



No. 14-189356-00002-0000

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Act. 608 MODIFICASOLICIT Folios: 41

DIRECCIÓN DE NUEVAS CREACIONES
MODIFICACIONES Y/O CORRECCIONES

1. Identificación del Trámite

☐ Error material

☒ Modificación a una Solicitud en trámite

☒ Patente de Invención

☐ Patente de Modelo de Utilidad

☐ Registro de Diseño Industrial

☐ Esquema de Trazado de Circuitos Integrados

2. Datos del solicitante

Persona Natural ☐

Persona Jurídica ☒

CHELSEA THERAPEUTICS, INC.

Nombre o denominación / Nombre o razón social completa

Nombre representante legal

Tipo de empresa

Micro ☐

Pequeña ☐

Mediana ☐

Otra ☒

Documento de identificación:

☐ C.C.

☐ C.E.

☐ NIT

☐ Otro Número

Nacionalidad/País de constitución	Dirección y domicilio del titular	Ciudad
ESTADOS UNIDOS DE AMÉRICA	3530 TORINGDON WAY, OFICINA 200, CHARLOTTE, CAROLINA DEL NORTE 28277	CHARLOTTE
Dirección electrónica	No. Fax	Número telefónico



Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico

3. Datos del apoderado:

URIBE RESTREPO JUAN CARLOS

79.159.313

54.493

Apellidos y Nombre

Documento de identificación

Tarjeta profesional

Dirección y domicilio	Ciudad	
CALLE 93B No. 12-48, Piso 4o. BOGOTA, D.C., COLOMBIA	BOGOTA	
Dirección electrónica	No. Fax	Número telefónico
tum@tumnet.com	6-114209	6-019660

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sirvase indicar el número de su radicación o protocolo de poder general

2

4. Datos del trámite

Corrección:

Expediente No 14-189356

Aparece

Debe ser

Modificación:

☐ Modificación al capítulo reivindicatorio.

☐ Modificación al capítulo descriptivo.

☐ Modificación al resumen.

☐ Modificación a los dibujos.

☒ Modificación al solicitante.

CAMBIO DE DIRECCIÓN De : 3530 TORINGDON WAY, OFICINA 200, CHARLOTTE, CAROLINA DEL NORTE 28277 ESTADOS UNIDOS DE AMÉRICA

A : 4 PARKWAY NORTH, DEERFIELD, IL 60015, ESTADOS UNIDOS DE AMÉRICA

5. Anexos

☒ Comprobante de pago de la tasa para la presentación de la corrección y/o modificación

☒ Poder, si fuere el caso.

☒ Documento que contiene las modificaciones o correcciones.

☐ Copia de la solicitud y sus anexos en formato magnético.

6. Firma

JUAN CARLOS URIBE RESTREPO

Nombre y apellidos

Firma

C.C. 79.159.313

Tarjeta Profesional 54.493

Acknowledgement Certificate

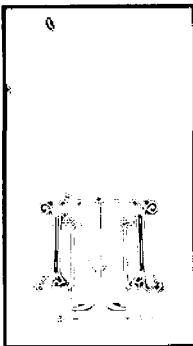
State of New Jersey)
) ss
County of Bergen)

On September 22, 2014 before me, Julie A. Prahm, Notary public in and for said county, personally appeared Stephen G. Kalinchak, signor, who has satisfactorily identified himself as the signer to the attached document.


Julie A. Prahm
Notary Public

My Commission Expires: March 14, 2017

NOTARY SEAL



TRIANA, URIBE & MICHELSEN

REPRESENTATION AND POWER OF ATTORNEY

I (we), the undersigned

Stephen G. Kalinchack

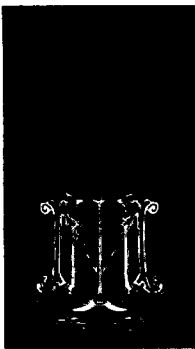
in representation of **LUNDBECK NA LTD.**, domiciled in 4 Parkway North, Deerfield, IL 60015, U.S.A., in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint **FERNANDO TRIANA**, tpa. No. 45.265 c.c. No. 79.154.036; **LAURA MICHELSEN**, tpa. No. 67.897 c.c. No. 39.783.287; **JUAN CARLOS URIBE**, tpa. No. 54.493 c.c. No. 79.159.313 and **JUAN PABLO TRIANA**, tpa. 63.077 c.c. No. 79.487.222; domiciled at Calle 93 B No. 12-48 P. 4, Bogotá, D.C., Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second or third alternate representative is to replace the first or second one, or when the second or third is to replace the principal one. In such cases, the principal representative, shall state his intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in cases of impediment, the appropriate certificate shall suffice.

REPRESENTACIÓN Y PODER

Yo (nosotros), abajo suscrito(s) _____

Stephen G Kalinchack

en representación de **LUNDBECK NA LTD.**, domiciliado(s) en 4 Parkway North, Deerfield, IL 60015, Estados Unidos de América, por el presente nombro (nombramos) a **FERNANDO TRIANA**, tpa. No. 45.265 c.c. No. 79.154.036; **LAURA MICHELSEN**, tpa. No. 67.897 c.c. No. 39.783.287; **JUAN CARLOS URIBE**, tpa. No. 54.493 c.c. No. 79.159.313 y **JUAN PABLO TRIANA**, tpa. 63.077 c.c. No. 79.487.222; domiciliados en la Calle 93 B No. 12-48 P. 4, Bogotá, D.C., Colombia, en obediencia a lo dispuesto en el parágrafo 1ro. del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquel. La misma regla se aplicará cuando el segundo y tercer representantes suplentes hayan de reemplazar al primero, al segundo o al principal. En tales casos, el representante principal, o el primero, o segundo suplente, o tercer suplente en su caso, o todos ellos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia,



TRIANA, URIBE & MICHELSEN

If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second or third alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second or third alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first or second or third alternates in their turn shall end at such time.

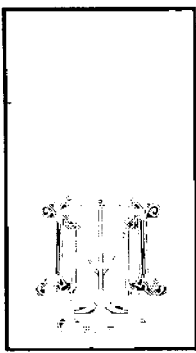
In addition, I (we) grant a Power of Attorney in favor of the above named attorneys-at-law so that they may obtain the protection of my (our) intellectual property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons, with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before national and/or international arbitration tribunals in all matters concerning the following:

- a) Obtainment of patents, layout-designs of integrated circuits, utility models and industrial designs; the registration of marks and trade slogans; the deposit of commercial names and trade emblems; the obtainment of the declaration and authorization of denominations of origin; renewal, payment of the annuity fees, assignment, license, change of name or domicile, voluntary cancellation; and the registration of commercialization agreements and licenses of use of the above rights;
- b) Protection of trade secrets;
- c) Obtainment of plant variety protection;
- d) Obtainment of functioning licenses, health registrations and sale licenses and any other petition before the sanitary or administrative authorities;
- e) Actions against protection to the consumers, restrictive commercial practices and competence promotion;

en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los nombrados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo o tercer suplente, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero o segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad intelectual y contra la competencia desleal, a cuyo efecto autorizo(amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento nacionales y/o internacionales en todo lo concerniente a los siguientes asuntos:

- a) Obtención de patentes de invención, de los esquemas de trazado de circuitos integrados, modelos de utilidad y diseños industriales; el registro de marcas y de lemas comerciales; el depósito de nombres comerciales y enseñas; la obtención de la declaración y de la autorización de denominaciones de origen; su renovación, pago de anualidades de mantenimiento, traspaso, licencia, cambio de nombre o domicilio, cancelación voluntaria; y el registro de acuerdos de comercialización y de licencias de uso de esos derechos;
- b) Protección de secretos empresariales
- c) Obtención de la protección para variedades vegetales;
- d) Obtención y tramitación de todo lo relacionado con licencias de funcionamiento, registros sanitarios, licencias de venta y cualquier otra petición ante las autoridades sanitarias o



