



No. 14-122226- -00012-0000

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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

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REF: Expediente No. PCT/14-122226

TÍTULO SOLICITADO: "PROCESO DE RECUPERACIÓN DE CLORHIDRATO DE NALMEFENO"

PUBLICACIÓN: Gaceta 697 del 13/06/2014, N° de publicación 605.

SOLICITANTE: H. LUNDBECK A/S

APODERADO: CAROLINA MERCEDES DAZA MONTALVO.

TRÁMITE: Recurso de Reposición y en subsidio el de apelación en contra de la Resolución 64497 de septiembre 17 de 2015 por la cual se concede una patente de invención tramitada bajo el número de expediente PCT/14-122226.

TITO NOÉ PARRA MURILLO, mayor de edad, identificado como aparece al pie de mi firma, reconocido apoderado de la sociedad LAFRANCOL S.A.S. en el asunto de la referencia, de manera respetuosa, y dentro de los términos de ley, presento Recurso de Reposición y en subsidio de apelación contra la Resolución 64497 de septiembre 17 de 2015 por la cual se concedió a la solicitud PCT/14-122226 el privilegio de patente de invención.

I. PETICIÓN

Sírvase, Señor Superintendente, reponer íntegramente la Resolución 64497 de septiembre 17 de 2015, por la cual se declaró infundada la oposición presentada y se otorgó el privilegio de patente solicitado en el expediente de la referencia, y en su remplazo emitir otra que, con fundamento en los argumentos expuestos en el escrito de observación y en el presente escrito, declare fundada dicha oposición y niegue el privilegio de patente mencionado, procediendo luego al definitivo archivo del expediente en cuestión.

II. ARGUMENTOS SOBRE LOS FUNDAMENTOS DE LA CONCESIÓN Y

MOTIVOS DE INCONFORMIDAD

La Resolución 64497 de septiembre 17 de 2015, que concede el privilegio de patente de invención solicitado para el capítulo reivindicatorio del expediente 14-122226 del título de referencia, viola flagrantemente la Decisión 486 si se tiene en cuenta que existían motivos suficientes para afectar los requisitos de novedad y nivel inventivo de la solicitud en mención. Es evidente que el solicitante y la Resolución cometen un error cuando afirman que la oposición presentada por mi representada no muestra ningún tipo de argumento soportado técnicamente, ni desvirtúa la patentabilidad del objeto de estudio, declarándola infundada por cuanto, al momento de presentación del escrito de oposición se dejó en claro que para el presente caso nos encontramos frente a una combinación de compuestos, lo cual indudablemente afecta el requisito de nivel inventivo, éste mismo indispensable para acceder a cualquier beneficio patentario.

Así las cosas, me permito reiterar que la concesión de patente objeto del presente escrito se ve afectada por los documentos del estado del arte que fueron presentados inicialmente en el escrito de observación, por lo cual, basado en lo siguiente, solicito respetuosamente a ese Despacho dar análisis completo y a cabalidad sobre los siguientes documentos, los cuales sin lugar a dudas objetan la concesión en mención, toda vez que develan de manera expresa y sucinta lo que se pretende proteger en la presente solicitud.

También es necesario reiterar que la solicitud de la referencia pretende proteger mediante el derecho patentario objetos que no son considerados invenciones. Es claro que una invención es toda creación humana que permita transformar la materia o energía que existe en la naturaleza, para su aprovechamiento por los seres humanos y satisfacer sus necesidades concretas. De igual modo, como ya se mencionó, según los parámetros de la Decisión 486 y normas concordantes, serán patentables las invenciones que cumplan con los requisitos de novedad, nivel inventivo y aplicación industrial. No obstante, puede observarse que la solicitud en comento pretende reivindicar combinaciones, las cuales no se consideran invenciones. En este sentido, la mezcla (Combinaciones) de productos (Moléculas) conocidos y su variación, bien sea en uso, forma, dimensión o de materia, NO se consideran invenciones por cuanto no son susceptibles de aplicación industrial, nivel inventivo y novedad, luego NO pueden acceder a beneficios patentarios. Por lo tanto, se suma una circunstancia más que imposibilita definitivamente la concesión de la solicitud en mención.

