un "Uso", categoría no incluida en el concepto de "Productos o Procedimientos" que establece el artículo 14 de la Decisión 486 de 2000. Lo anterior, además, en consonancia con la reiterada interpretación de la SIC sobre este punto.

183
4
H
98

II. COMPLEMENTO DE INFORMACIÓN.

No siendo suficientes los argumentos dados en la oposición presentada anteriormente, se adicionan otros documentos de carácter científico que demuestran el amplio conocimiento y estudios que se han relacionado al uso farmacológico del escitalopram:

➤ **The Brown University Child and Adolescent Psychopharmacology Update¹.**

Forest Laboratories has submitted a New Drug Application (NDA) to the FDA, seeking approval to market **escitalopram** for the treatment of depression. Escitalopram the single isomer of Celexa (citalopram), is a more potent and selective serotonin reuptake inhibitor (SSRI). A press release from Forest states that citalopram is a racemic mixture with two mirror image halves, the S- and R-isomers. The S-isomer of citalopram is the active isomer in terms of its contribution to citalopram's antidepressant effects, while the R-isomer does not contribute to its antidepressant activity. With escitalopram, the R-isomer has been removed, leaving only the active S-isomer or a single isomer. (Source: Forest Laboratories Inc., Web site: www.frx.com)

➤ La publicación internacional WO 00/12044 publicada el 09 de marzo de 2000 y titulada "METHOD FOR THE PREPARATION OF CITALOPRAM" revela:

The active S-enantiomer of citalopram may be prepared from the compound of Formula III by separation of the S-enantiomer and the R-enantiomer followed by ring closure of the S-enantiomer as described in US Patent No 4,943,590. The R-enantiomer of the compound of Formula III has previously not been used after separation.

(...)

¹ FDA Update. Brown University Child & Adolescent Psychopharmacology Update, Sep2002, Vol. 4 Issue 9, p6, 1p; (AN 7396110)

184 5 #3
94

The racemic compound of Formula III may be separated into the optically active enantiomers by the procedure described in US Patent No 4,943,590 thereby obtaining the S-enantiomer of the compound of Formula III, which is used in the preparation of S-citalopram. The R-enantiomer of the compound of Formula III can be recycled once more in the process cycle described above.

(...)

In this way, the R-enantiomer of Formula III may be converted to S-citalopram.

(...)

The compound of general Formula I may be used as the free base or as a pharmaceutically acceptable acid addition salt thereof. As acid addition salts, such salts formed with organic or inorganic acids may be used. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene sulfonic and theophylline acetic acids, as well as the 8-halothephyllines, for example 8-bromothephylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

(...)

The acid addition salts of the compounds may be prepared by methods known in the art. The base is reacted with either the calculated amount of acid in a water miscible solvent, such as acetone or ethanol, with subsequent isolation of the salt by concentration and cooling, or with an excess of the acid in a water immiscible solvent, such as ethylether, ethylacetate or dichloromethane, with the salt separating spontaneously.

(...)

The pharmaceutical compositions of the invention may be administered in any suitable way and in any suitable form, for example orally in the form of tablets, capsules, powders or syrups, or parenterally in the form of usual sterile solutions for injection.

(...)

Además reivindica:

186

7 FEB 1997

sion between drug use stages shift dramatically across birth cohorts. The gateway phenomenon emerged in the 1960s as the baby boom generation came of age.

What this means, the authors say, is that recent increases in marijuana use among teenagers may not portend

an increase in hard drug use as well. Simply restricting youths' access to gateway drugs will not necessarily reduce hard drug use. Instead, it is necessary to try to understand and influence prevailing norms, especially those affecting early initiators of alcohol, tobacco and marijuana use.

Golub A, Johnson BD: Variation in youthful risks of progression from alcohol and tobacco to marijuana and to hard drugs across generations. *American Journal of Public Health* 2001; 91:225-232. Reprint requests to: Dr. Golub, National Development and Research Institutes, Two World Trade Center, New York, NY 10048.