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f) Obtainment of copyright registrations for any type of artistic, literary, scientific, musical, video, films, video games, choreography works, software or any other production in the artistic, scientific or literary fields capable of being reproduced or expressed by any means known now or in the future; Registration of agreements related with the execution or transfer of intellectual property rights; Obtention of reduced postal tariff; g) Registration of domain names; their renewal, assignment, change of name, change of domicile, cancellation and any other acts related with their management. h) Actions of repossession, of opposition, cancellation, nullity, infringement of rights, preventive injunction, custom procedures, writ of mandamus, unfair competition, granting of licenses; and in general the civil, constitutional, criminal and administrative suits relating to all those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, execute license agreements, settlement agreements, assignment agreements, file extraordinary remedies such as nullification and/or revision and/or supplication of court decisions, conciliate, admit the facts of the case, to bid in public auction and allocate on behalf of an existing credit, desist, cancel, assign, receive, resign, notify and ratify acts done by representatives without a Power of Attorney.

administrativas; e) Acciones por protección al consumidor, por prácticas comerciales restrictivas y promoción de la competencia; f) Obtención del registro del derecho de autor para cualquier tipo de obra artística, literaria, científica, musical, videográfica, cinematográfica, coreográficas, soporte lógico o cualquier otra producción, en el campo artístico, científico, o literario capaz de ser reproducido o expresado por cualquier medio conocido ahora o por conocer en el futuro; Registro de contratos relacionados con la ejecución o transferencia de derechos intelectuales; Obtención de tarifa postal reducida; g) Registro de nombres de dominio, su renovación, traspaso, cambio de nombre, cambio de domicilio, cancelación y demás actos relacionados con su administración. h) Las acciones reivindicatorias, de oposición, de cancelación, de nulidad, de infracción de derechos, de medidas cautelares, de medidas en frontera, de tutela, de competencia desleal, de concesión de licencias y en general los procesos civiles, constitucionales, penales, administrativos o contencioso-administrativos relacionados con todos estos derechos; acciones y procesos que promovamos o se nos promuevan; y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, suscribir contratos de licencia, contratos de transacción, contratos de cesión, presentar recursos extraordinarios de casación y/o revisión y/o suplica, conciliar, admitir los hechos del proceso, rematar o licitar por cuenta del crédito, desistir, cancelar, ceder, recibir, renunciar, notificarse y ratificar los actos de agentes oficiosos.

Given and Signed this/Dado y firmado hoy 22 September, 2014.

in/en USA

Signature/Firma 
Attorney for
Lowbuck WA Ltd.

Acknowledgement Certificate

State of New Jersey)
) ss
County of Bergen)

On September 22, 2014 before me, Julie A. Prahm, Notary public in and for said county, personally appeared Stephen G. Kalinchak, signor, who has satisfactorily identified himself as the signer to the attached document.



Julie A. Prahm
Notary Public

My Commission Expires: March 14, 2017

NOTARY SEAL

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

WOMBLE CARLYLE SANDRIDGE & RICE, LLP
P.O. Box 7037
Atlanta GA 30357-0037
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(PCT Rule 71.1)

Date of mailing
(day/month/year)

04.08.2014

Applicant's or agent's file reference
C63756 1260WO(0135.2)

IMPORTANT NOTIFICATION

International application No.
PCT/US2013/023828

International filing date (day/month/year)
30.01.2013

Priority date (day/month/year)
31.01.2012

Applicant
Chelsea Therapeutics, Inc.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international
preliminary examining authority:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Authorized Officer

Stark, Saskia

Tel. +49 89 2399-4764



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference C63756 1260WO(0135.2)		FOR FURTHER ACTION		See Form PCT/PEA/416
International application No. PCT/US2013/023828		International filing date (day/month/year) 30.01.2013		Priority date (day/month/year) 31.01.2012
International Patent Classification (IPC) or national classification and IPC INV. A61K31/198				
Applicant Chelsea Therapeutics, Inc.				
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>15</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ (sent to the applicant and to the International Bureau) a total of <u>16</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions). ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2). ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)). b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3bis of Annex C of the Administrative Instructions).				
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ 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 Article 35(2) with regard to novelty, inventive step or 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				
Date of submission of the demand		Date of completion of this report		
14.11.2013		04.08.2014		
Name and mailing address of the international preliminary examining authority:		Authorized officer		
 European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465		Baumgärtner, Heike Telephone No. +49 89 2399-8480 		

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2013/023828

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
 - ☒ 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 (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))
2. With regard to the **elements*** of the International application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-39 as originally filed

Claims, Numbers

1-30 filed with telefax on 14-11-2013

Drawings, Sheets

1/5-5/5 as originally filed

- ☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
 4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
 - ☐ the description, pages
 - ☒ the claims, Nos. 24
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 5. ☐ This report has been established:
 - ☐ taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-bis) and 70.2(e)).
 - ☐ without taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91(Rules 66.4bis and 70.2(e)).

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2013/023828

6. ☒ With regard to top-up searches (Rules 66.1 ter and 70.2(f)):
- ☒ A top-up search was carried out by this Authority on 24.07.2014 (all discovered documents are listed in the Supplemental Box Relating to Top-up Search).
 - ☐ No top-up search was carried out by this Authority.
7. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

Box No. V Reasoned statement under Article 35(2) with regard to novelty, Inventive step or Industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	<u>1-30</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-30</u>
Industrial applicability (IA)	Yes: Claims	<u>1-30</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

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 I

Basis of the report

subject-matter

Claim 1 A method of **improving postural instability** in a **Parkinson's disease (PD)** patient, the method comprising administering an effective amount of **droxidopa** or a pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof to the PD patient, wherein the **improved postural instability** is defined by at least one of the following:

a **reduction in falls** as evidenced by a **post-administration reduction** in the **mean number of falls per patient per week** as compared to a **baseline mean number of falls per patient per week before administration** of the droxidopa or a pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof;

a **baseline Hoehn and Yahr rating scale score indicative of the postural instability** and a **post-administration Hoehn and Yahr rating scale score** for the patient that is improved as compared to the baseline score;

a **baseline Unified Parkinson's Disease Rating Scale (UPDRS) score** indicative of PD-related motor or non-motor symptoms, and

wherein a **post-administration UPDRS score** for the patient that is improved as compared to the baseline score

d2 of claim 1, wherein the **post-administration** mean number of falls per patient per week is **reduced by at least 20%**

d3 of claim 1, wherein the **post-administration** mean number of falls per patient per week is **reduced by at least 50%**

d4 of claim 1, wherein the **number of falls** is identified based upon reporting by the patient or the patient's caregiver

d5 of claim 1, wherein **prior to administration**, the PD patient is a **recurrent faller**

d6 of claim 5, wherein the PD patient has **experienced a mean of at least 0.2 falls per week over a period of at least six weeks prior to administration**

d7 of claim 1, wherein the **post-administration Hoehn and Yahr rating scale score** is **improved by at least 0.2 points**

d8 of claim 1, wherein the **post-administration Hoehn and Yahr rating scale score** is **improved by at least 0.3 points**

d9 of claim 1, wherein the **post-administration Hoehn and Yahr rating scale score** is **improved by at least 0.4 points**