Y sobre el particular, es imprescindible señalar que un efecto sinérgico nuevo no se considera inventivo como tal, dado que puede ser obvio para una persona versada en la materia, cosa que sucede en el presente caso. En palabras del Doctor Carlos Correa, “El

efecto sinérgico entre dos o más drogas se puede considerar un “descubrimiento” y no una “invención”, dado que la sinergia ocurre en el cuerpo y se descubre a través de ensayos clínicos. Asimismo, cabe destacar que, en algunos casos, las reivindicaciones de combinaciones pueden equivaler, en términos prácticos, a reivindicaciones sobre tratamientos médicos (cuya patentabilidad está excluida en la mayoría de los países), cuando sólo brindan un método para administrar una combinación de drogas conocidas. Asimismo, la combinación de drogas para evitar la resistencia particular a una de ellas es una práctica normal en el desarrollo farmacéutico y, por lo general, es evidente para el hombre del oficio de nivel medio” (Pautas para el examen de patentes farmacéuticas, CEIDIE, Pág. 8). En estos términos, está claro que nos encontramos frente a un tema totalmente sensible que merece toda la evaluación por cuanto las combinaciones deben considerarse excluidas de beneficios de patente.

Y en caso que ese Despacho decidiera insistir en el cabal cumplimiento de los requisitos exigidos para acceder al beneficio de patente, me permito allegar copia del International Search Report y el respectivo Written Opinion Of The International Searching Authority, documentos en los cuales se resalta que la presente invención no cumple con los requisitos de novedad y nivel inventivo por cuanto existen documentos citados del estado del arte que afectan de manera definitiva tales exigencias. Lo anterior deja entrever, sin lugar a equívocos, que la presente solicitud no debió ser concedida, por lo cual es procedente la revocatoria de la Resolución objeto de este escrito.

En este sentido, reitero con el debido respeto la necesidad de analizar a profundidad los requisitos de novedad y nivel inventivo para así determinar si la presente solicitud es merecedora de concesión de privilegio de patente.

ANEXOS

International Search Report y el Written Opinion Of The International Searching Authority de la equivalente internacional WO 2013/083685

En subsidio apelo.

Señor Superintendente,

TITO NOÉ PARRA MURILLO
C.C. 79.579.680 de Bogotá
T.P. 71168 del C. S de la J.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 0817-WO-PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/EP2012/074623	International filing date (day/month/year) 06/12/2012	(Earliest) Priority Date (day/month/year) 06/12/2011
Applicant H. LUNDBECK A/S		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 04 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6bis(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/074623

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D489/08 A61K31/485 A61P25/30
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2011/251228 A1 (LOPEZ DE DIEGO HEIDI [DK] ET AL) 13 October 2011 (2011-10-13) cited in the application example 4	1-15
Y	EP 2 121 699 A1 (VORAMCO INC [US]) 25 November 2009 (2009-11-25) example 4	1-15
Y	US 2008/312442 A1 (BUEHLER HENRY J [US] ET AL) 18 December 2008 (2008-12-18) the whole document	1-15
A	US 3 896 226 A (FISHMAN JACK) 22 July 1975 (1975-07-22) the whole document	1-15
	-/--	



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier application or patent not published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Z document member of the same patent family

Date of the actual completion of the international search

15 March 2013

Date of mailing of the international search report

22/03/2013

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HZ Rijswijk
Tel. (+31-70) 340-2043,
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Authorized officer

Megido, Benigno

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/074623

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 814 768 A (FISHMAN J) 4 June 1974 (1974-06-04) the whole document -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/074623