News Update

- The publishers of the Physicians' Desk Reference (PDR) have released a 700-page reference volume that summarizes and analyzes the research data behind nutritional supplements and weighs in on whether or not the health claims are valid. By consulting the *PDR for Nutritional Supplements*, says author Sheldon Hendler, Ph.D., M.D., consumers and their doctors can learn which nutritional supplements may improve health and which supplements may interact with foods or prescription or nonprescription medicines. Hendler is clinical professor of Medicine at the University of California at San Diego. (Source: Thomson Healthcare. For more information, call Randie Levine-Miller 212-362-3616.)
- GlaxoSmithKline's **Paxil (paroxetine)** has become the first FDA approved SSRI for treatment of generalized anxiety disorder (GAD). Paroxetine is also approved for treatment of depression, panic disorder, obsessive-compulsive disorder and social anxiety and is under FDA review for treatment of post-traumatic stress disorder (PTSD). In two

multi-center studies of patients with GAD, researchers found that patients taking Paxil experienced a nearly 60 percent reduction in anxiety symptoms as measured by the Hamilton Anxiety Scale. (Source: BehaveNewsNet by Manisses.com)

- Par Pharmaceutical Inc. has received approval from the FDA for its Abbreviated New Drug Application (ANDA) to market **buspirone 7.5 mg tablets**. Par will be entitled to 180 days of exclusivity on this dosage form. Buspirone is the generic equivalent to Bristol-Myers Squibb's (BMS) BuSpar®. BMS markets a 15 mg Dividose® tablet, which for certain prescriptions, is broken in half for a 7.5 mg dose. The brand does not currently market a 7.5 mg tablet. Shipping of the product will begin immediately. (Source: Pharmaceutical Resources, Inc., 845-425-7100)
- In related news, Mylan Laboratories Inc. received FDA approval to manufacture and market **buspirone 15 mg tablets**. Buspirone, a generic equivalent of Bristol-Myers Squibb's BuSpar tablets, is used to treat anxiety

disorders. Mylan will be entitled to 180 days of exclusivity on this dosage. The approval comes after extensive legal maneuvers by BMS. Mylan had anticipated launching the 15 mg buspirone product on November 22, 2000, when pediatric exclusivity was scheduled to expire. (Source: Mylan Laboratories Inc.)

- Forest Laboratories has submitted a New Drug Application (NDA) to the FDA, seeking approval to market **escitalopram** for the treatment of depression. Escitalopram the single isomer of Celexa (citalopram), is a more potent and selective serotonin reuptake inhibitor (SSRI). A press release from Forest states that citalopram is a racemic mixture with two mirror image halves, the S- and R-isomers. The S-isomer of citalopram is the active isomer in terms of its contribution to citalopram's antidepressant effects, while the R-isomer does not contribute to its antidepressant activity. With escitalopram, the R-isomer has been removed, leaving only the active S-isomer or a single isomer. (Source: Forest Laboratories Inc., Web site: www.frx.com)

Earn CEs for reading *The Brown University Child and Adolescent Psychopharmacology Update*

Continuing Education (1.0 Clinical Credit) is now available for reading *The Brown University Child and Adolescent Psychopharmacology Update* — an added service to you, our subscribers. To visit Manisses Online Continuing Education Center, go to www.manisses.com/2manisses/credit.html

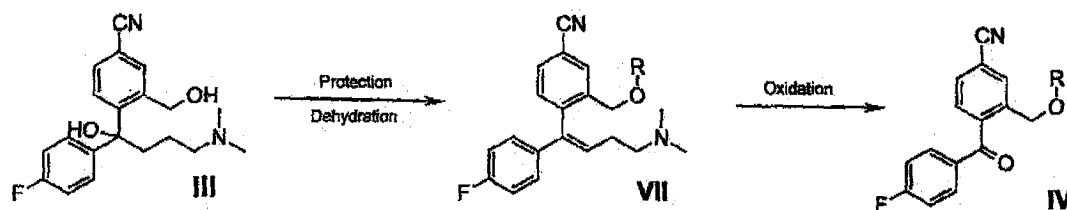
After registering, you can select this issue from the psychopharmacology section of the Testing Area. You will need to enter an additional password: interact. Each online credit is \$5. After passing the test you will receive your "Letter of Completion" via e-mail.