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/US2013/023828

d10 of claim 1, wherein the **improvement is defined by** at least one of the following:

the **baseline Hoehn and Yahr score is greater than 4.0** and the **post-administration Hoehn and Yahr score is less than 4.0**;

the **baseline Hoehn and Yahr score is greater than 3.0** and the **post-administration Hoehn and Yahr score is less than 3.0**;

the **baseline Hoehn and Yahr score is greater than 3.0** and the **post-administration Hoehn and Yahr score is less than 2.8**;

the **baseline Hoehn and Yahr score is greater than 3.0** and the **post-administration Hoehn and Yahr score is less than 2.5**;

the **baseline Hoehn and Yahr score is greater than 3.0** and the **post-administration Hoehn and Yahr score is less than 2.2**;

the **baseline Hoehn and Yahr score is greater than 2.5** and the **post-administration Hoehn and Yahr score is less than 2.5**;

the **baseline Hoehn and Yahr score is greater than 2.5** and the **post-administration Hoehn and Yahr score is less than 2.3**;

the **baseline Hoehn and Yahr score is greater than 2.5** and the **post-administration Hoehn and Yahr score is less than 2.0**;

the **baseline Hoehn and Yahr score is greater than 2.5** and the **post-administration Hoehn and Yahr score is less than 1.8**;

the **baseline Hoehn and Yahr score is greater than 2.0** and the **post-administration Hoehn and Yahr score is less than 2.0**;

the **baseline Hoehn and Yahr score is greater than 2.0** and the **post-administration Hoehn and Yahr score is less than 1.8**;

the **baseline Hoehn and Yahr score is greater than 2.0** and the **post-administration Hoehn and Yahr score is less than 1.5**;

the **baseline Hoehn and Yahr score is greater than 2.0** and the **post-administration Hoehn and Yahr score is less than 1.2**;

the **baseline Hoehn and Yahr score is greater than 1.8** and the **post-administration Hoehn and Yahr score is less than 1.8**;

the **baseline Hoehn and Yahr score is greater than 1.8** and the **post-administration Hoehn and Yahr score is less than 1.5**;

the **baseline Hoehn and Yahr score is greater than 1.8** and the **post-administration Hoehn and Yahr score is less than 1.2**; or

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

International application No.

PCT/US2013/023828

the **baseline Hoehn and Yahr score** is **greater than 1.8** and the **post-administration**
Hoehn and Yahr score is **less than 1.0**.

d11 of claim 1, wherein the **improvement is defined by** at least one of the following:

the **baseline Hoehn and Yahr score** is **at least 4** and the **post-administration** Hoehn and
Yahr score is **3.5 or less**;

the **baseline Hoehn and Yahr score** is **at least 4** and the **post-administration** Hoehn and
Yahr score is **3.0 or less**;

the **baseline Hoehn and Yahr score** is **at least 3.5** and the **post-administration** Hoehn and
Yahr score is **3.0 or less**;

the **baseline Hoehn and Yahr score** is **at least 3.5** and the **post-administration** Hoehn and
Yahr score is **2.5 or less**;

the **baseline Hoehn and Yahr score** is **at least 3.0** and the **post-administration** Hoehn and
Yahr score is **2.5 or less**;

the **baseline Hoehn and Yahr score** is **at least 3.0** and the **post-administration** Hoehn and
Yahr score is **2.0 or less**;

the **baseline Hoehn and Yahr score** is **at least 2.5** and the **post-administration** Hoehn and
Yahr score is **2.0 or less**;

the **baseline Hoehn and Yahr score** is **at least 2.5** and the **post-administration** Hoehn and
Yahr score is **1.5 or less**;

the **baseline Hoehn and Yahr score** is **at least 2.0** and the **post-administration** Hoehn and
Yahr score is **1.5 or less**;

the **baseline Hoehn and Yahr score** is **at least 2.0** and the **post-administration** Hoehn and
Yahr score is **1.0 or less**;

the **baseline Hoehn and Yahr score** is **at least 1.5** and the **post-administration** Hoehn and
Yahr score is **1.0 or less**; or

the **baseline Hoehn and Yahr score** is **at least 1.0** and the **post-administration** Hoehn and
Yahr score is **0.5 or less**.

d12 of claim 1, wherein the **post-administration UPDRS score** is **improved by at least 5 points**

d13 of claim 1, wherein the **post-administration UPDRS score** is **improved by at least 10 points**

d14 of claim 1, wherein the **symptom is a motor symptom**

d15 of claim 14, wherein the **motor symptom is related to recurrent falls in the PD patient**

d16 of claims 1 to 15, wherein **PD patient further suffers from neurogenic orthostatic hypotension (NOH)**

d17 of claims 1 to 16, further comprising administering **one or more additional active agents** selected from the group consisting of DOPA decarboxylase inhibiting compounds, catechol-O-methyltransferase inhibiting compounds, monoamine oxidase inhibiting compounds, cholinesterase inhibiting compounds, and combinations thereof

d18 of claim 17, wherein the **one or more additional active agents are administered with the droxidopa** or a pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof in a **single pharmaceutical composition**

d19 of claim 17, wherein the **one or more additional active agents are administered separately from the droxidopa** or a pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof

d20 of claims 1 to 19, wherein the **droxidopa** or a pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof is administered in a **sustained release form**

d21 of claims 1 to 19, wherein the **droxidopa** or a pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof is administered in a **controlled release form**

d22 of claims 1 to 19, wherein the **droxidopa** or a pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof is administered in an **immediate release form**

d23 of claims 1 to 22, wherein **droxidopa** or a pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof is administered in the form of a **mixture enantiomerically enriched in the L-threo isomer**

d24 cf. claims 1-23, wherein the **postural instability is non-responsive to levodopa therapy**

Claim 25 A **composition comprising an effective amount of droxidopa** or a pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof **for use in improving postural instability in a Parkinson's disease (PD) patient exhibiting symptoms of postural instability** as defined by at least one of the following:

a **reduction in falls;**

a **baseline Hoehn and Yahr rating scale score indicative of the postural instability** and a **post-administration Hoehn and Yahr rating scale score** for the patient that is improved as compared to the baseline score;

a **baseline Unified Parkinson's Disease Rating Scale (UPDRS) score** indicative of PD-related motor or non-motor symptoms, and

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wherein **a post-administration UPDRS score** for the patient that is improved as compared to the baseline score

~~d29 of claim 28, wherein the **improved postural instability** is defined by a **reduction in falls**~~

~~d30 of claim 28, wherein the **postural instability** is defined by a **baseline Hoehn and Yahr rating scale score** indicative of the postural instability, and wherein the **improvement** in the postural instability is defined by a **post-administration Hoehn and Yahr rating scale score** for the patient that is improved as compared to the baseline score~~

~~d31 of claim 28, wherein the **postural instability** is defined by a **baseline Unified Parkinson's Disease Rating Scale (UPDRS) score** indicative of PD-related motor or non-motor symptoms, and wherein the **improvement** in the postural instability is defined by a **post-administration UPDRS score** for the patient that is improved as compared to the baseline score~~

d26 of claim 25, wherein the **composition further comprises** one or more **additional active** agents selected from the group consisting of DOPA decarboxylase inhibiting compounds, catechol-O-methyltransferase inhibiting compounds, monoamine oxidase inhibiting compounds, cholinesterase inhibiting compounds, and combinations thereof

d27 of claims 25 or 26, wherein the **droxidopa** or a pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof is in a **sustained release form**

d28 of claims 25 or 26, wherein the **droxidopa** or a pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof is in a **controlled release form**

d29 of claims 25 to 26, wherein the **droxidopa** or a pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof is in an **immediate release form**

d30 of claims 25 to 29, wherein **droxidopa** or a pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof is in the form of a mixture **enantiomerically enriched in the L-threo isomer**

Amended claims 1-30 have been filed with the Fax dated 14th Nov 2013.

New independent claim 1 combines the subject-matter of original claims 1, 2, 3, 9 and 15 and new independent claim 25 incorporates the subject-matter of original claims 28-31.

A new dependent claim 24 has been introduced which is said to find a basis on p.2/l. 27-31. However, the passages on p. 2 relate to the prior discussion and do not refer to the "summary of the invention". Hence it appears that no true basis for such a claim in combination with the original claims 1-23 is present in the application.

Claim 24 is thus considered to introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT.

Irrespective of the above objection the following should be noted:

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The documents which are referred to in this communication are numbered in the order of their listing in the International Search Report.

D1 WO2006123678 A1 20061123 DAINIPPON SUMITOMO PHARMA [X]

Tablet composition **useful for treating e.g. Parkinson's disease**, comprises **droxidopa** and excipients selected from mannitol, lactose, erythritol, glucose, sucrose, crystalline cellulose and starch

A droxidopa is a chemical/medical agent mainly used **for the Parkinson disease person's frozen gait**, or the treatment of the **orthostatic-hypotension disease** in improvement which leaves and feels dizzy, and a dialysis patient.