Patent document cited in search report	Publication date	Patent family members)	Publication date
US 2011251228 A1	13-10-2011	AR 074507 A1 AT 546453 T AU 2009321898 A1 CA 2744932 A1 CN 102325778 A CO 6362012 A2 DK 2360479 T3 EA 201170753 A1 EP 2300479 A1 EP 2441766 A1 ES 2330297 T3 HR P20120247 T1 JP 2012510954 A KE 20110689333 A PT 2300479 E RS 52255 B SG 171910 A1 SI 2300479 T1 SM T201200014 B TW 201022273 A US 2011251228 A1 WO 2010063292 A1	19-01-2011 15-03-2012 14-07-2011 10-05-2010 18-01-2012 20-01-2012 26-03-2012 30-12-2011 30-03-2011 18-04-2012 10-05-2012 31-05-2012 17-05-2012 05-08-2011 10-04-2012 31-10-2012 28-07-2011 31-07-2012 10-07-2012 16-06-2010 13-10-2011 10-06-2010
EP 2121699 A1	25-11-2009	AL 2007329453 A1 CA 2671518 A1 CN 101652370 A EP 2121699 A1 ES 2393221 T3 JP 2010511726 A US 2008139814 A1 US 2011144340 A1 WO 2008070658 A1	12-06-2008 12-06-2008 17-02-2010 25-11-2009 19-12-2012 15-04-2010 12-06-2008 16-06-2011 12-06-2008
US 2008312442 A1	18-12-2008	AT 448231 T AU 2007224221 A1 CA 2544095 A1 CN 101395159 A EP 1994034 A2 JP 2309528366 A US 2008312442 A1 US 2012059167 A1 WO 2007103105 A2	15-11-2009 13-09-2007 13-09-2007 25-03-2009 26-11-2008 06-08-2009 18-12-2008 08-03-2012 13-09-2007
US 3896226 A	22-07-1975	NONE	
US 3814768 A	04-06-1974	CA 974235 A1 CH 578568 A5 DE 2257715 A1 FR 2160957 A1 GB 1411129 A JP 48058000 A JP 56053556 B US 3814768 A	09-09-1975 13-08-1976 30-05-1973 06-07-1973 22-10-1975 14-08-1973 19-12-1981 04-06-1974

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2012/074623

International filing date (day/month/year)
06.12.2012

Priority date (day/month/year)
06.12.2011

International Patent Classification (IPC) or both national classification and IPC
INV. C07D489/08 A61K31/485 A61P25/30

Applicant
H. LUNDBECK AS

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040
Fax: +31 70 340 - 3016

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2012/074623

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:
 - a. (means)
 - ☐ on paper
 - ☐ in electronic form
 - b. (time)
 - ☐ in the international application as filed
 - ☐ together with the international application in electronic form
 - ☐ subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-15</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-15</u>
Industrial applicability (IA)	Yes: Claims	<u>1-15</u>
	No: Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2012/074623

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V.

1 State of the art

1.1 Referred documents.

- D1 US 2011/251228 A1 (LOPEZ DE DIEGO HEIDI [DK] ET AL) 13 October 2011 (2011-10-13) cited in the application
- D2 EP 2 121 699 A1 (NORAMCO INC [US]) 25 November 2009 (2009-11-25)
- D3 US 2008/312442 A1 (BUEHLER HENRY J [US] ET AL) 18 December 2008 (2008-12-18)
- D4 US 3 896 226 A (FISHMAN JACK) 22 July 1975 (1975-07-22)
- D5 US 3 814 763 A (FISHMAN J) 4 June 1974 (1974-06-04)

2 Novelty

- 2.1 The present application is new in the sense of Article 33(2) PCT.
- 2.2 The present application refers to a process for recovery of nalmefene hydrochloride from an aqueous composition containing nalmefene hydrochloride and naltrexone, said process comprising the step of isolating nalmefene hydrochloride from an aqueous suspension comprising naltrexone bisulphite adduct and solid nalmefene hydrochloride and to the involved naltrexone bisulphite adduct.
- 2.3 The available prior art documents D1 to D5 fail to disclose this adduct nor any use thereof.
- 2.4 Therefore the claimed subject matter has to be considered new over the prior art in the sense of Article 33(2) PCT.

3 Inventive Step

- 3.1 The present application contravenes the requirements of Article 33(3) PCT.
- 3.2 The present application refers to a process for recovery of nalmefene hydrochloride from an aqueous composition containing nalmefene hydrochloride and naltrexone, said process comprising the step of isolating

nalmefene hydrochloride from an aqueous suspension comprising naltrexone bisulphite adduct and solid nalmefene hydrochloride and to the involved naltrexone bisulphite adduct.