187 8
R18

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K	A2	(11) International Publication Number: WO 00/12044 (43) International Publication Date: 9 March 2000 (09.03.00)
(21) International Application Number: PCT/DK99/00581 (22) International Filing Date: 25 October 1999 (25.10.99) (71) Applicant (for all designated States except US): H. LUNDBECK A/S [DK/DK]; Ottiliavej 9, DK-2500 Valby Copenhagen (DK). (72) Inventors; and (75) Inventors/Applicants (for US only): ROCK, Michael, Harold [GB/DK]; Risbjergvej 28, DK-2650 Hvidovre (DK). PETERSEN, Hans [DK/DK]; Guldagervej 11, DK-2720 Vanløse (DK). ELLEGAARD, Peter [DK/DK]; Knud Lavardsvej 98, DK-4174 Jystруп (DK). (74) Common Representative: H. LUNDBECK A/S; John Meidahl Petersen, Ottiliavej 9, DK-2500 Valby Copenhagen (DK).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SI, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Upon the request of the applicant, before the expiration of the time limit referred to in Article 21(2)(a). Without international search report and to be republished upon receipt of that report. Without classification; title and abstract not checked by the International Searching Authority.</i>
(54) Title: METHOD FOR THE PREPARATION OF CITALOPRAM (IV) (57) Abstract A method for the preparation of citalopram comprising reaction of a compound of Formula (IV), wherein R is C₁₋₆ alkyl, acyl, C₁₋₆ alkylsulfonyl or arylsulfonyl, with 3-(N,N-dimethylamino)-propyl magnesium halide, to prepare citalopram.		

6



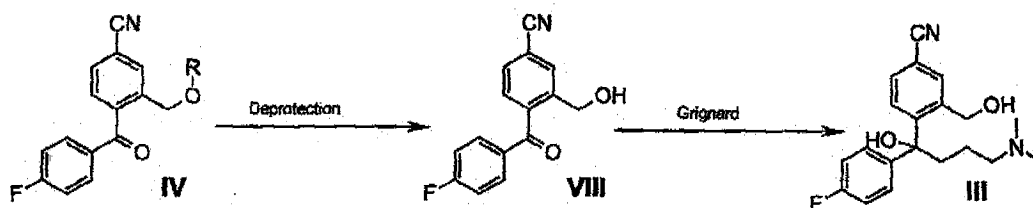
In this way, the R-enantiomer of Formula III may be used in the preparation of racemic citalopram.

The oxidative cleavage of the compound of Formula VII is effected by oxidation, preferably performed by MnO_4^- (permanganates), or ozone, RuCl_3 , OsO_4 .

Citalopram is on the market as an antidepressant drug in the form of the racemate. However, in the near future the active S-enantiomer of citalopram is also going to be introduced to the market.

The active S-enantiomer of citalopram may be prepared from the compound of Formula III by separation of the S-enantiomer and the R-enantiomer followed by ring closure of the S-enantiomer as described in US Patent No 4,943,590. The R-enantiomer of the compound of Formula III has previously not been used after separation.

Furthermore, according to a further aspect of the invention, after conversion of the R-enantiomer of Formula III to the non-optically active compound of Formula IV, the racemic compound of Formula III may be prepared as illustrated below:



The racemic compound of Formula III may be separated into the optically active enantiomers by the procedure described in US Patent No 4,943,590 thereby obtaining the S-enantiomer of the compound of Formula III, which is used in the preparation of S-citalopram. The R-enantiomer of the compound of Formula III can be recycled once more in the process cycle described above.

In this way, the R-enantiomer of Formula III may be converted to S-citalopram.

Other reaction conditions, solvents, etc. for the reactions described above are conventional conditions for such reactions and may easily be determined by a person skilled in the art.