D2 XP002500633 Aug 2001 Mathias et al. [X/IS]

L-threo-dihydroxyphenylserine (**L-threo-DOPS; droxidopa**) in the management of **neurogenic orthostatic hypotension**

Orthostatic (postural) hypotension is a **major disabling manifestation of autonomic failure**. It is **associated with** increased morbidity and sometimes mortality, especially **In the elderly, who are at increased risk of injury due to falls**. [...]. **Reducing orthostatic hypotension** should improve patients' mobility and function, improve quality of life, and **prevent falls** and associated trauma - cf. p. 235/bottom.

D3 XP019567565 March 2008 Kaufmann et al. [X/IS]

L-dihydroxyphenylserine (Droxidopa): a new therapy for neurogenic orthostatic hypotension

Autonomic failure, like **Parkinson's disease**, is a **neurotransmitter disorder**. While **Parkinson's disease** is a **disorder of dopamine neurotransmission**, **autonomic failure** [NB: should read probably neurogenic orthostatic hypotension] is a **disorder of norepinephrine neurotransmission**.

Dopamine beta hydroxylase is the **rate-limiting enzyme** and it creates a "bottle neck" like effect, so that taking levodopa orally results in an increase in dopamine levels but not to a significant increase in norepinephrine levels.

Fortunately, the possibility of **overcoming this limitation** and realizing another therapeutic breakthrough **using a precursor amino acid to replace** a deficient catecholamine neurotransmitter, in this case **norepinephrine**, was made possible by the discovery, in the 1950', that an **artificial amino acid, 3,4-threodihydroxyphenylserine**, identical to levodopa but **with an added beta hydroxyl group** (Fig. 2) **was converted to norepinephrine in a single step** by the enzyme L-aromatic amino acid decarboxylase, thus **bypassing the need for dopamine beta hydroxylase and its bottle neck effect**. [...] after **oral administration, droxidopa was taken up by post-ganglionic sympathetic neurons, decarboxylated to NE**, stored and released appropriately when standing up - c.f p.20.

In summary: Droxidopa effectively raises standing blood pressure and **ameliorates symptoms of orthostatic hypotension in patients with central and**

D4 . XP009168148 Jan 2008 Gupta et al. [Y]

Neurogenic orthostatic hypotension: chasing "the fall".

Orthostatic hypotension (OH) is a frequently encountered problem affecting **nearly 30% of the population aged more than 60 years**. It can result from neurological and non-neurological derangements which compromise the perfusion of the brain in an erect posture. **Neurogenic OH is a manifestation of autonomic failure. It is an important cause of recurrent falls in the elderly**, syncopal events and also has been shown to be associated with increased long term mortality from vascular and non-vascular causes.

D5 XP002694399 June 2002 Wood et al. [Y]

Incidence and prediction of **falls in Parkinson's disease**: A prospective multidisciplinary study

Falls are a common problem in PD and some of the major risk factors are potentially modifiable. There is a need for future studies to look at interventions to prevent falls in PD.

NB

Claims 1-24 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) and Rule 67.1(iv) PCT.

The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable claims to the use of a compound in medical treatment, but may allow, however, claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Definitions

- Parkinson Disease

The primary symptoms of Parkinson's disease result from greatly reduced activity of dopamine-secreting cells caused by cell death in the pars compacta region of the substantia nigra.

There are **five major pathways in the brain** connecting other brain areas with the basal ganglia. These are known as the **motor, oculo-motor, associative, limbic and orbitofrontal circuits**, with names indicating the main projection area of each circuit. **All of them are affected in PD, and their disruption explains many of the symptoms of the disease** since these circuits are involved in a wide variety of functions including movement, attention and learning. Scientifically, the **motor circuit has been examined the most intensively**.

Postural instability is typical in the **late stages of the disease**, leading to impaired balance and frequent falls, and secondarily to bone fractures. Instability is often absent in the initial stages, especially in younger people. Up to 40% may experience falls and around 10% may have falls weekly, with **number of falls being related to the severity of PD**.

Two stages are usually distinguished: an initial stage in which the individual with PD has already developed some disability for which he needs pharmacological treatment, then a **second stage** in which an **individual develops motor complications related to levodopa usage**.

from D3: **Autonomic failure**, like **Parkinson's disease**, is a **neurotransmitter disorder**. While **Parkinson's disease** is a disorder of **dopamine neurotransmission**, **neurogenic orthostatic hypotension** is a disorder of **norepinephrine neurotransmission**. Droxidopa was first used successfully to treat one particular form of autonomic failure: congenital deficiency of the enzyme dopamine beta hydroxylase [...] showed that after oral administration, droxidopa was taken up by post-ganglionic sympathetic neurons, decarboxylated to NE, stored and released appropriately when standing up.

Droxidopa has now been used to treat orthostatic hypotension in several autonomic disorders, including ... Parkinson's disease!

- Postural Instability

from D2: **Orthostatic (postural) hypotension** is a major disabling manifestation of **autonomic failure**.

Postural instability can be caused by Parkinson's disease or can be related to syncope (fainting), **orthostatic hypotension as a side effect of medications taken either for PD**, neurogenic orthostatic hypotension as a result of a condition such as MSA (multiple system atrophy); a cardiac condition, medication-induced dyskinesia, or another issue (cf. <http://parkinsonsfocustoday.blogspot.de/2010/04/coping-with-problems-of-postural.html>).

The **postural instability**, dizziness and syncope that characterize symptomatic NOH increase the risk of falls in patients with Parkinson's disease. By treating NOH and reducing the frequency of falls, the new Chelsea drug could potentially make life much more enjoyable for patients with Parkinson's disease - (cf. <http://www.businesswire.com/news/home/20110315005094/en/PHT-Corporation-LogPad%C2%AE-System-SitePad%C2%AE-Tablet-Chelsea#.Uz0chVPsx8E> of March 15, 2011 06:00 AM Eastern Daylight Time - and cf. the reference further above in this publication: Chelsea Therapeutics is a biopharmaceutical company seeking approval for its lead therapeutic agent, Northera™ (droxidopa) for the treatment of symptomatic NOH).

Novelty(i) and Inventive Step(ii) - Art. 33 (1)-(3)PCT

(i)

Contrary to the arguments of the Applicant, it is considered that - although D1 and D3 do not explicitly mention "postural instability" - those documents are still considered to implicitly disclose the treatment of Parkinson's patients with postural instability by administering droxidopa, in particular D3.

From the above definitions, in particular D2 and D3 it can be taken that orthostatic (postural) hypotension which leads eventually to falls (in particular in elderly, i.e. "late stage" patients) is an autonomic failure (i.e. a disorder norepinephrine transmission). Also in Parkinson patients this aspect of the autonomic failure (i.e. the NE neurotransmission disorder) is discussed (cf. p.20 and infra "bottle neck" role of dopamine-beta-hydroxylase): D3 thus proposes to use droxidopa to treat orthostatic hypotension in several autonomic disorders, including Parkinson's disease (cf. p.20/r-h col/top).

From D3 it can be (further) taken that

Dopamine beta hydroxylase is the rate-limiting enzyme and it creates a "bottle neck" like effect, so that taking levodopa orally results in an increase in dopamine levels but not to a significant increase in norepinephrine levels.

Fortunately, the possibility of **overcoming this limitation** and realizing another therapeutic breakthrough **using a precursor amino acid to replace** a deficient catecholamine neurotransmitter, in this case **norepinephrine**, was a **3,4-threodihydroxyphenylserine**, identical to levodopa but **with an added beta hydroxyl group** (Fig. 2) **was converted to norepinephrine in a single step** by the enzyme L-aromatic amino acid decarboxylase, thus **bypassing the need for** dopamine beta hydroxylase and its **bottle neck effect**. [...] after **oral administration**, **droxidopa was taken up by post-ganglionic sympathetic neurons**, **decarboxylated to NE**, stored and released appropriately when standing up - cf p.20.