- 3.3 The closest prior art document D1 discloses a process for recovery of nalmefene hydrochloride from the mother liquor by basification of the mother liquor followed by extracting with an organic solvent.
- 3.4 Example 4 of prior art document D1 states:
- 3.4.1 "The mother liquors obtained in Example 3 were concentrated under vacuum. Ammonium hydroxide was added till pH 8-9. The mixture was extracted with dichloromethane at a temperature of 30-35[deg.] C. The organic phase was separated and cooled down to 25[deg.] C. Concentrated hydrochloric acid was added and the product was allowed to precipitate. The solid was filtered and washed with dichloromethane thus giving 1.35 Kg of Nalmefene HCl with a chemical purity of 98.9%, which can be transformed into the dihydrate applying the procedure described in Example 3".
- 3.4.2 The recovered amount (1.35kg) corresponds to 59.5% of the total amount in the mother liquor (2.27kg).
- 3.5 Example 1 of the present application states:
- 3.5.1 "Nalmefene HCl aqueous mother liquor (400 g); containing about 36 g of "residue of evaporation" with the following composition (% by HPLC area): nalmefene 92.08%, naltrexone 0.49%, methyldiphenylphosphine oxide 0.77%, triphenylphosphineoxide 4.0%; was treated with 0.34 g of sodium bisulphite and concentrated under vacuum distilling 323 g of solvent. The concentrated mixture was cooled down to 0[deg.]C and maintained at this temperature overnight. The solid was filtered and washed with acetone (34 mL) obtaining 21 g of nalmefene HCl. HPLC analysis (% by area): nalmefene 98.92%, naltrexone 0.09%, methyldiphenylphosphine oxide 0.04%, triphenylphosphineoxide 0.16%".
- 3.5.2 The recovered nalmefene hydrochloride amounts to 58.3% of the total amount in the mother liquor.
- 3.6 It is clear from this two examples that the claimed and disclosed purity and quantity of the recovered nalmefene hydrochloride is the same (98.9% purity and about 59% recovery) in both cases, prior art document D1 and present application.

- 3.7 According to comparative example 4 of the present application, the recovery of nalmefene hydrochloride from the mother liquor without using bisulphite nor extraction with organic solvent yield 64.7% recovered nalmefene hydrochloride with a purity of 97.42%.
- 3.8 Therefore, and taking into account that both methods, the disclosed in D1 and the claimed by the present application, yield similar results, the problem to be solved by the present application has to be considered to be the provision of an alternative method for the recovery of nalmefene hydrochloride from an aqueous media wherein the recovered substance has a reduced amount of impurities, specially of naltrexone.
- 3.9 Prior art document D2 refers to the preparation of the very similar and related compound oxycodone. This document teaches how to reduce the amount of 14-hydroxycodeinone impurity in the synthesis and purification of oxycodone by using sodium bisulphite (paragraph [024] on page 4, paragraph [030] on page 5).
- 3.10 Prior art document D3 explores further this idea (cf. specially paragraph [084] and reaction scheme 12A on pages 10 and 11) and teaches that not only the alpha,beta-unsaturated ketones like 14-hydroxycodeinone, but also the ketone compounds such as oxycodone or naltrexone (both of them can be represented by the general formula (2) on Reaction Scheme 12A on page 11 of prior art document D3) will react with bisulphites to give the corresponding adduct.
- 3.11 For the person skilled in the art and confronted with the problem of providing an alternative recovery process of nalmefene hydrochloride (which contains neither an alpha,beta-unsaturated ketone nor a ketone but an exo carbon-carbon double bond) wherein the amount of naltrexone (a ketone compound) is reduced, will starting from prior art document D1 and in the light of the teaching of prior art document D3 specially, combine those teaching (and if needed complement them with the general knowledge of the chemical field) and come to the use of bisulphites for the formation of bisulphite adducts with the ketone impurities (here the naltrexone) to reduce their amount in the desired non-ketone compound (here nalmefene).
- 3.12 Therefore, and in doing so the person skilled in the art will arrive to the proposed solution (use of bisulphites) without any undue burden, unnecessary experimentation or inventive skills with reasonable expectations of success.
- 3.13 Therefore, the claimed subject matter contravenes the requirements of Article 33(3) PCT.

Re Item VIII.

4 **Clarity and content of the description**

- 4.1 On the description the prior art relevant to the background of the invention is discussed and "incorporated by reference", the attention of the applicant is called to PCT-GL-4.26 where the reference in international applications to other documents is discussed.