Throughout the specification and claims, the term C₁₋₆ alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, 2,2-dimethyl-1-ethyl and 2-methyl-1-propyl.

The term aryl refers to a mono- or bicyclic carbocyclic aromatic group, such as phenyl and naphthyl, in particular phenyl or ring substituted phenyl.

The term heteroaryl refers to a mono- or bicyclic heterocyclic aromatic group, such as indolyl, thienyl, pyrimidyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzofuranyl, benzothienyl, pyridyl, and furanyl, in particular pyrimidyl, indolyl, and thienyl.

Acyl is used in the meaning of C₁₋₆ alkyl- or aryl- or heteroarylcarbonyl wherein C₁₋₆ alkyl and aryl and heteroaryl are as defined above.

Halogen means chloro, bromo or iodo.

Preferably leaving group means halogenide or sulphonate.

In a preferred embodiment of the invention, R is acyl, preferably pivaloyl, acetyl or optionally substituted benzoyl.

The compound of general Formula I may be used as the free base or as a pharmaceutically acceptable acid addition salt thereof. As acid addition salts, such salts formed with organic or inorganic acids may be used. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene sulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

The acid addition salts of the compounds may be prepared by methods known in the art. The base is reacted with either the calculated amount of acid in a water miscible solvent, such as acetone or ethanol, with subsequent isolation of the salt by concentration and cooling, or with

an excess of the acid in a water immiscible solvent, such as ethylether, ethylacetate or dichloromethane, with the salt separating spontaneously.

The pharmaceutical compositions of the invention may be administered in any suitable way and in any suitable form, for example orally in the form of tablets, capsules, powders or syrups, or parenterally in the form of usual sterile solutions for injection.

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art. For example, tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tableting machine. Examples of adjuvants or diluents comprise: Corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive colourings, aroma, preservatives etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by solving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to the desired volume, sterilisation of the solution and filling in suitable ampoules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

Examples

The invention is further illustrated by the following examples.

Example 1

2,2-Dimethyl-propionic acid 5-cyano-2-[1-(4-fluoro-phenyl)-1-hydroxy-methyl]-benzyl ester.
To a stirred solution of (4-cyano-2-hydroxymethylphenyl)(4-fluorophenyl)methanol (9.2 g, 0.037 mol) and triethylamine (4.0 g, 0.04 mol) was added pivaloyl chloride (4.2 g, 0.39 mol). After stirring for 60 minutes the reaction mixture was poured onto ice, extracted with diethyl ether (2 x 75 mL), dried (MgSO₄), and concentrated under reduced pressure to give a colourless oil (12.0 g). The compound was purified by chromatography (eluent hexane/ ethyl acetate 1:9 to give the title compound (8.2 g, 70%).

¹H NMR (DMSO-D₆): 1.1 (s, 9H), 5.15 (m, 2H), 6 (bs, 1H), 6.25 (d, J = 6 Hz, 1H), 7.1-7.2 (m, 2 H), 7.3-7.4 (m, 2H), 7.7-7.9 (m, 3 H).

Example 2

2,2-Dimethyl-propionic acid 5-cyano-2-[1-(4-fluoro-phenyl)-methanoyl]-benzyl ester.

2020
Bogotá, D.C.,

Doctor:
Emilio Ferrero
Apoderado

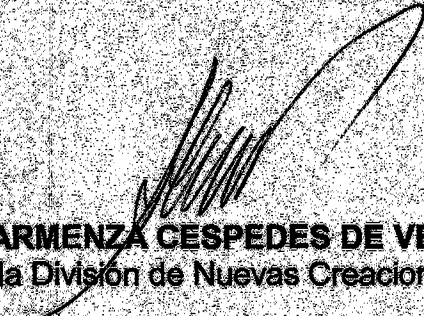
Oficio N°: 14639

ASUNTO:	Radicación PCT N°	05-67473
	Trámite	011
	Evento	379
	Actuación	440
	Folios	044

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de Laboratorio Franco Colombiano - Lafranco S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior oficio fue notificado por fijación en lista de fecha, 13.6 NOV. 2007

202021