Hence, from D3 it can be seen that indeed the true treatment is to increase the reduced norepinephrine level (the production of which is limited after (long) levodopa treatment). This is even more evident as in late stage PD patients these negative effect of levodopa is known.

*The Applicant's arguments that "[a] medical doctor attempting to treat a Parkinson's patient would be expected according to knowledge in the art to primarily begin pharmacology intervention by administration of levodopa" is generally correct. However, cf. supra, **postural instability is known to represent a symptom of late***

stage Parkinson patients and it is also known that indeed levodopa is responsible for negative motor effects. Hence, this underscores that the medical doctor treating a patient suffering for a long time from Parkinson would - with due care - look for an alternative treatment to levodopa, for instance droxidopa.

The parameters - which have now been introduced into claims 1 and 25 and describe "improved **postural instability**" as being defined by a **baseline Hoehn and Yahr rating scale score** and by a **baseline Unified Parkinson's Disease Rating Scale (UPDRS) score**" - are still not considered to represent technical features which allow to delimit the claimed subject-matter from the prior art (cf. infra).

For completeness it is also pointed out to the above reference to internet articles, in particular <http://www.businesswire.com/news/home/20110315005094/en/PHT-Corporation-LogPad%C2%AE-System-SitePad%C2%AE-Tablet-Chelsea#.Uz0chVPsx8E> which is indeed a press release concerning the present Applicant and his invention to use droxidopa for NOH in Parkinson patients. Together with the above explanations given in the article that postural instability i.a. characterizes NOH increasing the risk of falls, even this press release would be considered novelty destroying.

This assessment appears to be supported by the description of the present application, cf. 4 "Since **recurrent falls is a recognized symptom of PD, particularly in PD patients suffering from neurogenic orthostatic hypotension ("NOH")**, the present disclosure **particularly describes the invention in relation to this condition or combination of conditions**. It is intended, however, that the present subject matter encompasses further conditions, as noted above.

In certain embodiments, the **invention can provide a method of reducing falls in a PD patient, particularly a PD patient suffering from NOH**" - [emphasis added]; and cf. p.16 "Thus, the **present invention specifically can relate to treatment of PD patients suffering from NOH**" - [emphasis added].

Hence, in any case there is a clear overlap of subject-matter and nothing in the claimed subject-matter so far allows to make a separation of allegedly PD patients suffering from postural instability due to NOH and PD patients suffering from postural instability not due to NOH (whereby no causes with regard to the latter seem to have been elucidated in the claims/description - except for the measurements of falls, but again, these parameters are firstly no mean to define a condition to be treated cf. infra and secondly also falls due to NOH would fall within the parameters, i.e. again no distinction would be possible).

(ii)

Equally for completeness in view of inventiveness, it is considered that the Applicant - besides - has not proven that the treatment is based on a different mechanism/cause (cf. supra Novelty) but on the contrary (cf. unallowable dependent claim 24) has - indirectly - proven that exactly the long levodopa therapy is the problem of the postural instability of late stage PD patients.

Re Item VIII

Certain observations on the international application

The parameters used in independent claims 1 and 25 to define the improvement of postural instability represent in fact a definition of a result to be achieved. However, such parameters are not considered to represent clear technical features (to define a disease) that can be used to delimit the claimed subject-matter in view of prior art documents.

EUROPEAN PATENT OFFICE
INTERNATIONAL PRELIMINARY EXAMINING
AND SEARCHING AUTHORITY

Applicant: CHELSEA THERAPEUTICS, INC.
International Appln. No. PCT/US2013/023828
International Filing Date: 30-January-2013

Title: IMPROVING POSTURAL STABILITY AND
INCIDENT FUNCTIONS IN PATIENTS

Authorized Officer: BAUMGARTNER, Heike
Applicant's Docket No.: C63756 1260WO (0135.2)

14-November-2013

European Patent Office
D-80298 Munich
Germany

RESPONSE TO WRITTEN OPINION OF
THE INTERNATIONAL SEARCHING AUTHORITY

Sir:

This is in response to the Written Opinion dated 19 April 2013 from the International Searching Authority ("ISA"). Applicants respectfully request reconsideration in light of the attached claim amendments and the remarks provided below, and Applicants further request issuance of a favorable International Preliminary Report on Patentability.

CLAIM AMENDMENTS

Claim 1 combines the subject matter of original claims 1, 2, 3, 9, and 15.

Claims 2-6 correspond to original claims 4-8.

Claims 7-11 correspond to original claims 10-14.

Claims 12-23 correspond to original claims 16-27.

Claim 24 is new and finds support in the original specification at page 2 (lines 27-31).

Claim 25 incorporates the subject matter of original claims 28-31.

Claims 26-30 correspond to original claims 32-36.

Applicants submit that no new matter has been introduced by the amendments to the pending claims.

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Applicant: Chelsea Therapeutics, Inc.
International Application No. PCT/US2013/023828
International Filing Date: 30-January-2013

REMARKS

Applicants have reviewed the examiner's comments in the first Written Opinion and believe that there are reasonable grounds for the examiner to reconsider the objections. In particular, Applicants respectfully submit that the examiner has failed to recognize certain distinctions of the presently claimed subject matter over the disclosures of the cited references. Moreover, Applicants submit that the examiner has incorrectly characterized the manner in which one of ordinary skill in the art would evaluate the potential use of droxidopa in a Parkinson's patient.

The examiner argues that the disclosure in the art that droxidopa may be administered to Parkinson's patients implicitly anticipates the present claims because, as alleged, any administration of droxidopa to a Parkinson's patient would have implicitly performed the presently claimed method. The examiner also argues that postural instability is not a new condition or a new patient group because Parkinson's patients and patients suffering from Orthostatic Hypotension ("OH") are known to fall. This is an incorrect conclusion that is arrived at by using a hindsight reconstruction. One of skill in the art, however, would understand that Parkinson's patients may exhibit a variety of symptoms. For example, it is known that motor symptoms of Parkinson's disease can include the following: tremor at rest; rigidity; akinesia (or bradykinesia); postural instability; shuffling gait; festination; flexed posture; freezing; and several additional symptoms. Not all Parkinson's patients exhibit all of the above motor symptoms. As such, the mere previous administration of droxidopa to Parkinson's patients cannot properly be viewed as inherently disclosing treatment of postural instability.

As discussed further below, it is clear that none of the art cited by the examiner identifies postural instability as a condition that is responsive to treatment with droxidopa or even as a condition that is responsive to known treatments for Parkinson's disease. Rather, the examiner has drawn a correlation to "connect the dots" between the presently claimed invention and the peripheral disclosure in the art. The examiner argues that since patients with Orthostatic Hypotension and Parkinson's patients both may suffer from falls associated with their conditions, and since postural instability may be defined in part by falls, treatment of Parkinson's patients and OH patients with droxidopa "must" (in the examiner's position) also treat postural instability. That is clearly a hindsight reconstruction based on supposition and not on any actual disclosure from the cited art.

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Since the examiner's position arises from the conclusions drawn from the combined disclosures of D1 through D5, the disclosures of these documents are addressed individually below. As will be shown, one of ordinary skill in the art viewing these disclosures would not consider that the documents individually or together disclose that droxidopa is an effective treatment for postural instability.

D1 - WO 2006/123678

The examiner correctly notes that D1 teaches the following (taken from paragraph [0002] of US 2009/0074861, the U.S. national stage application of D1).

Droxidopa is a pharmaceutical agent mainly used for improving frozen gait and orthostatic dizziness in patients with Parkinson's syndrome, as well as for treating orthostatic hypotension in dialysis patients.

Apart from the foregoing, D1 provides absolutely no teaching whatsoever in relation to the mode of action of droxidopa in Parkinson's patients or OH patients. Thus, taken on its face, D1 can only be viewed as disclosing that droxidopa may be used for the single symptom of freezing gait in Parkinson's patients and may be used for dizziness in OH patients. The prior art, however, shows that postural instability manifests separately from these conditions, and nothing in D1 (or the remaining cited art) links droxidopa therapy to any improvement in postural instability. Moreover, while the examiner has attempted to reconstruct the issue at hand to merely preventing falls, the known art clearly delineates falls from postural instability and falls from other causes, including freezing or dizziness.

As pointed out in the present specification, prior testing has shown a clear delineation between postural instability and freezing gait or dizziness from OH. For example, the examiner is directed to the following.

- One test found that Parkinson's patients commonly had center of mass falls (most often while turning around), which suggests that an underlying balance disorder caused most falls. See Bloem et al. (2001) *J. Neurol*, 248: p. 950-958.
- Another test found that the underlying cause in Parkinson's patients for most falls from standing (69%) was loss of balance. On the other hand, freezing, festination, or a leg not

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moving as expected only accounted for about 5% each of the recorded falls. See Ashburn et al. (2008) *Disability and Rehabilitation*, 30(16): 1205-1212.

- Another test found that recurrent fallers among Parkinson's patients showed increased postural sway when compared to non-recurrent fallers. See Matinolli et al. (2011) *Acta Neurol. Scand.*, 123: 193-200.
- Matinolli et al. also pointed out that other studies have suggested that postural instability in Parkinson's disease is resistant to conventional pharmacotherapy. See Bloem et al. (1996) *Mov. Disord.*, 11: 509-521; Bonnet et al. (1987) *Neurology*, 37: 1539-1542; and Klawans, HL (1986) *Mov. Disord.*, 1: 187-192.
- Another test concluded that frequent falling in Parkinson's patients is caused by postural instability, that such instability is not reversible with dopaminergic therapy (e.g., levodopa), and falling in Parkinson's patients generally does not respond well to drug therapy. See Koller et al. (1989) *Clin. Neuropharmacol.*, 2: 98-105.

While testing indicates that postural instability is a main factor for recurrent falls in Parkinson's patients, the known art has only considered droxidopa therapy for addressing freezing gait. For example, Narabayashi et al. (Proc. Japan Acad., 57, Ser. B, No.9, 351-354(1981)) reported a beneficial effect on freezing gait when administered to Parkinson's patients. However, the efficacy rate of droxidopa in freezing gait has not been necessarily high in the reported studies. In the Societas Neurologica Japonica PA disease guideline, therefore, droxidopa is regarded as a medicament to be optionally tried in Parkinson's patients. Further, the effectiveness of droxidopa in freezing gait has been previously questioned. See Quinn et al., "Acute administration of DL-threo DOPS does not affect the freezing phenomenon in parkinsonian patients", *Neurology*, 1984, 34:149.

As can be seen from the foregoing, a person of skill in the art would recognize a distinction between treatment of freezing gait and treatment of postural instability in Parkinson's patients. Nothing in D1 discloses the use of droxidopa in treating postural instability, which is not necessarily present in all Parkinson's patients suffering from freezing gait. Moreover, since the efficacy of droxidopa in freezing gait has been questioned, there is no disclosure in D1 showing that droxidopa has been sufficiently widely administered to Parkinson's patients to have implicitly treated postural instability. The same reasoning likewise applies to treatment of OH since nothing in D1 discloses that patients suffering from OH necessarily suffer from postural instability, which is

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clearly recognized to be a distinct motor symptom of Parkinson's disease that would not necessarily be present in all OH patients.

D2 – Mathias et al.

The examiner relies upon D2 solely for its teaching that droxidopa is an effective treatment for OH and that reducing incidence of OH can prevent falls and associated trauma. This, however, is completely irrelevant to the claims at issue.

One of skill in the art would clearly recognize that postural instability is a condition that is distinct from OH, which arises from the body's inability to manage necessary blood pressure changes between lying and standing positions. Although some Parkinson's patients may exhibit OH, this in no way discloses that treatment of OH implicitly treats any other condition suffered by the Parkinson's patient, including postural instability. Further, it is important to note that although D2 calls OH "orthostatic (postural) hypotension", one of skill in the art would still recognize that OH and postural instability are distinct conditions.

Moreover, as the examiner alleges that the cited art destroys novelty, it is important to note that in D2, the presence of Parkinson's disease was an exclusion criterion (see p. 236, left column, second paragraph under "Methods"). Thus, any disclosure from D2 cannot be correlated to any effect of droxidopa in Parkinson's patients, particularly those exhibiting postural instability.

D3 – Kaufmann et al.

Again, the examiner relies upon D3 solely as teaching that droxidopa is useful in treating OH. This in no way discloses the presently claimed subject matter. D3 is limited to reviewing the pressor effect of droxidopa in patient populations. The ability of droxidopa to help regulate blood pressure in no way discloses that droxidopa may be effective in treating postural instability in any patient population.

D4 – Gupta et al.

The examiner relies upon D4 as disclosing that OH is a manifestation of autonomic failure and is a cause of recurrent falls. Yet again, this disclosure is irrelevant to any allegation that the present claims lack novelty over the cited art. D4 provides no disclosure related to postural instability or to the use of droxidopa in treating postural instability. Likewise, D4 does not correlate OH to postural instability. In D4, falling by OH patients is correlated only to dizziness arising from the abnormal

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drop in blood pressure. Thus, any disclosure related to falls in D4 is limited and cannot be relied upon to suggest that treatment of postural instability is disclosed.

D5 – Wood et al.

The examiner relies upon D5 as disclosing that falls are a common problem in Parkinson's disease and some of the major risk factors are potentially modifiable. The examiner has pointed to nothing in D5 from which one of skill in the art could draw the conclusion that droxidopa may treat postural instability or even falls generally. D5 discloses numerous factors associated with falls and only concludes that some factors are potentially modifiable. Thus, it is clear that D5 does nothing more than identify a problem and then provide no plausible solution to the problem. In particular, nothing in D5 indicates that any one pharmacological intervention may implicitly treat multiple factors associated with falls in Parkinson's patients. Any disclosure in D5 related to falls is only informational and does not disclose any type of treatment.

Novelty

The examiner has provided no evidence from the cited art that droxidopa may treat postural instability. A finding of lack of novelty requires that each and every aspect of a claim be found in a single cited art document. The examiner has done nothing more than show that the art discloses that droxidopa can be used to treat OH and to treat freezing gait in Parkinson's patients. The examiner has provided no cited art teaching that droxidopa has any effect on postural instability.

Since the examiner can point to nothing in the cited art that discloses that actually claimed subject matter, the examiner has tried to condense the claims into reciting administering droxidopa to Parkinson's patients. This is ineffective and incorrect.

The examiner argues that postural instability is not a condition that can be addressed separate from Parkinson's disease. Specifically, the examiner argues that a medical doctor would not separate Parkinson patients being treated for Parkinson syndrome from Parkinson patients that might additionally be prone to fall more frequently. This argument, however, simply underscores the examiner's incorrect summarization of what is actually being claimed.

One of skill in the art understands that Parkinson's disease is a very complex condition which manifests itself in many different and distinct symptoms. A medical doctor attempting to treat a Parkinson's patient would be expected according to knowledge in the art to primarily begin pharmacologic intervention by administration of levodopa, which is the most often prescribed drug

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for treating Parkinson's disease. It is known in the art, however, that some symptoms of Parkinson's disease are non-responsive to levodopa therapy, and this may be ascribed to wide neurodegeneration other than of dopamine neurons. This failure is what led to testing that recognized that droxidopa may be beneficial in treating freezing gait in Parkinson's patients as an adjunct therapy to levodopa administration (although such finding was later questioned). Thus, it is clear that pharmacological interventions for Parkinson's disease are not prescribed based solely on the overarching condition. Rather, multiple drugs are commonly prescribed to Parkinson's patients based upon responsiveness to levodopa therapy and the presence of untreated symptoms. These untreated symptoms are what define patient populations which, while being subsets of Parkinson's patients generally, are distinct populations because they are filled with patients that exhibit symptoms that are unresponsive to other drug therapies.

Postural instability is a distinct subpopulation within the group of Parkinson's patients, and this is seen in the various art documents referenced above where falls in Parkinson's patients were attributed to this symptom separately from other symptoms, such as freezing gait. As such, Applicants do not argue that a new patient population has been discovered. Rather, Applicants have found that droxidopa is an effective treatment for the known condition of postural instability, and this finding is not otherwise shown in the cited art.

The examiner's argument regarding how a medical doctor may divide Parkinson's patients for treatment is misleading because the examiner makes the argument in relation to the effect (falling) and not in relation to the symptom itself. Many symptoms of Parkinson's disease may result in falls, and Applicants have not alleged that falling generally is treated. Rather, Applicants submit that a medical doctor treating a Parkinson's patient would assess the symptoms suffered by the patient, identify any symptoms that are not controlled by the primary treatment (typically levodopa therapy), and then consider additional therapies to address the untreated symptoms. As such, a medical would indeed treat a Parkinson's patient suffering an uncontrolled symptom differently than a Parkinson's patient whose symptoms are all generally well controlled. To this end, the examiner is directed to present claim 24, which recites that the postural instability is non-responsive to levodopa therapy.

In light of the foregoing, Applicants submit that the examiner's position regarding novelty is not supported by the cited art for at least the following reasons:

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1. Postural instability is a recognized symptom of Parkinson's disease that is identified separately from the other, various symptoms of the condition.
2. Falls in Parkinson's patients may be caused by different symptoms, and nothing in the cited art indicates that any single drug therapy necessarily ameliorates all possible symptoms of Parkinson's disease.
3. A Parkinson's patient exhibiting a symptom that is not controlled by the primary drug therapy would be treated by a medical doctor as an independent subpopulation of Parkinson's patients generally.
4. The examiner has cited to nothing in the art indicating that postural instability is a symptom of Parkinson's disease that is necessarily ameliorated by administration of any drug known to ameliorate any of the remaining symptoms of the condition.
5. The examiner has cited to nothing in the art indicating that Parkinson's patients exhibiting freezing gait or OH necessarily also exhibit the symptom of postural instability.
6. The examiner has cited to nothing in the art indicating that treatment of freezing gait or OH in a Parkinson's patient necessarily treats any other symptom that may be exhibited by the Parkinson's patient.
7. The examiner has cited to nothing in the art disclosing the use of droxidopa for treating postural instability in Parkinson's patients or any other patient population.

Applicants submit that the examiner has made an improper conclusion regarding lack of novelty. Novelty cannot be evaluated based upon the end result of the claimed treatment – i.e., reducing falls. Falling is simply an end result of a condition. Postural instability is one of the many different conditions that may cause falls in patients, and the mere fact that droxidopa may be disclosed as treating other conditions that result in falls in no way discloses that droxidopa also is effective in treating the distinct condition of postural instability. The cited art simply fails to disclose that administration of droxidopa to patients with freezing gait or patients with OH provided any effect other than possible treatment of freezing gait and treatment of OH. Since postural instability does define a valid patient population that is separable from patients exhibiting freezing gait or OH, and since the cited art nowhere discloses that droxidopa can be used to treat postural instability, the present claims cannot be properly alleged to lack novelty over any one of D1-D5.

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Inventive Step

The examiner has alleged a lack of inventive step based primarily upon the incorrect allegation that the present claims lack novelty. As discussed above, however, none of D1-D5 discloses each and every aspect of the present claims, either expressly or implicitly.

Applicants recognize that the cited art teaches that droxidopa may be administered to patients exhibiting OH and to Parkinson's patients exhibiting freezing gait. Applicants submit, however, that the art as a whole would not lead the person of skill in the art to conclude that droxidopa would be effective in treating Parkinson's patients suffering from postural instability.

OH is a very different condition from postural instability and relates to the body's inability to properly regulate blood pressure. Although OH patients fall, it is because the rapid lowering of the blood pressure upon standing causes lightheadedness. Postural instability is unrelated to blood pressure regulation, and the examiner has pointed to nothing in the cited art indicating that blood pressure regulation and postural instability share similar etiologies and thus would benefit from similar therapies. The person of skill in the art seeking to ameliorate postural instability would not be motivated to use droxidopa simply because droxidopa is also used to treat OH.

Similarly, the use of droxidopa in treating freezing gait in Parkinson's patients would not necessarily suggest to the person of skill in the art that droxidopa would be useful in treating postural instability. As pointed out above, droxidopa is only an adjunct therapy in Parkinson's patients, and the cited art only suggests its efficacy in treating the lone symptom of freezing gait. Thus, there is no motivation to generally administer droxidopa to any and all Parkinson's patients.

As noted above, efficacy of droxidopa in treating freezing gait has been questioned. While the person of skill in the art may recognize that droxidopa may be effective in treating freezing gait, the art does not support any broad application of droxidopa in ameliorating any other symptom of Parkinson's disease. Likewise, the examiner has pointed to no testing in the art showing that droxidopa therapy has been effective in treating any other symptom of Parkinson's disease.

The present application includes test data indicating that administration of droxidopa to Parkinson's patients did improve postural instability. This is underscored by the importance of the subjective measures of success, namely the Hoehn and Yahr rating scale score and the UPDRS score. In particular, the Hoehn and Yahr rating scale is heavily weighted towards postural instability as the primary index of disease severity. Thus, improvements in the Hoehn and Yahr score (as seen in the example of the present specification) may be viewed as a strong indicator that improvements in postural instability underlie the reduction in falls that were seen in the study.

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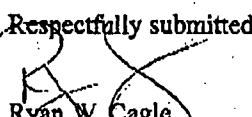
CONCLUSION

In light of the foregoing, Applicants submit that the pending rejections should be withdrawn. Postural instability is a distinct symptom of Parkinson's disease, and the cited art nowhere suggests that pharmacological interventions for other, different symptoms of Parkinson's disease inherently treat the postural instability. In particular, the cited art does not disclose that droxidopa may be effective in treating postural instability.

Applicants have recognized that a subpopulation of Parkinson's patients is the group of patients whose postural instability resulting in falls is not necessarily controlled through administration of levodopa. As a solution to the problem, Applicants have found that droxidopa can prevent falls arising from postural instability in Parkinson's patients. The cited art does not suggest that droxidopa is an effective treatment for postural instability. Although the cited art teaches that droxidopa improves OH and may be useful in freezing gait, the art does not suggest that postural instability in particular may be treated through administration of droxidopa. On the other hand, the present specification presents experimental data showing that droxidopa therapy was effective to reduce falls in Parkinson's patients, and the reduction in falls correlated to improvements in postural instability, as evidenced by the improved scores on the Hoehn and Yahr test scale. Applicants submit this supports the presence of inventive step.

All of the points raised by the ISA in the first Written Opinion have now been addressed by clear and proper amendments to the claims of the pending application and the foregoing comments. Accordingly, Applicants respectfully request that a favorable International Preliminary Report on Patentability indicate the same.

Respectfully submitted,


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AttyDktNo. C63756 1260WO (0135.2)

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CLAIMS:

1. A method of improving postural instability in a Parkinson's disease (PD) patient, the method comprising administering an effective amount of droxidopa or a pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof to the PD patient, wherein the improved postural instability is defined by at least one of the following:

5 a reduction in falls as evidenced by a post-administration reduction in the mean number of falls per patient per week as compared to a baseline mean number of falls per patient per week before administration of the droxidopa or a pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof;

10 a baseline Hoehn and Yahr rating scale score indicative of the postural instability, and a post-administration Hoehn and Yahr rating scale score for the patient that is improved as compared to the baseline score; and

a baseline Unified Parkinson's Disease Rating Scale (UPDRS) score indicative of PD-related motor or non-motor symptoms, and a post-administration UPDRS score for the patient that is improved as compared to the baseline score.

15

2. The method of claim 1, wherein the post-administration mean number of falls per patient per week is reduced by at least 20%.

20 3. The method of claim 1, wherein the post-administration mean number of falls per patient per week is reduced by at least 50%.

4. The method of claim 1, wherein the number of falls is identified based upon reporting by the patient or the patient's caregiver.

25 5. The method of claim 1, wherein prior to administration, the PD patient is a recurrent faller.

6. The method of claim 5, wherein the PD patient has experienced a mean of at least 0.2 falls per week over a period of at least six weeks prior to administration.

30

7. The method of claim 1, wherein the post-administration Hoehn and Yahr rating scale score is improved by at least 0.2 points.

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8. The method of claim 1, wherein the post-administration Hoehn and Yahr rating scale score is improved by at least 0.3 points.

5 9. The method of claim 1, wherein the post-administration Hoehn and Yahr rating scale score is improved by at least 0.4 points.

10. The method of claim 1, wherein the improvement in the Hoehn and Yahr rating scale score is defined by at least one of the following:

10 the baseline Hoehn and Yahr score is greater than 4.0 and the post-administration Hoehn and Yahr score is less than 4.0;

the baseline Hoehn and Yahr score is greater than 3.0 and the post-administration Hoehn and Yahr score is less than 3.0;

15 the baseline Hoehn and Yahr score is greater than 3.0 and the post-administration Hoehn and Yahr score is less than 2.8;

the baseline Hoehn and Yahr score is greater than 3.0 and the post-administration Hoehn and Yahr score is less than 2.5;

the baseline Hoehn and Yahr score is greater than 3.0 and the post-administration Hoehn and Yahr score is less than 2.2;

20 the baseline Hoehn and Yahr score is greater than 2.5 and the post-administration Hoehn and Yahr score is less than 2.5;

the baseline Hoehn and Yahr score is greater than 2.5 and the post-administration Hoehn and Yahr score is less than 2.3;

25 the baseline Hoehn and Yahr score is greater than 2.5 and the post-administration Hoehn and Yahr score is less than 2.0;

the baseline Hoehn and Yahr score is greater than 2.5 and the post-administration Hoehn and Yahr score is less than 1.8;

the baseline Hoehn and Yahr score is greater than 2.0 and the post-administration Hoehn and Yahr score is less than 2.0;

30 the baseline Hoehn and Yahr score is greater than 2.0 and the post-administration Hoehn and Yahr score is less than 1.8;

the baseline Hoehn and Yahr score is greater than 2.0 and the post-administration Hoehn and Yahr score is less than 1.5;

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the baseline Hoehn and Yahr score is greater than 2.0 and the post-administration Hoehn and Yahr score is less than 1.2;

the baseline Hoehn and Yahr score is greater than 1.8 and the post-administration Hoehn and Yahr score is less than 1.8;

5 the baseline Hoehn and Yahr score is greater than 1.8 and the post-administration Hoehn and Yahr score is less than 1.5;

the baseline Hoehn and Yahr score is greater than 1.8 and the post-administration Hoehn and Yahr score is less than 1.2; or

10 the baseline Hoehn and Yahr score is greater than 1.8 and the post-administration Hoehn and Yahr score is less than 1.0.

11. The method of claim 1, wherein the improvement in the Hoehn and Yahr rating scale score is defined by at least one of the following:

15 the baseline Hoehn and Yahr score is at least 4 and the post-administration Hoehn and Yahr score is 3.5 or less;

the baseline Hoehn and Yahr score is at least 4 and the post-administration Hoehn and Yahr score is 3.0 or less;

the baseline Hoehn and Yahr score is at least 3.5 and the post-administration Hoehn and Yahr score is 3.0 or less;

20 the baseline Hoehn and Yahr score is at least 3.5 and the post-administration Hoehn and Yahr score is 2.5 or less;

the baseline Hoehn and Yahr score is at least 3.0 and the post-administration Hoehn and Yahr score is 2.5 or less;

25 the baseline Hoehn and Yahr score is at least 3.0 and the post-administration Hoehn and Yahr score is 2.0 or less;

the baseline Hoehn and Yahr score is at least 2.5 and the post-administration Hoehn and Yahr score is 2.0 or less;

the baseline Hoehn and Yahr score is at least 2.5 and the post-administration Hoehn and Yahr score is 1.5 or less;

30 the baseline Hoehn and Yahr score is at least 2.0 and the post-administration Hoehn and Yahr score is 1.5 or less;

the baseline Hoehn and Yahr score is at least 2.0 and the post-administration Hoehn and Yahr score is 1.0 or less;

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the baseline Hoehn and Yahr score is at least 1.5 and the post-administration Hoehn and Yahr score is 1.0 or less; or

the baseline Hoehn and Yahr score is at least 1.0 and the post-administration Hoehn and Yahr score is 0.5 or less.

5

12. The method of claim 1, wherein the post-administration UPDRS score is improved by at least 5 points.

13. The method of claim 1, wherein the post-administration UPDRS score is improved by at least 10 points.

10

14. The method of claim 1, wherein the symptom is a motor symptom.

15. The method of claim 14 wherein the motor symptom is related to recurrent falls in the PD patient.

15

16. The method of any one of claims 1 to 15, wherein PD patient further suffers from neurogenic orthostatic hypotension (NOH).

20

17. The method of any one of claims 1 to 16, further comprising administering one or more additional active agents selected from the group consisting of DOPA decarboxylase inhibiting compounds, catechol-O-methyltransferase inhibiting compounds, monoamine oxidase inhibiting compounds, cholinesterase inhibiting compounds, and combinations thereof.

25

18. The method of claim 17, wherein the one or more additional active agents are administered with the droxidopa or a pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof in a single pharmaceutical composition.

19. The method of claim 17, wherein the one or more additional active agents are administered separately from the droxidopa or a pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof.

30

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20. The method of any one of claims 1 to 19, wherein the droxidopa or a pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof is administered in a sustained release form.

5 21. The method of any one of claims 1 to 19, wherein the droxidopa or a pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof is administered in a controlled release form.

10 22. The method of any one of claims 1 to 19, wherein the droxidopa or a pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof is administered in an immediate release form.

15 23. The method of any one of claims 1 to 22, wherein droxidopa or a pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof is administered in the form of a mixture enantiomerically enriched in the L-threo isomer.

24. The method of any one of claims 1 to 23, wherein the postural instability is non-responsive to levodopa therapy

20 25. A composition comprising an effective amount of droxidopa or a pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof for use in improving postural instability in a Parkinson's disease (PD) patient exhibiting symptoms of postural instability as defined by at least one of the following:

a reduction in falls;

25 a baseline Hoehn and Yahr rating scale score indicative of the postural instability, and a post-administration Hoehn and Yahr rating scale score for the patient that is improved as compared to the baseline score; and

30 a baseline Unified Parkinson's Disease Rating Scale (UPDRS) score indicative of PD-related motor or non-motor symptoms, and a post-administration UPDRS score for the patient that is improved as compared to the baseline score.

26. The composition of claim 25, wherein the composition further comprises one or more additional active agents selected from the group consisting of DOPA decarboxylase inhibiting

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compounds, catechol-O-methyltransferase inhibiting compounds, monoamine oxidase inhibiting compounds, cholinesterase inhibiting compounds, and combinations thereof.

27. The composition of claim 25 or claim 26, wherein the droxidopa or a
5 pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof is in a sustained release form.

28. The composition of claim 25 or 26, wherein the droxidopa or a pharmaceutically
acceptable ester, amide, salt, solvate, or prodrug thereof is in a controlled release form.

10 29. The composition of claim 25 or 26, wherein the droxidopa or a pharmaceutically
acceptable ester, amide, salt, solvate, or prodrug thereof is in an immediate release form.

15 30. The composition of any one of claims 25 to 29, wherein droxidopa or a
pharmaceutically acceptable ester, amide, salt, solvate, or prodrug thereof is in the form of a
mixture enantiomerically enriched in the L-threo isomer.

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